Care and Cure for
Infantile Hemangioma

Marlies de Graaf

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Care and Cure for Infantile Hemangioma

De zorg voor en behandeling van infantiele hemangiomen

(met een samenvatting in het Nederlands)

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Marlies de Graaf
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Promotoren:
Prof.dr. C.A.F.M. Bruijnzeel-Koomen
Prof.dr. S.G.M.A. Pasmans

Copromotor:
Dr. C.C. Breugem

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General introduction

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This general introduction will provide a brief overview of the clinical features, associated anomalies, pathogenesis, complications, and current treatment methods of Infantile Hemangioma (IH). This will be followed by an outline of the thesis.

Infantile Hemangioma

IH is the most common benign vascular tumor of infancy. IH are found in approximately 10% of Caucasian infants.[1-3] Females, premature infants, infants with a low birth weight (<1500 grams), and twins are at higher risk of IH development. Most IH (>60%) are found in the head and neck region, but they may affect any other region of the body including internal organs.[4,5]

Normally IH are absent at birth, but develop in the weeks and months thereafter. In some cases there is a precursor lesion present at birth, such as a small red macule, telangiectasia, or blue macule.[1,6] During the proliferation phase there is disproportionate growth for an average period of 3-9 months.[6] Most IH growth is seen in the first two months.[7] After the growth phase there is usually a stable period, before the regression phase starts. The involution is slow and gradual with a primary development of central whitening on the superficial component of the IH. The involution of subcutaneous IH is delayed, slower and more incomplete in comparison with superficial lesions.[8] Most IH do not improve significantly after the age of 3.5 years.[9] IH can resolve without sequelae. However, in 69% of all IH wrinkled atrophic skin, telangiectasia, pigmentation, scars or fibro-fatty tissue are left behind.[1,10]

Clinical features and diagnosis

IH may be classified according to the depth of the lesion into superficial (50-60%), deep (subcutaneous, approximately 15%) or mixed (25-30%) IH.[8,11] Furthermore, each type is subclassified according to the size, the anatomical localization or the morphological subtype into localized (nodular, 67%), segmental (13%), indeterminate (16.5%) or multifocal (3.6%).[8,11,12]

On palpation IH have a firm and elastic texture and may feel a little warm. They do not pulsate. IH are usually painless, except in case of ulceration.[8]

A superficial IH presents as a bright red tumor with an irregular surface and is often described as 'strawberry' hemangioma. A subcutaneous IH is a protruding swelling under normal or bluish skin. A mixed IH is a combination of a primary superficial component associated with a later subcutaneous extension.[8]

The size of an IH may vary greatly, but most cases (80%) are sized less than 3 cm in diameter.[12]

In most cases the diagnosis of IH can be made by the typical natural history and clinical picture. However, sometimes it is difficult to make an accurate first diagnosis if the natural

history is lacking at that time. Macfie et al.[13] found that the initial diagnosis regarding a child's vascular skin lesion given to parents by doctors was inaccurate in 69% of the patients. Misuse of terminology has probably contributed to this as well.

Nomenclature

IH has a history of confusing nomenclature due to the lack of a uniformly accepted classification system and the lack of a clear understanding of the natural history of this birthmark.[14]

Virchow and Wagner (1863) published an early classification in which vascular lesions were classified according to the pathological appearance of the vessels.[15] Vascular growths were divided into angiomas (simplex, cavernosum, and racemosum) and lymphangiomas (simplex, cavernosum, and cystoides). There was a tendency to identify any vascular anomaly as a hemangioma. Therefore, at the beginning of the twentieth century, there was confusion about the use of eponyms to describe syndromes associated with vascular malformations and underlying systemic abnormalities.[16]

In 1982, Mulliken and Glowacki helped to clarify this confusion by proposing a classification in which the biologic behavior and natural history of vascular lesions were considered.[17] This classification makes a distinction between vascular tumors, like IH, and vascular malformations and makes it possible to accurately classify vascular anomalies in up to 96% of patients.[17] In 1996, the classification was slightly modified to reflect the importance of other types of vascular tumors that exhibit different clinical and histological characteristics than the common IH (including kaposiform hemangioendotheliomas, tufted angiomas, and others) (Table 1).[18] This is the accepted classification of the International Society for the Study of Vascular Anomalies (ISSVA).

This classification is now widely used by clinicians to differentiate between vascular birthmarks. It is useful for managing patients and provides a framework for studying IH and

Table 1. Vascular anomalies: ISSVA/Mulliken classification 1996.

Vascular tumors	**Vascular malformations**	
	Simple	Combined
infantile hemangioma	capillary	arteriovenous fistula (AVF)
congenital hemangioma	lymphatic	arteriovenous malformation (AVM)
tufted angioma	venous	capillary or capillary-lymphatic AVM
kaposiform hemangioendothelioma	arterial	capillary-lymphatic venous malformation
hemangiopericytoma		capillary venous malformation
pyogenic granuloma		lymphatic venous malformation
spindle-cell hemangioendothelioma		

vascular malformations.[18] However, misuse of terminology in describing vascular anomalies is still commonly seen in both the medical and surgical field.[19] Furthermore, the differential diagnosis of IH is broad and even contains rare malignancies.[87]

Associated structural anomalies

The occurrence in the same patient of an IH and structural anomalies has long been described. Segmental IH can be associated with underlying congenital anomalies and have a much higher risk for the development of complications.[12] Two syndromes are now identified: PHACES syndrome and LUMBAR syndrome (also known as SACRAL/PELVIS syndrome). The exact etiology of these syndromes is as yet unknown, but an anomaly in the field of morphological development related to the defect of one or more regulatory genes is suspected.[8]

PHACE syndrome

In 1978, Pascual-Castroviejo[20] was the first to report on an association between capillary hemangiomas and craniocervical arterial anomalies. PHACE is an acronym that was introduced in 1996 by Frieden et al.[21] to describe the association of *Posterior fossa malformations, Hemangiomas, Arterial anomalies, Cardiac anomalies, and Eye abnormalities*. In case of sternal clefting or supraumbilical raphe, this acronym is expanded to PHACES syndrome. Not all anomalies of the PHACE spectrum are necessary to fit the syndrome since about 70% of the children with PHACE syndrome present with a single extracutaneous anomaly.[22]

The exact frequency of PHACE syndrome is unknown. In a prospective multicenter cohort study of 1096 children with IH, 20% of the 200 segmental facial IH met the criteria for PHACE syndrome and 88% of these cases were girls.[23] PHACE syndrome is therefore not a rare clinical entity.[24]

LUMBAR syndrome

Different terms have been suggested for describing segmental IH in the lumbar and perineal region and their associated anomalies: PELVIS syndrome (*Perineal Hemangioma, External genitalia malformations, Lipomyelomeningocele, Vesicorenal abnormalities, Imperforate anus, and Skin tag*)[25-28], SACRAL syndrome (*Spinal Dysraphism, Anogenital, Cutaneous, Renal and Urologic Anomalies, Associated with an Angioma of Lumbosacral Localization*)[29], and LUMBAR syndrome (*Lower body IH and other skin defects, Urogenital anomalies and Ulceration, Myelopathy, Bony deformaties, Anorectal malformations and Arterial anomalies, and Renal anomalies*)[30].

Since different terms are used in the literature there is little data about incidence and prevalence of the associated anomalies in lumbosacral and perineal IH. And, in contrast to PHACE syndrome there is no consensus about the diagnostic criteria for LUMBAR syndrome. Further-

more it is unclear which diagnostic investigations should be performed when confronted with a child with an IH located in the lumbosacral and perineal area.

Pathogenesis

When unraveling the pathogenesis of IH it is of interest to look at all aspects of IH during both the proliferation and involution phase.

Characteristics of IH cells and histological findings

IH consist of multiple cell types including a small proportion of multipotent stem cells (CD133+), a majority of immature endothelial cells (CD31+), pericytes (SMA+), dendritic cells (factor XIIIa+) and mesenchymal cells with an adipogenic potential.[17,31-34] Mast cells and myeloid cells may also be found within the tumor.[8]

During the proliferation phase IH show an increased endothelial cellularity with the formation of syncytial masses without a defined vascular architecture. During this phase, these endothelial and interstitial cells strongly express the monoclonal antibody MIB-1, a marker of proliferation. In a later phase lumenized capillary-like structures are organized with multilaminated basement membranes. During involution lumina become larger and blood vessels are replaced by a fibro-fatty residuum and capillary-sized channels.[8]

IH originate from stem cells, but the origin of these IH stems cells is still debated. Itinteang et al.[35] showed that the IH stem cells have a neural crest stem cell phenotype. They have proposed a model that may account for the natural progression of IH in both the proliferation and involution phase based upon the multipotent expression profile of the primitive mesoderm and their neural crest stem cell phenotype.[35]

Hypotheses of etiology of IH

Currently there are three hypotheses of the etiology of IH:

The placental hypothesis of origin

IH endothelium uniquely co-expresses with placental microvasculature specific markers such as glucose transporter protein 1 (GLUT-1), Lewis Y antigen (CD14), Fc γ receptor II (CD32), CCR6, CD15, indoleamine 2,3-deoxygenase (IDO) and merosin.[34,36,37] GLUT 1, Ley, FcRcII and merosin-markers are positive in the three phases of IH evolution, whereas they are absent in other tumors, vascular malformations and normal skin.[36] In vitro studies have identified a multipotential stem cell that forms a lesion with GLUT-1-positive microvessels and involutes by differentiation into adipocytes.[34]

The placental hypothesis of origin suggests that placental tissue shears off during gestation and embolizes fetal cutaneous vessels. IH arise from the embolized placental stem cells to

receptive fetal tissues or, less likely, from fetal angioblasts that differentiate to placental phenotypes as a result of intrinsic somatic mutations at these sites. Postnatal growth of the IH may be explained by the lack of angiogenesis-inhibiting factors produced by the placenta, which would normally prevent the proliferation of placental progenitors and are lost after delivery.

The placental hypothesis may explain the increased incidence of IH following placental complications or placental trauma (e.g. abruptio placenta, placenta previa, and chorionic villous sampling).[37,38]

In line with the placental theory it has been demonstrated that IH are a developmental anomaly involving proliferation of a hemogenic endothelium derived from a primitive mesoderm/mesenchymal phenotype.[35,89-91] Itinteang et al.[92] showed a possible placental chorionic villous mesenchymal core cellular origin of IH. They hypothesized that primitive mesoderm derived cells shed from the primitive capillaries of the placental chorionic villi, via the umbilical vein, into the fetus circulation.[92] This occurs spontaneously during early pregnancy or following an obstetric intervention. The extra-uterine environment, with high levels of plasma renin during infancy and early childhood, may then provide an environment for the development of IH (see also 'working mechanism of propranolol').[72]

Stimulation and inhibition of angiogenesis

The proliferation phase of IH is characterized by stimulation of endothelial proliferation by pro-angiogenic factors, like vascular endothelial growth factor (VEGF) and fibroblast growth factor (bFGF). Expression of VEGF-receptor (VEGFR) 1 is reduced in IH endothelial cells.[40] Low VEGFR1 expression results in VEGF-induced activation of VEGFR2 and downstream signaling pathways, leading to stimulation of angiogenesis.[33]

IH arise from bone marrow-derived endothelial progenitor stem cells (EPC) capable of inducing postnatal formation of vascular tissue.[41,42] EPC express hypoxia-inducible factor 1a (HIF-1a) which in turn promotes local production of VEGF.[40] During the proliferation phase mediators of EPC trafficking VEGF-A, MMP-9, SDF-1a, HIF-1a are upregulated in IH.[43] Furthermore there have been suggestions that both activation of the HIF-2a (hypoxia-induced factor) pathway and consequent overexpression of VEGF by endothelial cells are involved in the pathogenesis of IH.[44]

During the involution phase apoptosis of the endothelial cells plays an important role in the regression of the IH.[45] Increased expression of ICAM-1 (a marker of endothelial cell maturation) and /or the loss of stimulation by pro-angiogenic factors such as VEGF has been suggested as triggering factors for apoptosis.[8,46] However the exact intermediary mechanisms are still unknown.

In summary, intrinsic defects in local endothelial cells and /or intrinsic activation of VEGF signaling and the contribution of recruited circulating endothelial progenitors are probable pathways in the pathogenesis of IH.

Tissue hypoxia

Since tissue hypoxia seems to be a very powerful inducer of angiogenesis, the role of fetal hypoxic stress has been suggested as a triggering signal for the development of IH.[42,47] Different studies have shown an association between placental hypoxia and IH.[48,49] Furthermore a history of complicated pregnancy and low birth weight is associated with the development of IH and there seems to be an association of IH with retinopathy of prematurity.[12,50] Additionally, various placental abnormalities in neonates with IH have been described.[51] These data strongly suggest that neonates with an IH have been exposed to hypoxic conditions.
Both in placental and in IH tissue, GLUT-1 is upregulated by hypoxia via signaling proteins such as Hypoxic Induced Factor (HIF-1a).[52] In addition, hypoxia leads to the activation of a HIF by the stabilization of its subunit HIF-a1 and this subunit is responsible for an overexpression of VEGF leading to endothelial cell proliferation.[8] Furthermore, it has been demonstrated that the combination of hypoxia and an estrogenic environment has a synergistic effect on IH endothelial cell proliferation.[53]

Because none of the above mentioned hypotheses explain all features of IH, the exact pathogenesis of IH has still to be elucidated. Léauté-Labrèze et al.[8] suggested a possible scenario in which stem cells present in fetal skin receive a pathological signal of a 'dangerous hypoxic situation' resulting in the activation of the HIF-2a pathway responsible for the subsequent overexpression of VEGF. IH are probably the result of a complex combination between genetic predisposition and the influence of various environmental factors. [8] Since the pathogenesis of IH is not completely clear, the working mechanism of the different treatment modalities for IH is (partially) unclear as well.

Risks, complications and indications for treatment

Risks and complications

IH are benign tumors, most of them have an uncomplicated course and spontaneously go into regression. Therefore most IH do not need treatment (follow a "wait and see policy"). However, occasionally they may cause life-threatening risks, functional impairment, local complications, like ulceration or bleeding, or cosmetic risks. In those cases treatment may be indicated.

Life-threatening risk

IH in the beard region, subglottic IH, extensive IH or hepatic hemangiomatosis can cause a life-threatening risk by airway obstruction and heart failure respectively.[46,54-56] In the presence of four or more cutaneous IH, the clinician should be aware that hemangiomas may be located extracutaneously. These lesions are mostly located in the liver, and ultrasonography

is advised when four or more cutaneous IH are encountered. In case of hepatic hemangiomatosis, additional laboratory testing for thrombocytopenia and hypothyroidism should be performed.[46]

Functional risk

Especially IH located in the face can be responsible for functional impairment. Periocular IH and IH on the eyelid may occlude the visual axis or compress the eyeball and the cornea. This can lead to permanent impairment of the visual function due to strabismus, astigmatism or amblyopia.[57] Therefore, infants with IH within the orbital area should have eye examinations and sometimes additional imaging is indicated to explore the intra-orbital extension.[58]
IH on other locations in the face may also cause functional risks. IH on the lips and in the mouth may interfere with feeding and the development of maxillary and dental structures.[58] IH on the nose (called Cyrano's IH when located on the tip of the nose) may deform the underlying nasal structures. IH of the ear may occlude the auditory canal leading to ear infection and hearing loss. In girls IH on the breast may impede the development of the mammary glands.[58]

Ulceration

Ulceration is the most common complication of IH and found in approximately 23% of the patients.[12] Ulceration is more commonly seen in IH of the face and genital area and frequently occurs in the first three months after birth.[59] Ulceration can be very painful and therefore proper wound care and adequate pain relief is indicated. In case of secondary infection, treatment with antibiotics may be necessary. Ulceration will leave a scar after healing, which can be disfiguring.

Bleeding

In rare cases extensive bleeding may complicate IH, especially in IH in the gastrointestinal tract.[60] Ulceration can also be complicated by bleeding and occasionally may lead to severe anemia in need for transfusion.[58]

Cosmetic risk

IH may lead to cosmetic impairment. Especially in case of IH in the centre of the face in which plastic surgery may be challenging, IH with a large subcutaneous component leading to anatomical deformities and IH with extensive telangiectasias leading to necrosis.[58] Sometimes IH only go in regression partially. Disfiguring facial IH may have a psychological impact on parents and children and in those cases psychological support is desirable.[61]

Indications for treatment

In deciding whether to start treatment it is important to take all characteristics of the patient and his/her IH into account. Treatment of individual IH is determined by the size of the IH, its morphology (localized/segmental) and its location, as well as the presence or risk of complications, likeliness of scarring or (permanent) disfigurement, the age of the infant, and the growth or involution rate.[6,62]

Léauté-Labrèze et al.[58] suggested treating IH (based on the above mentioned risks and complications) in case of life-threatening risk (airway obstruction, cardiac distress or bleeding), functional risk (orbital, ear, nasal, and perineal IH), painful ulceration, and cosmetic risk (segmental facial IH, IH of the nose, lips or eyelids, breast IH in girls).

Treatment of IH

A range of medical and surgical treatment options for IH is described in the literature. From 1930 to 1950 X-irradiation therapy was widely used as an effective treatment of IH.[63] In the sixties systematic corticosteroids were found to be an effective treatment for IH and for long time this was the first choice treatment. However, besides varying efficacy, numerous serious side effects can complicate the treatment of IH with systemic corticosteroids.[64]
In 1989 the pulsed dye laser (PDL) became commercially available, and is now used in the treatment of IH.[65] Interferon-α was first described as a novel therapy for IH in 1991, but is associated with severe neurotoxicity.[65,66] Other treatment options described are intralesional corticosteroids and cytostatics, like vincristine and cyclophosphamide. Surgical debulking or complete resection are used in the treatment of IH as well.[46]

Propranolol

In 2008 the efficacy of propranolol, a non-selective beta blocker, on IH was accidentally discovered.[67] In two children propranolol treatment was started because of cardiac complications due to the treatment with systemic corticosteroids.[67] The IH stopped growing and early and rapid involution was observed.[67] Since then many others reported equally favorable effects of propranolol treatment in IH, even after the proliferation phase and in ulcerated IH. Propranolol is now seen as the first choice treatment for IH.[88]

Working mechanism of propranolol

Propranolol is a lipophilic, non-selective beta blocker released in 1964. Since then, the agent has been widely used in pediatric cardiology. The working mechanism of propranolol in the treatment of IH is not completely understood, but it is thought to originate from vasoconstriction of capillaries. This causes discoloration and softening of the tumor, as well as decreased

expression of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) leading to a decrease of proliferating endothelial cells.[68,69]

Furthermore, propranolol induces apoptosis of capillary endothelial cells by blocking IH Glut-1 receptors and inhibits the expression of angiogenic and extracellular matrix degrading proteinase (MMP-9) and human brain microvascular endothelial cells (HBMEC), which may result in an anti-angiogenic effect.[70,71] These mechanisms involve the beta-2 receptor blockade pathway.[68,71]

Itinteang et al.[72] suggested that propranolol may act via blockage of beta-1 receptors in the kidneys, leading to suppression of the renin-angiotensin-aldosterone system (RAAS system) by reduction of renin activity and thereby decreasing the conversion of angiotensinogen to angiotensin I, and finally to angiotensin II. This, together with a reduction of the VEGF concentration, causes inhibition of proliferating $CD34^{+}/VEGFR\text{-}2^{+}$ endothelial progenitor cells in the capillaries of proliferating IH.[72]

Finally, there may be currently unknown mechanisms through which beta blockers mediate their effect on IH.

Side effects of propranolol

Due to beta-2 receptor blockage, propranolol can be associated with side effects. The most common side effects are hypotension, hypoglycemia, bronchial hyperreactivity, cold extremities, restless sleep, hyperkalemia and diarrhea.[73-76] Symptomatic hypoglycemia can be a serious complication from propranolol usage. Non-selective beta blockers like propranolol are competitive antagonists of catecholamines at beta-1 and beta-2 adrenergic receptors. Beta-2 receptor blockage may result in hypoglycemia as a result of decreased glycogenolysis, gluconeogenesis and lipolysis. Patients using propranolol may be especially vulnerable to hypoglycemia during periods of prolonged fasting when counter-regulatory mechanisms may fail. As a result of beta-1 blockage, hypoglycemic symptoms like tachycardia, sweating and anxiety may be absent when hypoglycemia occurs.[77] Therefore propranolol should be given during feeding and caution should be taken with young children, in case of a low birth weight, illness, reduced food intake and in combination with oral corticosteroids.[70] Other side effects are less life-threatening and usually transient, but may lead to discontinuation of the treatment.

Other beta blockers

Propranolol seems to be a promising treatment for complicated IH. Randomized controlled trials should prove the efficacy, safety and treatment/dosing regimen of propranolol. Since the first publication of the effective treatment of IH with propranolol few other beta blockers, orally or topically, are described as effective in IH. Topical timolol has been described by different authors as effective in the treatment of small superficial IH and even ulcerated IH.[78-82] Timolol is a non-selective beta blocker and has already been used since 1978 by ophthalmolo-

gists for the treatment of glaucoma. In most IH studies a timolol 0.5% gel forming solution is used for topical application and good results have been described. However, timolol is a very potent beta blocker and systemic absorption has been suggested.[83] Therefore systemic side effects may occur and monitoring heart rate is recommended.[83] Topical propranolol 1% ointment has shown efficacy in the treatment of superficial IH as well.[84]
Bigorre et al.[85] described four patients successfully treated with the selective beta blocker acebutolol. Later on Blanchet et al.[86] published another three cases of subglottic IH where acebutolol treatment was effective in two out of three cases and they suggested acebutolol as first-line treatment. The use of a hydrophilic, selective beta-1 blocker could prevent the side effects attributable to the beta-2 activity and lipophilicity of propranolol.

Outline of the thesis

In the care for IH there is still much progress to be made. The aim of the studies described in this thesis is broadly twofold. First we aimed to optimize the care for IH by means of eHealth and better diagnosis of associated anomalies (part I). Secondly, we aimed to optimize the treatment of IH by reducing the risk of side effects (part II).

Part I: Care for Infantile Hemangiomas

Since most IH growth is accomplished by two months of age[7], IH at risk of complications need close observation during the first weeks of life. And, if necessary, the infant should be referred and seen as early as possible by a specialized doctor. Chang et al.[6] found that the mean age of the first visit to a specialist was five months. In our clinic, the Centre for Congenital Vascular Anomalies (CAVU) of the Wilhelmina Children's Hospital, University Medical Center Utrecht, we share this experience, since we frequently see patients at a late stage, e.g. when an eye is already closed due to the IH. This late presentation of IH in specialized centers might be caused by a lack of knowledge amongst primary caretakers and parents. We hypothesized that involving parents in diagnosing the vascular skin lesion of their child leads to a more accurate diagnosis and treatment process. To achieve timely presentation of high risk IH in specialized centers we have built an eHealth intervention (including an e-learning module) to improve the knowledge and (risk) evaluation of parents. Chapter 2.1 describes if parents are able to assess, after e-learning, whether their child has an IH, is at risk for complications, and/or needs to be seen (urgently) by a specialist. The eHealth intervention is evaluated with respect to compliance, acceptance and usability in chapter 2.2.
Since the discovery of propranolol, showing less adverse effects and being less invasive compared to previously used treatment options (like oral prednisone), the number of patients

eligible for treatment is increasing. Treatment of IH is currently reserved for multidisciplinary teams in specialized centers because of uncertainties regarding dose initiation, safety monitoring, dose escalation, its use in specific situations (e.g. PHACE syndrome), and long term safety.[88] Due to the patient load for these centers, waiting times for an appointment will increase. This, together with the often long travel distances, points out the need to develop a more efficient way to provide care for children needing treatment for IH. We hypothesized that treatment at a regional hospital, combined with academic support via eHealth, might be used to achieve more efficient care. Chapter 3 evaluates feasibility, acceptance and satisfaction among the users (parents and doctors) of this eHealth intervention.

Segmental IH in the lumbosacral and perineal region can be associated with anomalies, like intraspinal, urogenital, and anorectal malformations (LUMBAR syndrome). However, there is no consensus about the diagnostic criteria for LUMBAR syndrome and the right diagnostic approach. Therefore LUMBAR syndrome and its associated anomalies can easily be missed. A review of the associated anomalies and diagnostic approach of IH in the lumbosacral and perineal region is given in chapter 4.

Part II: Cure for Infantile Hemangiomas

Since propranolol has proven to be effective in the treatment of IH, the general 'wait and see' policy has changed. However, the treatment with propranolol can be associated with side effects. Chapter 5.1 reports an illustrative case of a child suffering from hypoglycemia during propranolol treatment. Chapter 5.2 describes the adverse effects we have observed in a cohort of patients treated with propranolol. Chapter 5.3 and 5.4 show our reply to comments on the safety of propranolol and the risk of hypotension.

Most side effects of propranolol treatment are attributable to its beta-2 activity. Atenolol, as a hydrophilic, selective beta-1 blocker, might prevent the side effects associated with the treatment of propranolol. In chapter 6.1 we show a good clinical response to atenolol treatment in two cases of complicated IH. Chapter 6.2 describes the efficacy and side effects of the treatment with atenolol and we compare these results with the historical group treated with propranolol (chapter 5.2). Finally, chapter 6.3 shows our response to comments on the treatment of IH with atenolol.

In the summary and discussion, the main results of this thesis are summarized and discussed, followed by clinical recommendations and suggestions for future research.

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Part I

Care for Infantile Hemangioma

2.1

E-learning enables parents to assess an infantile hemangioma

Marlies de Graaf[1,3], Mirjam J. Knol[2], Joan E.E. Totté[1,5], Harmieke van Os-Medendorp[3], Corstiaan C. Breugem[4], Suzanne G.M.A. Pasmans[1,5]

[1] Department of Pediatric Dermatology and Allergology, Wilhelmina Children's Hospital Utrecht.
[2] Epidemiology and Surveillance Unit, Centre for Infectious Disease Control National Institute for Public Health and the Environment, Bilthoven.
[3] Department of Dermatology and Allergology, University Medical Center Utrecht.
[4] Department of Pediatric Plastic Surgery, Wilhelmina Children's Hospital Utrecht.
[5] Current affiliation: department of Pediatric Dermatology, Erasmus University Medical Center Rotterdam.

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Abstract

Background Infantile hemangiomas (IH) at risk for complications need to be recognized early.

Objective To determine if parents are able to assess, after e-learning, whether their child has an IH, is at risk for complications, and needs to be seen (urgently) by a specialist.

Methods Prospective study of 158 parents participating in an IH e-learning module. Parents were asked to assess their child's skin abnormality. A dermatologist answered the same questions (by e-consult). The two assessments were compared.

Results Parents showed a 96% concordance with the dermatologist for correct diagnosis after e-learning. Concordances were 79%, 75%, and 84% ($p < 0.001$) respectively on assessing the risk of complications, the need to be seen by a specialist, and the urgency for specialized care.

Limitations Parents had a relatively high education level and were therefore not representative of the general population.

Conclusion Parents were able to correctly diagnose and evaluate an IH after completing an e-learning module. E-learning by parents could result in earlier presentation and treatment of high risk IH.

Introduction

Infantile hemangiomas (IH) are common vascular tumors with a unique growth pattern.[1-3] Although most IH have an uncomplicated course.[4,5,6] 24% of patients experience complications, of which 38% need treatment.[4] Also, a segmental IH can be associated with congenital malformations and require diagnostic evaluation.[4] Correct initial diagnosis and timely referral of at risk IH is imperative, since early intervention may prevent complications.[4]
However, the mean age of the first visit to a specialist is 5 months.[7,8] This delay could be due to a lack of knowledge among parents and healthcare professionals.[8]
E-learning might enable parents and primary caretakers to identify IH at risk for complications and to decide on the need to consult a specialist. E-learning as a tool to increase the knowledge of patients or improve disease control and quality of care has been reported previously.[9-15] We developed an e-learning module to teach parents about IH. The aim of this study was to determine if parents were able to assess, after completing the e-learning module, whether: (1) their child had an IH, (2) the IH was at risk for complications, (3) the IH needed to be seen by a specialist, and (4) urgent specialized care was needed.

Patients and methods

Design and participants

A prospective pretest-posttest study was carried out to determine if parents were able to assess the skin abnormality of their child. An eHealth intervention (URL: http://www.aardbeivlek.nl (in Dutch)) was designed, consisting of an e-learning module and an e-consult (Figure 1). Parents completed a questionnaire before and after e-learning. An IH-specialized dermatologist (MdG) completed the same questionnaire during the e-consult. The assessment of the parents was compared with the assessment of the dermatologist and concordances were calculated (see analyses).
Questionnaires, e-learnings, and e-consults (including a photograph of the skin abnormality), completed between October 2010 and September 2012, were included in the study. Children >1 year of age were excluded. The study was approved by the ethics committee of the University Medical Center, Utrecht.
Parents were referred to the eHealth intervention by the Dutch patient support group for Hemangiomas and Vascular Anomalies (HEVAS) by means of a link on their home page (URL: http://www.hevas.eu), by their child's youth or primary health caretaker (the eHealth intervention was included in their IH guideline), or by surfing the internet. Participation was voluntary and free of charge. To guarantee safe uploading of personal information, parents received a password for the eHealth intervention.

Parents	**Login**	Registration	Registration on the website with password Demographic information
		Questionnaire	Four questions about skin abnormality of the child: 1. Is the skin abnormality an IH? 2. Is the IH at risk of developing complications? 3. Is assessment by a specialist required? 4. Is urgent (within 1 week) assessment by a specialist required?
	E-learning	1. Information	Information about IH: • features and natural course • different types of IH • possible complications and risk factors to recognize IH in need for specialized care
		2. Case 1	Case to bring information about IH in practice: • IH that threatens the eye
		3. Case 2	Case to bring information about IH in practice: • IH on the scalp
		Questionnaire	Four questions about skin abnormality of the child: 1. Is the skin abnormality an IH? 2. Is the IH at risk of developing complications? 3. Is assessment by a specialist required? 4. Is urgent (within 1 week) assessment by a specialist required?
	E-consult	1. History	Age of the child and growth characteristics of the IH
		2. Photograph	Upload photograph of skin abnormality of the child
Dermatologist		*Questionnaire*	Four questions about skin abnormality of the child: 1. Is the skin abnormality an IH? 2. Is the IH at risk of developing complications? 3. Is assessment by a specialist required? 4. Is urgent (within 1 week) assessment by a specialist required?

Figure 1. Design and content of the eHealth intervention.
This figure shows the layout of the eHealth intervention (http://www.aardbeivlek.nl (in Dutch)), consisting of an e-learning module and an e-consult. Parents completed a questionnaire before and after e-learning. An IH-specialized dermatologist (MdG) completed the same questionnaire during the e-consult.
A translation of the content of the e-learning module can be found online.
IH = infantile hemangioma

E-learning module

The purpose of the e-learning module was to teach parents to differentiate between IH and vascular malformations, to recognize IH at risk of complications, and to appreciate the need for assessment by a specialist. The information was based on a national medical guideline for IH (based on criteria used in the literature[4,5,8,16]). A translation of the e-learning module can be found online.

Questionnaire

Parents were asked the following 4 questions before and after the e-learning module:
(1) Is the skin abnormality of your child an IH?;
(2) Is the IH at risk of complications?;
(3) Is assessment by a specialist required?;
(4) Is urgent assessment by a specialist required?.

Complications considered were 1) ulceration or risk of ulceration (perineal, perioral of flexural location); 2) life-threatening or functional risk ((peri)orbital, (peri)auricular or nasal tip location); 3) risk for involvement of internal organs (large segmental IH on the face or lumbosacral area, or >4 IH).[4,5,8,16] Presentation to a specialist was considered necessary when an IH was at risk of the complications described above or if there was (severe) cosmetic impairment. Urgent referral was required in case of a potentially life-threatening IH, (severe) pain from ulceration, or rapid growth of an IH at risk for complications.[4,5,8,16]
Before e-learning parents had the option to answer questions 2, 3 and 4 with 'unsure' while after e-learning they had to choose between 'yes' or 'no'.

E-consult

The e-consult was provided by a dermatologist (MdG) attached to the Center for Congenital Vascular Anomalies Utrecht (CAVU), Wilhelmina Children's Hospital, after a photograph of the child was uploaded and information regarding the growth pattern was obtained. The aim of the e-consult was to guarantee quality of care for the child and to evaluate the parents' ability to assess the skin abnormality by comparing their assessment to the assessment of the dermatologist. Parent questionnaires were not accessible to the dermatologist until the e-consult was finished. Parents were given individualized advice about their child's skin abnormality based on the provided information and photograph.

Analyses

The percentage concordance between parents' answers on the questionnaire after e-learning and the dermatologist's answers was calculated. Corresponding 95% confidence intervals were calculated using the Wilson Score method.[17]
Prior to the study it was determined that a concordance of 90% between parents and the dermatologist should be reached to qualify parents as being able to assess their child's skin abnormality comparable with an IH specialist. A previously performed sample size calculation showed that inclusion of 138 parents was needed to estimate a concordance between the dermatologist and the parents of 90% with 5% precision.
A McNemar test was used to compare the concordance measured before and after the e-learning. Parents who responded with 'unsure' were considered as non-concordant.
To evaluate which IH were correctly and incorrectly assessed after e-learning, all IH were classified with respect to type, depth, anatomical location, ulceration, and total number of IH. P-values were calculated using the Fisher's Exact Test to determine if there were differences between correct and incorrect assessed IH.

Results

The e-learning module, e-consult, and questionnaires were completed by 190 parents. Thirty-two parents were subsequently excluded: in 7 cases the uploaded photographs were of insufficient quality, 23 children were >1 year of age, and in 2 cases the child's doctor completed the questionnaires. A total of 158 parents were subsequently included. Because demographic information was optional, the characteristics of 90 (57%) parents were available. The mean age was 34 years (SD ±4.9), 94% were women and 69% had a high educational level.

The average time for completing the e-learning module was 12.54 minutes. Before participating, 95% of the parents had already received information about IH through the internet (n = 101) or from youth and primary caretakers (n = 90). The concordance between parents and the dermatologist before and after the e-learning module for the questionnaire is presented in Table 1.

Table 1. Concordance between parents and the dermatologist

Questionnaire		Concordance parents – dermatologist, % (CI 95%)			Answer of parent 'no' and answer of Dermatologist 'yes', n (%)[a]
		n =	Before e-learning	After e-learning	
Question 1:	Is the skin abnormality an IH?	158	89 (0.83-0.93)	96 (0.91- 0.97)	0 (0)
Question 2:	Is the IH at risk of developing complications?	154	42 (0.34- 0.49)	79 (0.72- 0.84)	11 (14)
Question 3:	Is assessment by a specialist required?	154	40 (0.32-0.48)	75 (0.68-0.81)	15 (18)
Question 4:	Is urgent assessment by a specialist required?	82	63 (0.52-0.73)	84 (0.74-0.90)	8 (50)

The percentage concordance between parents' answers on the questionnaire before and after e-learning and the dermatologist's answers are shown. Corresponding 95% confidence intervals were calculated. The number of parents that answered the questions with 'no', whereas the dermatologist answered with 'yes' after the e-learning module are shown.
n = number of parents
CI = confidence interval
[a] after the e-learning module

Question 1: Concordances between the dermatologist and the parents of respectively 89% and 96% were found before and after e-learning (p = 0.002). After e-learning there were no cases where the dermatologist diagnosed the skin abnormality as IH, whereas the parents diagnosed it as 'no IH'. Ten parents (6%) made an incorrect diagnosis before e-learning but diagnosed the skin lesion correctly after e-learning.

In 4 cases the dermatologist diagnosed the skin abnormality as 'no IH'. These patients were excluded for the second and third question and analyses were performed on the remaining 154 parents.

Question 2: Concordances of respectively 42% and 79% were found before and after e-learning for assessing the risk of complications ($p < 0.001$). Of the 78 IH that were considered at risk of developing complications by the dermatologist, 11 (14%) were not described as such by the parents after e-learning. Sixty-three parents (41%) answered correctly after e-learning where they did not before.

Question 3: Concordances of respectively 40% and 75% were found before and after e-learning module for assessing if the IH needed specialized care ($p < 0.001$). After e-learning, in 15 cases (18%) parents did not think assessment by a specialist was necessary whereas the dermatologist did. Fifty-eight parents (38%) answered correctly after e-learning where they did not before.

Question 4: Eighty-two cases, in which the dermatologist thought specialized care was needed urgently, were analyzed. Concordances of respectively 63% and 84% were found before and after e-learning ($p < 0.001$). After e-learning, 8 parents (50%) did not think their child's IH required urgent care, whereas the dermatologist did. Seventeen parents (21%) answered incorrectly before e-learning but correctly thereafter.

The relationship between IH characteristics and the assessment of the parents with respect to risk of complications (question 2) was evaluated. Combined (superficial and deep component) IH were assessed correctly in 88% and superficial IH in 73% of cases ($p=0.040$). There was no significant relationship between other IH characteristics and the assessment of the parents.

Discussion

This study demonstrates that, after e-learning, parents of children with IH are able to make the correct diagnosis and are able to evaluate the risk of complications, the need for evaluation by a specialist and the urgency for specialized care (concordance of 96%, 79%, 75%, and 84% respectively). The predetermined concordance of 90%, necessary to qualify parents as being able to assess their child's skin abnormality comparable with an IH specialist, was not completely reached. Although 95% of the parents had already received information about IH from a (primary) caretaker or by surfing the internet, an increase in concordance was seen after e-learning. The risk evaluation of the parents after e-learning was not strongly influenced by characteristics of the IH. Improvement of the e-learning module might result in better assessment by the parents.

The implementation of eHealth has some challenges. Accessibility and usability are important isues.[18-20] A link to the eHealth intervention on the website of the patients support group

might have improved access. By using e-learning, illiterates and people without internet access were excluded. To improve the usability of our e-learning module only relevant information was given, especially written for parents.[19,20] Different modalities (questionnaires, written information and cases) were used to satisfy different learning styles of the parents and to be able to reflect on their knowledge.[18] Further studies are needed to prove the usability of our e-learning module.

Some parents were not able to upload photographs. In 7 cases (excluded from the study) the photograph was of insufficient quality to make an accurate diagnosis. Improvement of the e-learning might solve this problem. Another limitation of the study is that the e-consult was used as gold standard. Parents were qualified as being able to assess their child's skin abnormality based on concordance with the dermatologist's assessment. Although this assessment was based on criteria used in the literature[4, 5,8,16,22], there is no consensus regarding the management of IH. Therefore other specialists might have assessed the IH differently (e.g. with respect to risk of complications). Furthermore, the parent population of this study was not representative for the general population. They had a relatively high education level (69%), compared to 32% in the Dutch general population.[21] Most parents previously received the diagnosis 'hemangioma' from a youth or primary caretaker and had to surf the internet to find our eHealth intervention, or were referred by the patient support group. This might have contributed to the high concordance (95%) between parents and the dermatologist for diagnosing the child's skin abnormality (question 1) and to the high number (53%) for IH in need for specialized care. Finally, the questionnaire before e-learning was not completely the same as after completing the e-leaning module. Before e-learning parents had the option to answer the questions 2, 3 and 4 with 'unsure' while afterwards they had to choose between 'yes' or 'no'. Parents who responded with 'unsure' were considered as non-concordant. This probably led to an underestimation of the concordance before e-learning and therefore we may have overestimated the effect of e-learning.

Involvement of parents by means of e-learning might result in earlier identification of high risk IH in need of specialist care. This might result in earlier presentation to a specialist and treatment of these IH.

Conclusion

This study shows that parents are able to correctly diagnose an IH after completing an e-learning module. After e-learning most parents are able to assess the risk of complications and the need for (urgent) specialized care. Involving parents in the care for IH through an e-learning module might result in earlier presentation and improved treatment. This could possibly prevent complications and influence costs and efficiency of IH care.

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2.2

Evaluation of the compliance, acceptance, and usability of a web-based eHealth intervention for parents of children with infantile hemangiomas

Marlies de Graaf[1,3], Joan E.E. Totté[1,4], Corstiaan C. Breugem[2], Harmieke van Os- Medendorp[3], Suzanne G.M.A. Pasmans[1,4]

[1] Department of Pediatric Dermatology and Allergology, Wilhelmina Children's Hospital Utrecht.
[2] Department of Pediatric Plastic Surgery, Wilhelmina Children's Hospital Utrecht.
[3] Department of Dermatology and Allergology, University Medical Center Utrecht.
[4] Current affiliation: department of Pediatric Dermatology, Erasmus University Medical Center Rotterdam.

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Abstract

Background Infantile hemangiomas (IH) are common benign vascular tumors in children. Recognition and timely referral of high risk IH to specialized centers is important. This might be achieved by involving parents in the care for IH by means of an eHealth intervention.

Objective to evaluate parent compliance, acceptance and usability of an open access, web-based eHealth intervention (including e-learning and e-consult) designed to increase parents' knowledge and (risk) evaluation of IH.

Methods A cross-sectional study of parents who completed the eHealth intervention between October 2010 and November 2012 was carried out. All parents were sent a study questionnaire. Questions to evaluate compliance (to the advice given by a dermatologist during e-consultation) were asked. Acceptance and usability were evaluated by using the modified Technology Acceptance Model (TAM).

Results A total of 224 parents completed the eHealth intervention and received the questionnaire, 135 parents responded (response rate: 60%). 128 questionnaires were completed and included. A total of 110 (86%) parents were compliant to the advice of the dermatologist. Ninety-one percent perceived the eHealth intervention as useful and almost all parents (99%) found the information in the e-learning clear. Twenty-three percent experienced technical problems. The majority of the parents (95%) found the eHealth intervention reliable and most of them (98%) would recommend the eHealth intervention to other parents. Non-compliant parents judged the eHealth intervention significantly less reliable compared to compliant parents (71% vs 97%, P = .003).

Conclusion Parents of children with an IH showed a high compliance (86%) to the advice of the dermatologist given via our web-based eHealth intervention. This high compliance might be positively influenced by the good acceptance and usability of the eHealth intervention and might result in timely presentation and treatment of children with high risk IH in specialized centers.

Introduction

Infantile hemangiomas (IH) are common benign vascular tumors with an unique growth pattern.[1-3] Although most IH have an uncomplicated course, 24% of the patients experience complications, like ulceration, bleeding, functional impairment, life-threatening risk, or cosmetic risk of which 38% need treatment.[4] Also, a segmental IH can be associated with congenital malformations and requires diagnostic evaluation.[4] Nowadays complicated IH can be treated with beta blockers, like propranolol.[5,6] Correct initial diagnosis and timely referral of patients at risk of complications is important, since early intervention may prevent complications.[4,7]

In order to ensure timely referral of high-risk IH, it is imperative for parents and healthcare professionals to have knowledge about IH and risk factors for developing complications. E-learning is widely used to increase knowledge, including in the field of dermatology.[8-14] Parents use the internet as an information source for the disease of their child and the use of an educational e-learning module to increase patients' knowledge has been reported.[15-18]

To increase parents' knowledge about IH and its complications we have developed an open access web-based eHealth intervention.[19-20] This eHealth intervention consisted of an e-learning module and an e-consult (including a teledermatology consultation). Advice on diagnosis, risk of complications, and need to be seen by a medical specialist was given. If parents follow this advice (compliance to the advice) it might contribute to timely referral of high risk patients to a medical specialist.

Patient/parent-compliance ('the extent to which the parent's behavior coincides with the advice of the dermatologist') is essential for the success of this eHealth intervention. Compliance to medication has been extensively described in the literature. However, little is known about compliance to advice given via eHealth.

The goal of this study was to evaluate the compliance of the parents to the advice given by the dermatologist via the e-consult. Secondary, the acceptance and usability of this eHealth intervention were determined.

Methods

Design and participants

A cross-sectional study was carried out after participation in the open access web-based eHealth intervention.[19], consisting of an e-learning module and e-consult (illustrative screenshots are shown in Figure 1).

The eHealth intervention was supported by the Dutch patient support group for Hemangiomas and Vascular Anomalies (HEVAS) and the University Medical Center Utrecht (UMCU) and their logos were displayed on the homepage. Parents were referred to the eHealth interven-

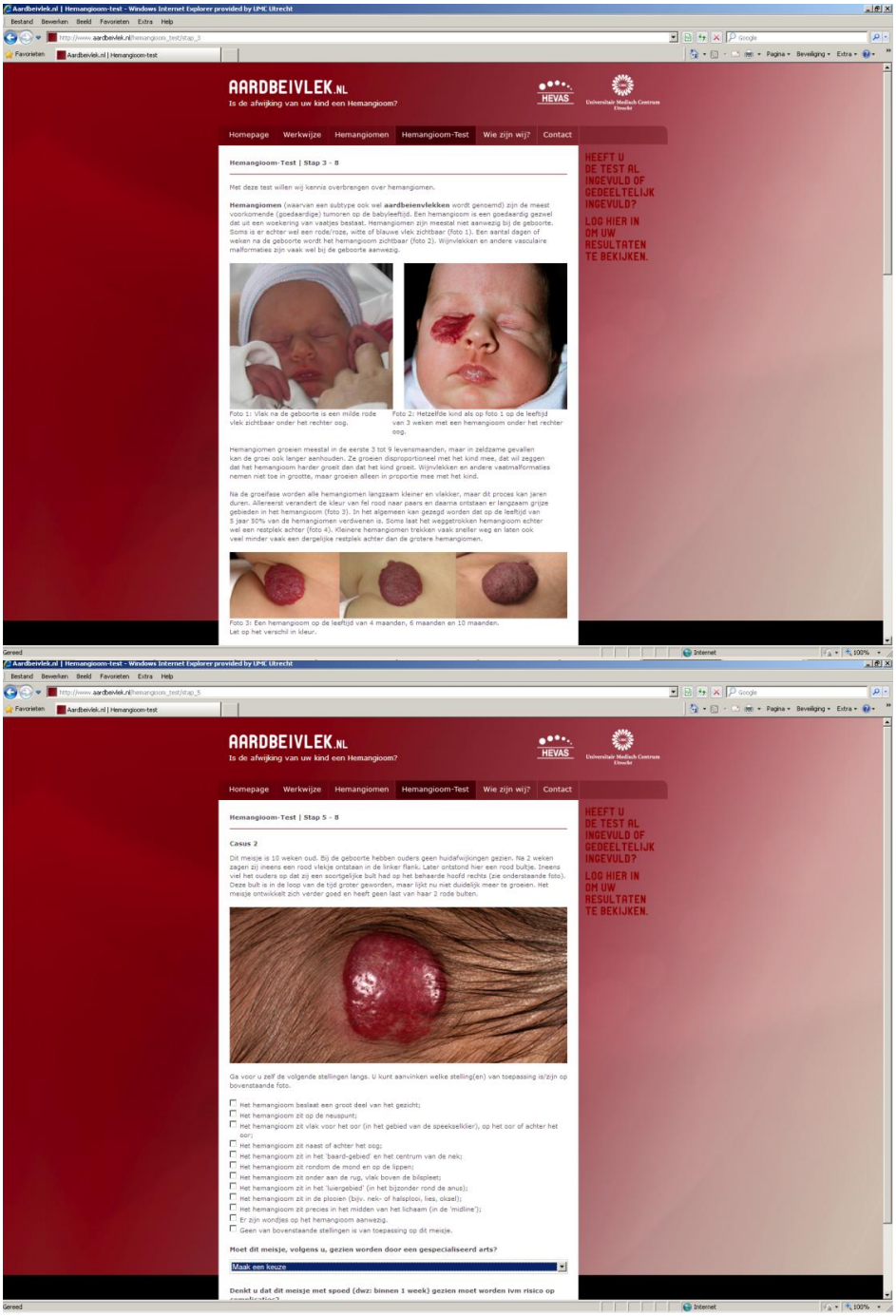

Figure 1. Illustrative screenshots of the e-learning module (in Dutch).
(a) General information about Infantile Hemangiomas;
(b) Case scenario of an Infantile Hemangioma on the scalp (case 2).

tion by a link on the home page of HEVAS[20], by their child's youth or primary healthcare provider, or by surfing the internet. Participation was voluntary and free of charge.
After registration on the website, parents received a password to start the e-learning module and e-consult. By using a password, safe uploading of personal information on the website was guaranteed. During the e-learning module parents were informed about IH and its complications and two illustrative cases were presented. During the e-consult parents were asked to provide one photograph of the skin lesion of their child and to give information regarding its growth pattern. This was judged by a dermatologist of the Center for Congenital Vascular Anomalies Utrecht (CAVU). In case the dermatologist was unable to make a proper diagnosis, due to lack of quality of the photograph, parents were asked for a new photograph or referred to their general practitioner (GP). Advice on diagnosis, risk of complications, and need to be seen by a medical specialist was given within 5 working days by email.[21] Parents were advised whether or not to go to a medical specialist and whether there was urgency. All parents of a child with a suspected IH, who fully went through the e-learning and e-consult between October 2010 and November 2012, were eligible for study participation and received a study questionnaire by email. The time between participation in the eHealth intervention and completing the questionnaire was variable. Demographic information of the parents was obtained. The study was approved by the ethics committee of the University Medical Center Utrecht.

Theoretical framework and study questionnaire

A questionnaire was developed to evaluate the variables: compliance, acceptance, and usability of the eHealth intervention.

Compliance: Compliance was defined as the extent to which the parent's behavior coincides with the advice of the dermatologist. By means of the e-consult parents were given an advice about the diagnosis of the skin lesion of their child (IH/no IH/uncertain) and about the need to visit a medical specialist (no need/need/urgent need). In case of 'need to visit a specialist' parents were first referred to their GP because in the Netherlands a referral of the GP is required for visiting a medical specialist. In case of 'no need to visit a specialist' parents were only advised to go to their GP if the IH was growing rapidly or became ulcerated. In all cases of 'no IH' or 'uncertain diagnosis' (in which the dermatologist was unable to diagnose the skin abnormality using the provided information by the parents) parents were advised to go to their GP. In order to determine the compliance, questions regarding visits to GP/medical specialists, additional diagnostics, and initiated treatment were asked. The time between the advice and the actual appointment with a specialist was also evaluated by asking the parents.

Acceptance and usability: The acceptance and usability of the eHealth intervention were evaluated by using a modified Technology Acceptance Model (TAM). The TAM is the most widely applied model to describe consumer acceptability.[22,23] Technology acceptance is defined as 'an individual's psychological state with regard to his or her voluntary or intended

use of a particular technology'.[24] The TAM theorizes that an individual's behavioral intention to use a technology is determined by two beliefs: perceived usefulness (PU) and perceived ease of use (PEU).[25] It has proved to be suitable for different genders, age groups, cultures, levels of information technology competency, and in both obligatory and voluntary usage settings.[26] The TAM has been tested for the prediction of adoption of telemedicine by health-care professionals and its reliability, robustness, and validity has been demonstrated.[26-28] To determine the acceptance and usability of our eHealth intervention we have modified the TAM based on the Chau and Hu's model of telemedicine acceptance.[29] We have added the dimension 'attitude towards use' to the original TAM, because behavioral intention is also determined by attitude, which is influenced by PU and PEU.[29,30] Attitude can be defined as 'the perception by an individual of the positive or negative consequences related to adopting the technology'. Questions to evaluate acceptance and usability were developed following the modified TAM.

Study questionnaire: The study questionnaire consisted of 24 questions, grouped into three variables (demographic information, compliance, acceptance and usability) (Table 1). Acceptance and usability was subdivided using the three dimensions of the TAM (PU, PEU, and attitude). Twelve questions were rated on a three-point scale (agree-no agreement/no disagreement-disagree). Seven questions could be answered with yes or no, and with the final question parents were asked to rate the eHealth intervention (including e-learning and e-consult) on a 0-10 scale (0=very bad, 10=excellent). At the end of the questionnaire there was an open field for comments and suggestions.

Table 1. Questions used to evaluate compliance, acceptance and usability.

Variable	Dimension	Related questions	Example
demographic information		1-4	Gender, age, relation to the patient, and education level
compliance to advice		5-15	Did you visit your general practitioner after our advice?
acceptance and usability	perceived usefulness	16a-16e, 19a-19d	The e-learning module is useful to determine if my child is at risk for complications
	perceived ease of use	17, 20, 21a-21d, 23	The information of the e-learning is understandable
	attitude	8, 18, 22, 24	I would recommend the e-learning module to other people

Analyses

Only fully completed questionnaires were used for evaluation. Descriptive analyses were used to evaluate the compliance, acceptance and usability.

Fisher's exact tests were used to evaluate the difference in acceptance, usability and attitude between compliant parents and non-compliant parents.

Results

A total of 224 parents completed the eHealth intervention and received the questionnaire, 135 parents responded (response rate: 60%). 128 questionnaires were completed and included in this study. Reasons for not responding on the questionnaire are unknown. Parent characteristics are shown in Table 2.

Compliance: 119 (93%) skin lesions were diagnosed as an IH of which 58 (49%) parents were advised not to visit the medical specialist, and 61 (51%) parents were advised to visit a medical specialist. In 9 cases (7%) the skin lesion was not an IH or the diagnosis was uncertain. A total of 110 (86%) parents followed the advice of the dermatologist. Details are shown in Figure 2-4.

Eight parents, who were advised not to visit a specialist, did visit a medical specialist (for unknown reasons) (Figure 2). In four patients beta blocker treatment was initiated: 1 patient with a small, superficial, localized/nodular IH in the face was treated with oral propranolol, one patient with a superficial, localized/nodular IH on the lower arm was treated with topical timolol, and two patients with a small, superficial, localized/nodular IH in the face/neck area were treated with topical timolol. Three parents, who were advised to visit a specialist, did not (Figure 3): one small, superficial, localized/nodular IH close to the eye spontaneously went into regression, and two parents saw no need to visit a specialist (one patient with a big

Table 2. Characteristics of the parents.

Characteristic		Frequency (n(%))
Gender	men	10(8)
	women	118(92)
Age	< 20 y	0(0)
	20-29 y	20(16)
	30-39 y	85(66)
	> 40 y	21(16)
	unknown	2(2)
Relation to the child	parent	127(99)
	caretaker (grandparent)	1(1)
Highest educational level	low	6 (5)
	moderate	32 (25)
	high	88 (69)
	unknown	2 (1)
Previously received information[a]	none	4(3)
	internet	66(52)
	primary healthcare provider	58(45)
	specialist	6(5)
	unknown	32(25)

[a] Some parents previously received information from multiple sources.

Figure 2-4. Flowcharts of the compliance of the parents to the advice given by the dermatologist via e-consultation. The figures indicate the number of patients.

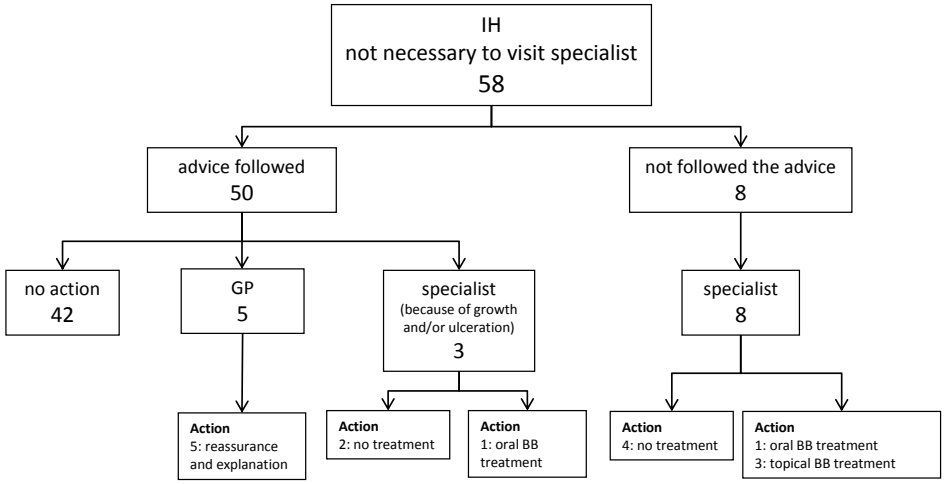

Figure 2 shows all patients, who were advised not to visit a medical specialist.

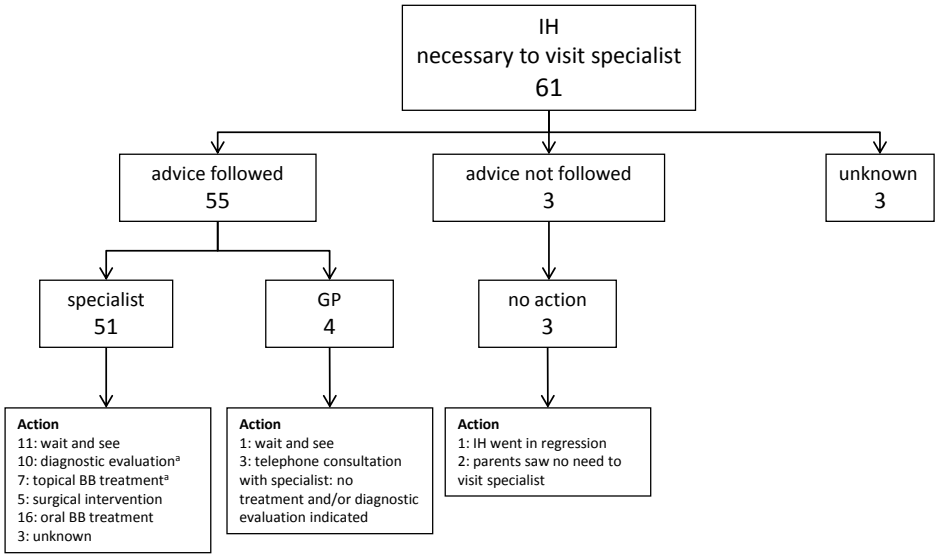

Figure 3 shows all patients, who were advised to visit a medical specialist.

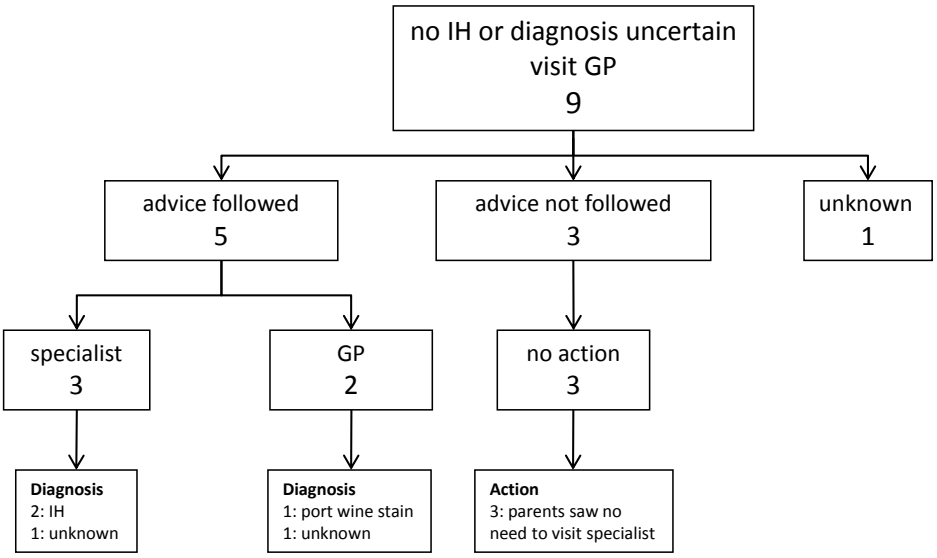

Figure 4 shows all patients with no IH or where it was not possible to make an accurate diagnosis.
All flowcharts show which doctor the parents visited and to what actions (e.g. diagnostic evaluation and/or treatment) it has led.
[a] One patient underwent further diagnostic evaluation and topical beta blocker treatment was initiated.
GP = general practitioner
BB = beta blocker

superficial IH on the arm (because of no functional impairment) and one patient with a small superficial IH on the tip of the nose (parents did not want treatment)). In three cases of 'no IH/uncertain diagnosis' the advice of the dermatologist was not followed because the parents saw no need to visit a specialist (Figure 4).

The time between the advice and the actual appointment with a medical specialist, sorted by referral indication, are shown in Table 3. These data were available for 33/71 cases.

Acceptance and usability: PU: On all questions concerning PU an average of 91% (range 87-99%) of the parents agreed. This means that the PU was high.

PEU: Almost all parents (99%) found the information of the e-learning understandable and clear, and 92% of them found the eHealth intervention easy to use. Three parents (2%) experienced technical problems with logging in, three (2%) with filling in the questionnaire, and 29 parents (23%) experienced technical problems with uploading the photograph of their child.

Attitude: The majority of the parents (95%) found the eHealth intervention reliable and most of them (98%) would recommend the eHealth intervention to other parents. Ninety-eight percent of them think the time investment was worth the effort (average time of completing the e-learning module (excl. e-consult) was 12.54 minutes). The average rate parents gave the eHealth intervention on a 0-10 scale was 8.4 (SD 1.1).

Comments and suggestions were evaluated. Positive comments were given about the reassurance parents experienced, the added value of the e-learning module for primary

Table 3. Compliance, time between the advice and the actual appointment with a specialist, and average age of the patient, sorted by referral indication.

Referral indication	N[a]	Compliance (n (%))	Average time to appointment in weeks ±SD[b]	Average age of the child (weeks) ±SD
(imminent) functional impairment	19	18 (95)	2.6 ±2.5	12.6 ± 9.1
ulceration	19	18 (95)	3.4 ± 2.6	13.5 ± 9.4
cosmetic impairment	18	17 (94)	3.9 ± 5.0	55.5 ± 143.4[c]
diagnostic	15	14 (93)	2.8 ± 3.1	9.3 ± 5.3

N = number of patients

[a] Some patients had multiple IH or multiple indications for referral

[b] Based on available data (33/71)

[c] One patient with cosmetic impairment was 12 year. Excluding this patient the average age was 22.1 ± 21.8 weeks.

healthcare providers, and timely and adequate care due to the eHealth intervention. Negative comments were given about 'shocking' photographs used in the e-learning module and difficulties in uploading photographs from an iPad.

Evaluation of difference in acceptance, usability and attitude between compliant parents and non-compliant parents showed that non-compliant parents judged the eHealth intervention significantly less reliable compared to the compliant parents (71% vs 97%, $P = .003$). There was no statistically significant difference between the percentage of highly educated parents in the compliant group (75 out of 110 (68%)) and the non-compliant group (12 out of 14 (86%) ($P = .23$). All parents with a low education level (n=6) found the eHealth intervention easy to use.

Discussion

This study shows that parents are highly compliant (86%) to the advice of the dermatologist given via the described eHealth intervention for IH. Overall the PU and PEU were very positively judged by parents and they had a positive attitude towards the eHealth intervention.

The compliance rate is high compared to patient compliance with telephone triage recommendations in emergency care (62%), compliance to advice given via web-based triage in primary care (57%), and family compliance to travel advice ([3]80%).[31-33] The high compliance of the eHealth intervention might have been positively influenced by its perceived reliability. Our eHealth intervention addresses the need of parents to get complementary information regarding diagnosis and treatment, to get a second opinion, to complement the information already provided by their doctor, or to confirm what they are already thinking.[8,34] It was developed in cooperation with the HEVAS and parents could find it by means of a link on

their homepage.[20] On the homepage of the open access eHealth intervention the logos of HEVAS and UMCU were shown, as well as the names of the specialists of the CAVU team. All this might have contributed to the reliability of our eHealth intervention and might have increased the compliance of the parents. This is confirmed by the fact that non-compliant parents judged the eHealth intervention significantly less reliable.

Little is known about (non-)compliance to advice given via eHealth. Compliance is a multifaceted process that is influenced by multiple factors, e.g. social and economic circumstances, particularly health literacy, patient belief systems and patient education.[35,36] Non-compliance to the advice may reflect ignorance or misunderstanding of the clinical situation and might result from the parents' inability to cope emotionally with the stresses surrounding the advice.[37] The advice, given by e-consultation, might have been in conflict with previously obtained advice by the parents from e.g. other healthcare takers, family, friends, media sources and health-related websites. Parents who encountered conflicting information might have been less compliant to the advice.[38] Principles to improve compliance to medication have been described and mostly apply in the case of a face to face contact between doctor and patient/parent.[19] Therefore most of these principles do not apply to compliance to the advice given via our eHealth intervention. Further studies are necessary to evaluate the factors influencing (non-) compliance to advice given via eHealth.

The advice given via the eHealth intervention was based on criteria used in the literature[4,39-41] and in line with a recently published consensus about the treatment of IH with propranolol.[6] However, treatment was initiated in four children who were advised not to visit a medical specialist (Figure 2) and in 15 children visiting a GP/medical specialist has not led to action (Figure 3). A possible explanation is that in some cases our advice was inadequate because of the lack of information given by the parents (e.g. photograph of the IH did not reflect the real situation). Another explanation might be that not all GPs and medical specialists are familiar with the most recent recommendations for the management of IH.

In accordance with findings about parental internet use for health-related information in the literature, the population of this study consisted of highly educated woman in the age group 30-35.[10,42,43] Higher education is associated via higher eHealth literacy.[9,44] Possibly low educated parents did not find the eHealth intervention on the internet or dropped out the e-learning module before finishing, because they were not able to locate, evaluate, integrate and apply the medical information (low eHealth literacy[44]), or had other needs and/or expectations. The small number of low educated parents in this study thought the eHealth intervention was easy to use and they were compliant to the advice. Our results show no significant difference in results between (the small number of) low educated and highly educated parents. Parents with a low socioeconomic status have access to the internet and their internet use is high.[9,42,45] The pressure to use the internet to empower patients and exchange information is increasing and therefore internet might still provide an opportunity to reach

low educated parents and may prompt them to consult their doctor.[9,45] Eventually this might contribute to timely presentation of high risk IH, also for children of low educated parents.
Chang et al. showed that the mean age of the first visit of IH patients to a specialist is 5 months.[39] The average age at the time of referral of IH leading to functional impairment (12.6 weeks) and the average time to appointment (2.6 weeks) suggest that this eHealth intervention might contribute to earlier presentation of patients with high risk IH in specialized centers. More studies are necessary to confirm this.
The acceptance and usability of the eHealth intervention were positively judged by the parents. A positive attitude leads to intentions to follow the advice[33] and this might have influenced the compliance to the advice in our study. Although 72% of the parents (Table 2) previously received information via internet and/or from their primary healthcare provider/ medical specialist this eHealth intervention seems to have added value. However, there is still progress to be made. Almost a quarter (23%) of the parents experienced technical problems with uploading of the photograph. Mostly, because uploading via a tablet was not supported by our website. This problem was temporally solved by giving parents the opportunity to send the photograph via email and is now completely resolved. Furthermore, parents commented on the lack of knowledge among primary healthcare providers. Initially we have developed the eHealth intervention for both parents and healthcare providers. Until now, mostly parents participated in the eHealth intervention. To stimulate usage among healthcare providers the link to our eHealth intervention is since 2013 included in the IH guideline for youth healthcare providers in the Netherlands. It might be interesting to investigate whether this will improve the usage by healthcare providers.

Conclusion

Parents of children with an IH show a high compliance (86%) to the advice (about risk of complications and need to be seen by a medical specialist) given by the dermatologist via the described web-based eHealth intervention. This high compliance might be positively influenced by the good acceptance and usability of the eHealth intervention. Our results implicate that increasing parents' knowledge and involving them in the care for IH might result in timely presentation and treatment of children with high risk IH in specialized centers.

Acknowledgement

We would like to thank the Dutch patient support group for Hemangiomas and Vascular Anomalies (HEVAS) for their support in developing the e-learning module and for showing the link of our eHealth intervention on their homepage.

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3

Treatment of infantile hemangioma in regional hospitals with academic support via eHealth: evaluation of the feasibility and acceptance by parents and doctors

Marlies de Graaf[1,2], Joan E.E. Totté[1,5], Harmieke van Os- Medendorp[2], Wilco van Renselaar[3], Corstiaan C. Breugem[4], Suzanne G.M.A. Pasmans[1,5]

[1] Department of Pediatric Dermatology and Allergology, Wilhelmina Children's Hospital Utrecht.
[2] Department of Dermatology and Allergology, University Medical Center Utrecht.
[3] Patient 1 BV, Markerkant 10-136a, 1316 AL, Almere.
[4] Department of Pediatric Plastic Surgery, Wilhelmina Children's Hospital Utrecht.
[5] Current affiliation: department of Pediatric Dermatology, Erasmus University Medical Center Rotterdam.

Authors De Graaf and Totté contributed equally to the manuscript

Submitted

Abstract

Background Since beta blockers became first choice treatment for infantile hemangiomas (IH), the number of patients eligible for treatment is increasing. Currently treatment of IH with beta blockers is mainly reserved for expert centers. Waiting times at expert centers are lengthening. This points out the need for development of a more efficient and accessible way to provide care for children needing treatment for IH. An eHealth intervention (Hemangioma Treatment Plan (HTP)) was developed to treat IH in regional hospitals with online support from an academic doctor.

Objectives To evaluate the feasibility of the eHealth intervention by determining its use, acceptance and usability. By evaluating the feasibility usage can be predicted and points for improvement can be defined, thereby facilitating implementation of the intervention.

Methods Parents of children with an IH, presenting between October 2012 and September 2013 at the tertiary expert Center for Congenital Vascular Anomalies Utrecht (CAVU), requiring treatment with a beta blocker, were asked to participate in the digital HTP. Both parents and regional doctors were sent a study questionnaire. Acceptance and usability of the HTP were evaluated by using the modified Technology Acceptance Model (TAM).

Limitations Small sample size.

Results A total of 30 parents and 18 regional doctors participated in the eHealth intervention and received the questionnaire, 21 parents and 12 doctors responded (response rates respectively 70% and 67%). All parents and 84% of the regional doctors thought the eHealth intervention is useful in the care for IH. Seventy-one percent of the parents and 42% of the regional doctors found the HTP is easy to use. Technical problems using the HTP were reported by 29% of the parents and 83% of the doctors. Ninety-one percent of the parents felt positive about usage of the HTP during treatment of their child. All regional doctors (100%) felt positive about transition of treatment from the tertiary expert center to them and 92% felt positive about using the HTP.

Conclusion Our eHealth intervention shows a good feasibility, especially among parents. Improvement with respect to technical problems, training of regional doctors and achieving organizational support might be needed for successful implementation in the future.

Introduction

Infantile hemangiomas (IH) are common benign vascular tumors, found in approximately 4-10% of Caucasian infants.[1,2] Most IH have an uncomplicated course and a general 'wait and see' policy is often justified.[3] However, 24% of the patients with IH experience complications, like ulceration, bleeding, functional impairment, life-threatening risk, or cosmetic risk of which 38% need treatment.[3] In 2008, the efficacy of propranolol, a non-selective beta blocker, in the treatment of complicated IH has been discovered and propranolol became the primary treatment of choice.[4,5] Atenolol, a selective beta blocker, has also been described as effective in the treatment of IH, showing less side effects compared to propranolol.[6]

Since beta blocker treatment for IH shows less adverse effects and is less invasive compared to previously used treatment options (like systemic corticosteroids, interferon and vincristine), the number of patients eligible for treatment is increasing.[5-7]

Treatment of IH is currently taking place particularly in multidisciplinary expert teams in tertiary centers, like our Center for Congenital Vascular Anomalies Utrecht (CAVU), Wilhelmina Children's Hospital, University Medical Center Utrecht, the Netherlands. Our waiting times are lengthening due to the increasing patient flow. This, together with the sometimes long travel distances for the parents, points out the need for development of a more efficient and accessible way to provide care for children needing treatment for IH.

As far as we know there are no publications about the use of eHealth in the care for IH. In the Netherlands an eHealth intervention to help parents in the diagnostic process of the vascular skin lesion of their child exists (http://www.aardbeivlek.nl).[8] This eHealth intervention helps parents to correctly diagnose and evaluate an IH after completing an e-learning module. To improve healthcare in children with skin diseases, we have developed an online pediatric Skin House (http://www.huidhuis.nl), a digital interactive platform for information, treatment and exchange of expertise of pediatric skin diseases; which is accessible for patients, their parents and health care providers.

This study describes a part of the pediatric Skin House: a web-based personalized eHealth intervention (Hemangioma Treatment Plan (HTP)) for treatment of IH. This eHealth intervention consists of a digital interactive platform of information, treatment and expertise about IH, including a Personal Health Record (PHR). The aim of this eHealth intervention is efficient and easily accessible care for children with IH by making disease knowledge, treatment protocols and the PHR easily available for both parents and involved healthcare providers. By using the eHealth intervention children with IH can be treated by their medical doctor in a regional hospital with online support of the experts of the CAVU team (tertiary academic care).

The goal of this study was to evaluate the feasibility of this eHealth intervention by determining its use, acceptance and usability by parents and doctors. By evaluating the feasibility usage can be predicted[9,10] and points for improvement can be defined, thereby facilitating implementation of the intervention in the future.

Patients and methods

Design

A cross sectional study was performed to evaluate the feasibility of the eHealth intervention judged by parents and medical doctors.

Participants

Parents: Parents of children with an IH, presenting between October 2012 and September 2013 at the CAVU and requiring treatment with an oral beta blocker, were asked to participate in the digital HTP. Indications for treatment were (risk of) ulceration, (risk of) functional damage and (risk of) cosmetic damage. Parents who did not have access to a computer were excluded. Other exclusion criteria were no/insufficient knowledge of the Dutch Language and complications of the IH (like ulceration) requiring specialized multidisciplinary care. Decisions on inclusion and exclusion based on above mentioned criteria were made by an expert member of the CAVU team.

Medical doctors: Regional medical doctors (pediatricians and dermatologists) were informed about the HTP by a digital mailing and/or by personal invitation. After showing their interest in participation they were included in our database. Children who needed beta blocker treatment were referred to the regional medical doctor closest to their home/residence. Other inclusion criteria were access to internet and ability to measure Blood Pressure (BP) in a young child.

The study was approved by the ethics committee of the University Medical Center Utrecht.

Intervention

Hemangioma Treatment Plan (HTP): In order to achieve more efficient and easily accessible care for IH, an eHealth intervention was designed (in Dutch), called HTP. This interactive digital treatment platform consisted of multiple elements providing the following functions: (1) storage and sharing of patient health information (in a digital PHR) through a secured web-based portal; (2) providing information about the disease and treatment protocols; (3) facilitating communication between parent and the medical doctor (e-consult); and (4) facilitating communication between the regional and academic doctor (tertiary teledermatology). The purpose of the HTP is first to warrant safe transition of IH treatment from academic doctors to regional doctors by using digital support. Secondly, its purpose is to involve parents in the care for IH by making information and contact with doctors more efficient and accessible. The HTP, including a PHR, is developed in collaboration with 'Patient1'. The PHR was compliant with all Dutch rules and regulation with respect to privacy protection and checked and approved by the Dutch Privacy Protection Authority. Participation in the HTP was free of charge. Instructions on the use of the HTP were given to the parents verbally and in writing. Parents created an individual account for their child on the PHR website by registering name, birth

date and personal identification number of the child. By using a password, safe uploading of personal information on the website was guaranteed. The PHR account contained information about IH treatment, the HTP, a message-function (for e-consultation and tertiary teledermatology), and a facility to upload photographs and to record about effect and side effects. Parents created the PHR themselves and gave access to the medical doctors into the PHR.
Regional doctors were given instructions on the use of the HTP in writing and sometimes verbally by phone. They also registered at 'Patient1' using name, birth date and their personal identification code (AGB code). After verification and authorization by 'Patient1' and the parents, the involved regional doctor had access to the individual account of the child(ren) he/she treated.

IH treatment protocol: Treatment of the IH was started with atenolol at the tertiary center, after evaluation of possible contra-indications (which included an electrocardiogram).[6] Follow-up was performed by the regional doctor near by the patient's home, using the HTP. At the age of 1 year all children were seen in the CAVU team of the academic center to decide whether or not to stop treatment. Regional doctors used an IH treatment protocol for follow-up of the child treated for IH, accessible via the HTP. The protocol described set moments for consultation and instructions on how to monitor effect and side-effects of treatment.

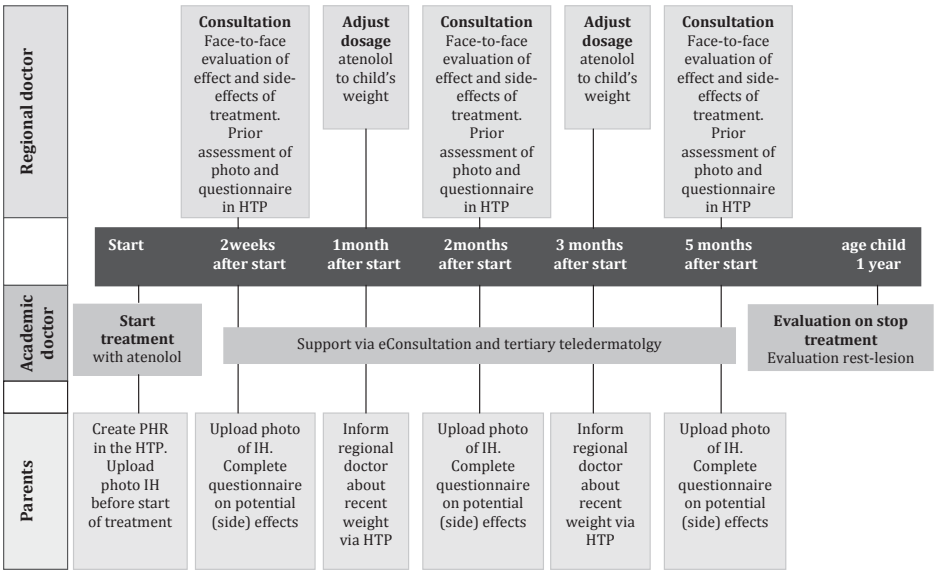

Figure 1. Overview of the IH treatment protocol.
This figure shows an overview of the IH treatment protocol as part of the Hemangioma Treatment Plan (HTP). Treatment of the IH was started with atenolol at the tertiary center and follow-up was performed by the regional doctor, using the HTP. The protocol described set moments for consultation and instructions on how to monitor effect and side-effects of treatment. At the age of 1 year all children were seen in the academic center to decide whether or not to stop treatment.

Prior to each consultation, parents uploaded photographs of the IH of their child, scored the severity of the IH and completed standardized questionnaires on potential side-effects. With the information provided by the parents and findings during the consultation, the regional doctor decided on further treatment policy, guided by the IH treatment protocol. Findings and policy were reported in the PHR of the HTP.

When an advice of the academic doctor (expert dermatologist of the CAVU team) was required, the parent or the regional doctor could send a message via the HTP (respectively e-consult or tertiary teledermatology). These questions were answered within 3 working days by the academic doctor. For urgent situations, such as severe side effects of treatment, parents were instructed to contact the academic doctor who was available 24 hours a day by phone. Patients and doctors received automatic notification messages in their personal e-mailbox when a message was placed in the HTP. Figure 1 shows an overview of the IH treatment protocol as part of the HTP.

Variables and measurement

A questionnaire to evaluate feasibility was developed consisting of the variables: use, acceptance, and usability of the eHealth intervention.

The questionnaire was developed based on a modified Technology Acceptance Model (TAM). The TAM model, proposed by Davis in 1989, is based on the Theory of Reasoned Reaction and proposes that Perceived Ease of Use (PEU) and Perceived Usefulness (PU) predict user acceptance of information technology.[9-11] Technology acceptance is defined as 'an individual's psychological state with regard to his or her voluntary or intended use of a particular technology'.[12] The TAM has been tested for the prediction of adoption of telemedicine by healthcare professionals and can predict technology acceptance in both obligatory and voluntary usage settings.[13,14] It is suitable for both genders, various age groups, most cultures and for individuals of all levels of information technology competency.[14] To determine the use, acceptance and usability of our eHealth intervention we have modified the TAM by adding the dimension 'attitude towards use' to the original TAM. Attitude can be defined as 'the perception by an individual of the positive or negative consequences related to adopting the technology'. Behavioral intention is also determined by attitude, which is influenced by PU and PEU.[15] Questions to evaluate use, acceptance and usability were developed following the modified TAM.

After at least one consultation at the regional doctor both parents and doctors were sent a structured study questionnaire. The study questionnaire of the parents and doctors consisted of respectively 38 and 29 questions, grouped into 3 variables (demographic information, use, acceptance and usability) (Table 1). Acceptance and usability were subdivided by the three dimensions of the TAM (PU, PEU, and attitude). Twenty-two and fifteen questions of respectively the parent and doctor questionnaire were rated on a three-point scale (agree-no agreement/no disagreement-disagree). Six and nine questions of respectively the parent and

Table 1. Questions used to evaluate feasibility of the eHealth intervention.

Variable	Dimension	Related questions Parent questionnaire	Related questions doctor questionnaire	Example
demographic information		1-6, 9, 11, 13	1-3, 6	Parent: gender, age, education level, residence, treatment indication Doctor: gender, age, medical specialism
use		7e-f, 10, 16, 17h	4c-d, 8, 10	Treatment at the regional doctor corresponds with information given by academic center
acceptance and usability	perceived usefulness	8, 17e, 19, 20a-c	4e, 5, 9f	The eConsult function of the HTP is useful
	perceived ease of use	15, 17d, 17f-g, 17i-j,	7, 9a-e, 9g-h, 12, 13a-d	The instruction letter of the HTP is understandable and clear
	attitude	7a-d, 7g, 12, 14, 17a-c, 18, 21	4a-b, 9i, 11, 14	I feel positive about treatment at a regional doctor, with digital support from an expert

doctor questionnaire could be answered with yes or no, and with the final question parents and doctors were asked to rate the eHealth intervention on a 0-10 scale (0=very bad, 10=excellent). Apart from the generic questions, all questions contained room to clarify the answer. At the end of the questionnaire there was an open field for comments and suggestions. Prior to the study it was determined that an average of 90% of the parents and doctors had to score positive on the items regarding feasibility to qualify the eHealth intervention as feasible.

Analyses

User statistics were recorded. The number of e-consultations, tertiary teledermatology consultations, and responding times were calculated.
Descriptive analyses were used to evaluate the use, acceptance and usability.

Results

A total of 30 parents and 18 regional doctors participated in the HTP and received the questionnaire. Twenty-one parents and 12 regional doctors responded (response rate of respectively 70% and 67%). Reasons for not responding on the questionnaire are unknown. Parent and regional doctor characteristics are shown in Table 2.
At the time of start of treatment all children were ≤5 months of age. All parents and doctors qualified themselves experienced with use of the computer and internet. Each regional doc-

Table 2. Characteristics of the parents and secondary caretakers.

	Parents (n=21)	Regional doctor (n=12)
Male-female ratio	1:6	1:1.4
Age respondent (years)		
- mean ± SD	32.3 ± 4.0	43.6 ± 9.0
- median (range)	32 (25-41)	38.5 (36-61)
Medical specialism (n (%))		
- dermatologist		5 (42)
- pediatrician		7 (58)
Level of education(n (%))		
- low	0 (0)	
- moderate	4 (19)	
- high	16 (76)	
- unknown	1 (5)	
Indication for treatment (n (%))[a]		
- cosmetic	6 (29)	
- functional	14 (67)	
- ulceration	4 (19)	

[a] In some cases were multiple indications for treatment

tor treated an average of 2 patients (range 1-5). Mean distance from parent's residence to the tertiary expert center was 55 kilometers.

Use: All parents and doctors (regional and academic doctors) used the HTP.

The e-consult function of the HTP was used by all parents. The average number of e-consultations was 0.5 per parent/month. E-consultations were mostly (97%) answered by the academic doctor within an average time of two days. All parents found that their e-consultations were answered adequately. Eighty-six percent of the regional doctors found the academic doctor easily accessible for consultation and questions. None of them used the tertiary teledermatology to contact the academic doctor. Instead, they contacted the academic doctor by email or phone.

The different functions of the HTP (e-consult, uploading photographs, completing questionnaires) were used by 75% (range 29-100%) of the parents.

Sixty-two percent (range 50-80%) of the parents agreed that treatment at the regional doctor corresponded with the information given by academic center. Parents saved time and costs because of treatment at a regional doctor in respectively 55% and 47% of the cases.

Ninety-two percent of the regional doctors felt informed enough to treat patients with IH.

Acceptance and usability: Perceived usefulness (PU): All parents and 84% of the regional doctors thought the eHealth intervention is useful in the care for IH. Parents agreed that different functions (e-consult, PHR, etc.) of the HTP were useful (average 86%, range 86-86%). The different functions of the HTP (e.g. IH treatment protocol, access to information about side effects and photographs prior to consultation) were useful according to an average of

83% (range 75-90%) of the regional doctors. Forty percent of the regional doctors and 86% of the parents thought the e-consult function to contact eachother was useful. The tertiary teledermatology was thought to be useful by 67% of the regional doctors.

Perceived ease of use (PEU): Instructions of the HTP and patient information were clear according to respectively 91% and 95% of the parents. Instructions of the HTP and the IH treatment protocol were clear according to respectively 67% and 75% of the regional doctors. Seventy-one percent of the parents and 42% of the regional doctors agreed on the statement that the HTP is easy to use. Technical problems using the HTP were reported by 29% of the parents and 83% of the doctors.

Table 3. Overview of the feasibility of the eHealth intervention sorted by variable.

Feasibility	Parents (n/ total (%))		Regional doctors (n/ total (%))
Use			
- use of different functions (eConsult, uploading photographs, questionnaires) (mean)	14/21 (75, range 29-100)	- use of different functions (tertiary teledermatology)	0/12 (0)
- eConsults were adequately answered	21/21 (100)	- informed enough about IH care	11/12 (92)
- treatment at regional doctor corresponds with information given by academic center (mean)	13/21 (62, range 50-80)	- easy contact with tertiary caretaker	6/7 (86)
Perceived usefulness			
- HTP is useful	21/21 (100)	- HTP is useful	10/12 (83)
- usefulness of different functions	18/21 (86)	- usefulness of different functions (mean)	10/12(83, range 75-91)
- usefulness of eConsult	18/21 (86)	- usefulness of tertiary teledermatology	6/9 (67)
		- usefulness of eConsult	4/10 (40)
Perceived ease of Use			
- instructions of the HTP	20/21 (93, 91-95)	- instructions of the HTP	9/12 (71, 67-75)
- the HTP is easy to use	15/21 (71)	- the HTP is easy to use	5/12 (41)
- technical problems	6/21 (29)	- technical problems	10/12 (83)
Attitude			
- positive about treatment at secondary caretaker	18/21 (86)	- positive about treatment at secondary caretaker	12/12 (100)
- positive about usage of HTP	19/21 (91)	- positive about usage of HTP	11/12 (92)
- worth the time investment	20/21 (95)	- worth the time investment	5/12 (42)
- more involved in care	15/21 (71)	- using the HTP is of educational value	10/12 (83)

HTP = Hemangioma Treatment Plan

Attitude: Eighty-five percent of the parents felt positive about treatment at a regional doctor and 62% found treatment at a regional doctor felt safe. All regional doctors (100%) felt positive about transition of treatment from the tertiary expert center to them. Ninety-one percent of the parents and 92% of the regional doctors felt positive about usage of the HTP. Almost all parents (95%) found the HTP was worth the time investment. Though, with 42% agreement, regional doctors reported that they have difficulties with the time investment in the HTP (documenting in the PHR and answering e-consultations). Seventy-one percent of the parents felt more involved in treatment due to the HTP.

The average satisfaction rates parents and regional doctors gave the eHealth intervention on a 0-10 scale were respectively 7.7 (SD ± 0.8).and 6.9 (SD ± 1.2). An overview of the main results is given in Table 3.

Comments and suggestions were evaluated. Positive comments of the parents were given about improvement of access to healthcare professionals and saving time. Positive comments of the regional doctors included improvement of contact between parents and experts. Points of attention of parents were privacy issues and lack of trust in expertise of regional doctors. Regional doctors were concerned about time investment.

Discussion

This study describes an eHealth intervention to make the care for children with IH efficient and easily accessible using an online Hemangioma Treatment Plan. Treatment of IH took place at regional doctors, supported by an expert at distance (academic doctor). The HTP was used to facilitate transition of treatment to regional doctors and to involve parents in the care for IH. Evaluation of the feasibility of this new way of providing care was performed by studying the small group of first patients and regional doctors that participated in this newly developed eHealth intervention.

The feasibility according to the parents ranged from 62-100% and according to the regional doctors from 40-100% (Table 3). The predetermined percentage of 90%, necessary to qualify the eHealth intervention as feasible, is not always reached. However, all parents thought the HTP was useful and all regional doctors had a positive attitude towards the HTP.

Although most results on feasibility are positive, only 41% of the regional doctors found the HTP easy to use. This can be influenced by the fact that 83% of them experienced technical problems and that they were mostly instructed in writing. Most technical problems, experienced by both parents and doctors, concerned logging in and uploading of photographs. The problems of logging in were due the prematurity of the intervention and are resolved now. The problem with uploading photographs was due to low capacity of the website and will be resolved in the near future.

Furthermore, the tertiary teledermatology to consult an academic doctor of the CAVU team was not used by the regional doctors. Mostly they consulted the CAVU team by phone or by sending emails. Probably the regional doctors are not used to this tool for consulting a colleague and the fact that parents could see the content of the e-consults of the regional doctor may have contributed to the low use as well. However, studies have shown that tertiary teledermatology might improve communication between regional and academic doctors and might reduce wait times.[16,17] They have advantages over telephone consultations, which require the need for both parties to be available at the same time, and e-mail, which does not meet current privacy requirements for sharing personal health information.[16,18]

Secondly, regional doctors were not positive about the e-consult with the parents. Only 42% considered that the HTP was worth the time investment. A possible explanation for this is that it might be that these doctors expect that e-consultations are time consuming or that they are not used to work with e-consultations. However, it has been shown that the use of e-consultations in dermatology is feasible and the majority of e-consultations will take only <10 min for the medical doctor to answer.[16,19,20] e-consultations to improve access to specialty care has been demonstrated as well.[21] On the other hand, Palen et al.[22] found that having online access to medical records and clinicians was associated with increased use of clinical services. However, this has been debated by others.[23,24] Further research should point out the consequences of e-consultations for time-investment and usual care.

Some parents felt that the regional doctor was less experienced with IH care. However, in our opinion, this is probably only a temporally problem since studies have demonstrated that online health communities of doctors from different echelons and patients can be used to exchange medical experience and knowledge and that knowledge of participants increased, and the adherence to guideline recommendations improved.[25,26] By partial transition of treatment of IH to secondary centers combined with support by an expert might have an educational value for the regional doctors. This is confirmed by the fact that 83% of the regional doctors agreed that the HTP was of educational value for them. On the long term, increased knowledge about IH treatment and treatment indications might result in better recognition and treatment of children with IH at risk for complications.

The implementation of the HTP requires a different way of acting and thinking from both doctor and patient. Overall parents were positive about the eHealth intervention. From the perspective of the regional doctor feasibility of treatment at local hospitals and system usability of the HTP should be further adapted to their needs to enhance acceptation, actual usage of the HTP and implementation on a larger scale. It is known that medical doctors have had some reservations about moving forward in the area of eHealth and PHRs, partly because of concern that they will be bombarded with questions and that patients will have trouble interpreting their findings.[27,28] However, most of the empirical experiences suggest that these problems do not represent major issues when patients are provided and adopt PHRs.[29,30] Solutions to reduce time investment could be involving specialized nurses in the triage of

e-consultations and to create a link between the patient file of the hospital and the PHR of the eHealth intervention. Nevertheless, results of this early evaluation of the HTP should be interpreted taking in consideration the psychology that goes along with changes in management. A hands-on training for set up could be necessary for structural implementation of the e-consultation functionality.[21] Besides patient-doctor interaction, also workforce items as workload and workflow as well as contextual factors like institutional policy regarding eHealth influences the implementation of eHealth interventions.[31] To realize treatment of IH on a larger basis at local hospitals, clear referral policy should be made. Regional doctors should make agreements on how to facilitate treatment of IH on a larger scale. Academic doctors do have an important role in warranting the quality of care as they are expected to recognize those patients that require treatment at the tertiary center. Hospital management of tertiary centers should incorporate e-consulting in daily practice to ensure the academic doctor can meet this important role.

This study has some limitations. All results must be interpreted taking the small sample size of both parents and doctors and the prematurity of the intervention in consideration. Furthermore, parents had a relatively high education level and were therefore not representative of the general population.

The implementation of eHealth interventions will incur costs. However, the transition of IH treatment to secondary centers might save (in)direct healthcare costs. Health insurances do already reimburse the implementation of eHealth in some fields of medicine. However, there is still no funding for the care provided through eHealth interventions. Studies have shown that eHealth, combining e-consultations, monitoring and self-management training, could lead to cost-savings and e-consultations could reduce the number of face-to-face consultations.[16,19,20] In this study parents reported a time and cost reduction with respect to traveling due to the use of the HTP. Lower costs can be expected due to a lower number of face-to-face consultations at the tertiary academic center. There might even be situations where digital contact through the HTP replaces face-to-face contact. Waiting times will shorten and more new patients can be seen in shorter time. Lower indirect costs can be expected due to lower work-absenteeism as parents can receive care closer to home. Further studies are necessary to confirm this.

The HTP is a new care innovation that was and will be continuously improved according to the users feedback. Points for improvement are resolving the technical problems, like extending the capacity for uploading of photographs, providing more detailed training for regional doctors, and taking care of organizational support. The HTP was a pilot to evaluate the feasibility of treating patients in a regional hospital with online support of the academic center and was part of the pediatric Skin House. After improvement this eHealth invention could be a helpful tool for efficient and accessible care for IH and might be used to expand the cooperation between different sectors of health care (primary, secondary, and tertiary care).

Conclusion

Our eHealth intervention to improve the efficiency and accessibility of care for children with IH shows a good feasibility, especially among parents. Improvement with respect to technical problems, training of regional doctors and achieving organizational support might be needed for successful implementation in the future.

Acknowledgement

We would like to thank the Patient1 for designing, building and supporting the eHealth intervention and Maaike Deltour for participating in patient care.

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4

Associated anomalies and diagnostic approach in lumbosacral and perineal hemangiomas: case report and review of the literature

Marlies de Graaf[1], Suzanne G.M.A. Pasmans[1], Anne Margreet van Drooge[1], Rutger A. Jan Nievelstein[2], Rob H. J. Gooskens[3], Martine F. Raphael[4], Corstiaan C. Breugem[5]

[1] Department of Pediatric Dermatology and Allergology, Wilhelmina Children's Hospital Utrecht.
[2] Department of Pediatric Radiology, Wilhelmina Children's Hospital Utrecht.
[3] Department of Pediatric Neurology, Wilhelmina Children's Hospital Utrecht.
[4] Department of Pediatric Hematology and Oncology, Wilhelmina Children's Hospital Utrecht.
[5] Department of Pediatric Plastic Surgery, Wilhelmina Children's Hospital Utrecht.

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Most infantile hemangiomas (IH) do not require further examination. However, some IH are associated with underlying congenital malformations or are part of a syndrome, like PHACE-syndrome.[1] IH in the lumbosacral and perineal region can be associated with anomalies, like intraspinal-, urogenital-, and anorectal malformations. Different terms, used to describe these IH and their associated anomalies, are PELVIS, SACRAL, and LUMBAR syndrome.[2]

We were confronted with a new-born girl (40+4 weeks gestation) with an imperforate anus, a rectovaginal fistula, and genital malformation with hardly distinguishable vagina and urethra. Two weeks after birth she developed an IH on the left labium major, progressively enlarging and expanding in the anogenital area towards the sacrum. The diagnosis of LUMBAR syndrome (Lower body IH and other skin defects, Urogenital anomalies and Ulceration, Myelopathy, Bony deformaties, Anorectal malformations and Arterial anomalies, and Renal anomalies)[2] was made (Figure 1). Ultrasonography of the spine and abdomen demonstrated a tethered spinal cord with the conus medullaris positioned at S1-S2, hydromyelia, and dilated pyelum of both kidneys. X-rays showed an intact lumbar spine.

At the age of one year additional MRI demonstrated a conus medullaris positioned at L5-S1 with an intraspinal lipoma and hydromyelia, agenesis of the coccyx, and dysraphic changes of the distal part of the sacrum. Urodynamic examination revealed an overactive detrusor

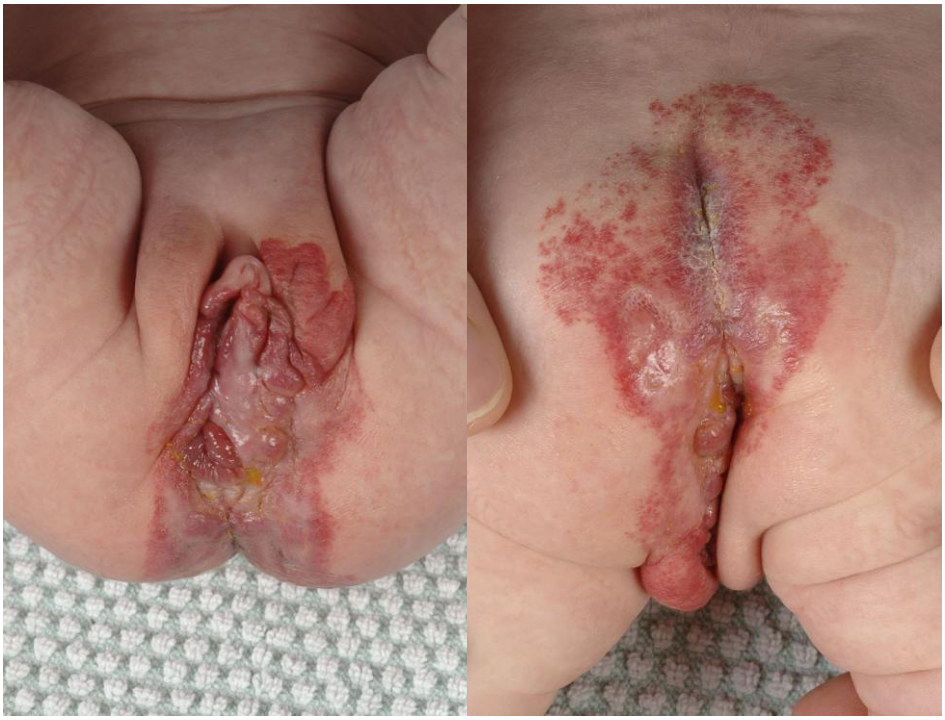

Figure 1. Patient at the age of five weeks with an infantile hemangioma in the genital area, anogenital malformations and intraspinal anomalies (LUMBAR syndrome).

with detrusor-sphincter dyssynergia (neurogenic bladder). Intermittent catheterization was started with good response. This made surgery of the intraspinal anomalies unnecessary.

There is little data about incidence or prevalence and the diagnostic approach of the associated anomalies in lumbosacral and perineal IH. However, literature review to define associated anomalies and a diagnostic approach for IH in the lumbosacral and perineal region suggests the following approach:

A combination of two or more congenital midline skin lesions (such as IH, port-wine stain, deviation of the gluteal fold, hypertrichosis, dimple, lipoma etc.) is the strongest marker for occult spinal dysraphism (OSD) for which further diagnostic imaging is advised.[3] Others suggest that all children with IH overlying the lumbosacral spine measuring ≥2.5 cm in diameter are at risk for underlying spinal anomalies and should undergo diagnostic imaging.[4] Unfortunately, in the literature, no evidence or consensus is available on the approach of small (<2.5 cm) IH overlying the spinal cord. In general, localized/nodular IH are associated with less complications when compared to segmental IH, like in LUMBAR syndrome.[1] LUMBAR seems to be the most accurate acronym because it takes all features of the syndrome into account. However, most patients do not show the complete spectrum of anomalies and the etiology of LUMBAR syndrome remains unclear.[2]

Recommendations about diagnostic imaging are mostly based on expert opinion. The gold standard in screening OSD is MRI. Ultrasonography can be used to detect bony malformations but also to define the spinal cord position and intraspinal pathology in infants up to approximately 3-6 months old. In older children, ossification of posterior elements of the lower spine makes ultrasonography of the lumbosacral spine difficult. An advantage of ultrasonography over MRI is that the movement of the spinal cord can be easily visualized. However, there have been reports of missed OSD by ultrasonography, while spinal dysraphism was demonstrated with MRI.[3] It has been suggested that all infants with IH overlying the lumbosacral spine measuring ≥2.5 cm in diameter should undergo MRI as part of their evaluation.[4] Although in our patient ultrasound seemed to be sufficient to examine internal anomalies, the accuracy of ultrasound is operator dependable and there is a chance of a false-negative result. Urodynamic evaluation can show involvement of the spinal cord, contributing to an early diagnosis of intraspinal pathologies.[5] To diagnose associated anomalies in segmental IH in the lumbosacral and perineal region Iacobas et al.[2] suggested to do ultrasound of the spine, abdomen, and pelvis with color Doppler in all children less than three months of age and an MRI of the spine at the age of 3-6 months.[2]

Since patients with anorectal malformations often have a disturbed lower urinary tract function, an urodynamic assessment for all children with an anorectal malformation and sacral anomalies during the first three months of life is recommendable.

In conclusion, plastic surgeons should be aware that all children with a large (≥2.5 cm) midline or segmental hemangioma in the lumbosacral and perineal region should be thoroughly investigated in a multidisciplinary team for structural anomalies. Physical examination

should be followed by ultrasonography of the spine, abdomen, and pelvis before the age of 3 months and MRI of the spine at the age of 3-6 months. In our opinion, urodynamic assessment should be part of the evaluation of all possible LUMBAR syndrome patients (Figure 2). Further research to determine the approach of smaller (<2.5 cm) midline IH and to define the diagnostic criteria for LUMBAR syndrome is necessary.

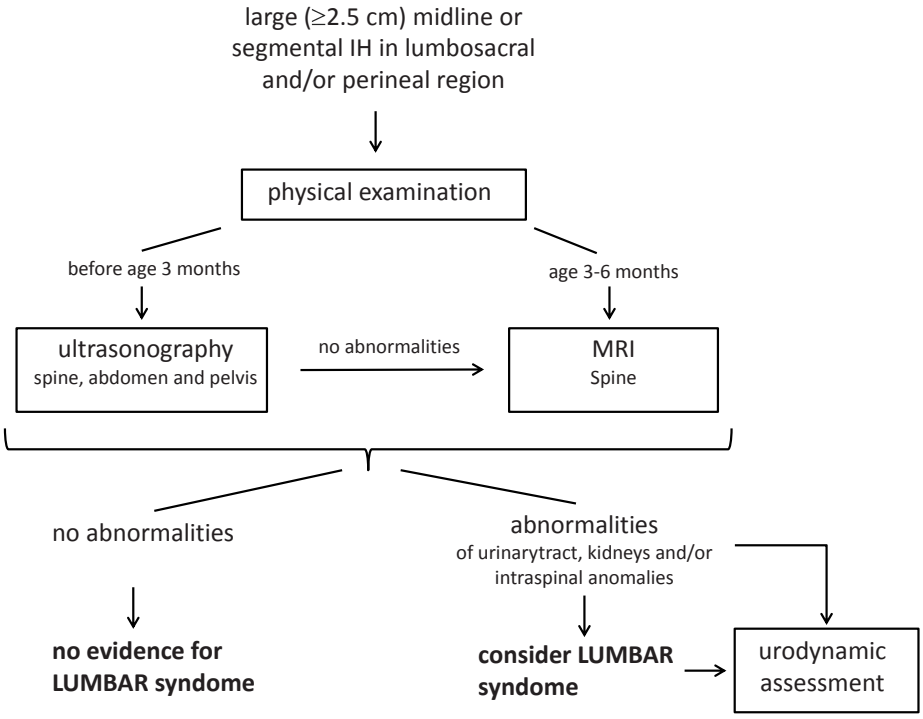

Figure 2. Diagnostic approach of lumbosacral and perineal infantile hemangiomas (IH).
MRI = magnetic resonance imaging
LUMBAR = lower body IH and other skin defects, urogenital anomalies and ulceration, myelopathy, bony deformaties, anorectal malformations and arterial anomalies, and renal anomalies.

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Part II

Cure for Infantile Hemangioma

5.1

Hypoglycemia as a result of propranolol during treatment of infantile hemangioma: a case report

Marlies de Graaf[1], Johannes M.P.J. Breur[2], Corstiaan C. Breugem[3], Suzanne G.M.A. Pasmans[1]

[1] Department of Pediatric Dermatology and Allergology, Wilhelmina Children's Hospital Utrecht.
[2] Department of Pediatric Cardiology, Wilhelmina Children's Hospital Utrecht.
[3] Department of Pediatric Plastic Surgery, Wilhelmina Children's Hospital Utrecht.

Authors De Graaf and Breur contributed equally to the manuscript

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Abstract

Propranolol is a new and promising treatment for hemangiomas of infancy. We report a patient in whom steroid maintenance therapy is successfully tapered after introduction of propranolol. This patient however developed symptomatic hypoglycemic events presumably due to a concurrent deficiency of epinephrine and cortisol as a direct result of both beta-blockage by propranolol and adrenal insufficiency due to prednisone use. Extreme care should be taken in patients treated with both propranolol and prednisone since they are at increased risk of hypoglycemia.

Case

A 1 month old term female infant presented at our outpatient clinic. Several days after birth she had developed a rapidly growing segmental facial hemangioma functionally endangering her vision by progressive obstruction of her right pupil (Figure 1). Prednisone (4 mg/kg/day) was started at that visit with almost immediate response. PHACE syndrome (Posterior fossa malformations, Hemangiomas, Arterial anomalies, Coarctation of the aorta and other cardiac defects, and Eye abnormalities) was ruled out by normal echocardiography, a normal MRI/MRA of the head and normal ophthalmologic exam. Tapering of prednisone was repeatedly associated with rebound growth and at age 14 months prednisone maintenance therapy (0.5 mg/kg/day) proved necessary. Observed adverse events of prednisone treatment included a Cushinoïd appearance, agitation, hypertension with repeated systolic and diastolic blood pressures above the 99th centile for her age. Because of slow motor development and suspected back pain a DXA-scan (Dual energy X-ray absorptiometry) was performed at the age of 18 months which showed bone mineral densities of 0.32 g/cm^2 at the lumbar spine, 0.36 g/cm^2 at the left hip and 0.33 g/cm^2 at the right hip (-2 SD). Calcium suppletion led to a significant increase is bone mineral densities; 0.49 g/cm^2 at the lumbar spine, 0.39 g/cm^2 at the left hip and 0.46 g/cm^2 at the right hip after one year. In her second year of life propranolol as novel therapy for treatment of infantile hemangiomas was reported in the literature[1]. Since our patient was steroid dependent and experienced severe side effects of prednisone maintenance therapy, she was hospitalized to initiate propranolol therapy (2 mg/kg divided bid). During admission blood pressure measurements before and one hour after administration of propranolol remained stable. Daily serum glucose levels were measured after the morning dosage of propranolol just before lunch until stable propranolol plasma concentrations were established.

Two weeks after initiation of propranolol treatment tapering of the prednisone was started. At the time of initiation of propranolol our patient was on a prednisone dosage of 2 times 2.5 mg (0.5 mg/kg/day). Every other week the prednisone dosage was decreased with 0.5 mg (0.1 mg/kg/day) until the dosage of 2 times 1 mg was reached. Thereafter only one of the daily dosages was decreased by 0.5 mg (0.05 mg/kg/day) every other week. Three weeks after initiation of propranolol regression of the hemangioma was observed. However, shortly after tapering the prednisone maintenance therapy to 1 times 1 mg daily (0,1 mg/kg/day) the patient's mother was unable to wake her in the morning. Her blood glucose, measured by paramedics, was 32 mg/dl (1,7mmol/l). In retrospect she had experienced several events of diminished responsiveness after nights fast since the introduction of propranolol. She was admitted to the hospital with glucose measurements before every meal and every 3 hours during nights fast. Three days later she experienced another hypoglycemic event (glucose 1,9 mmol/l (34 mg/dl)). Additional testing ruled out metabolic causes of hypoglycemia but did show undetectable levels of morning cortisol (<0.2 µmol/l (<0.7 µg/dL)). Cornstarch in

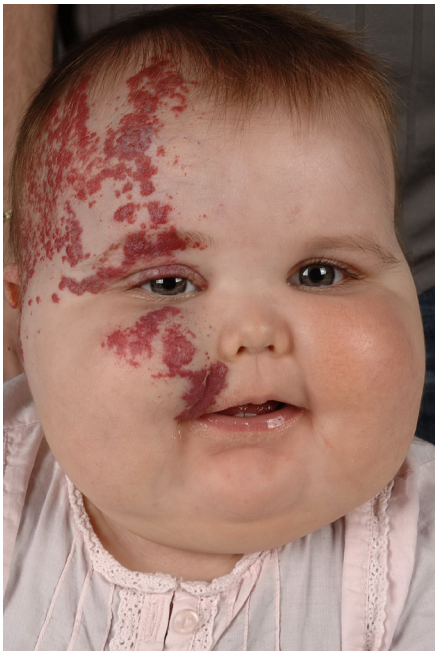

Figure 1. Age 45 weeks, notice the cushinoïd appearance during prednisone use.

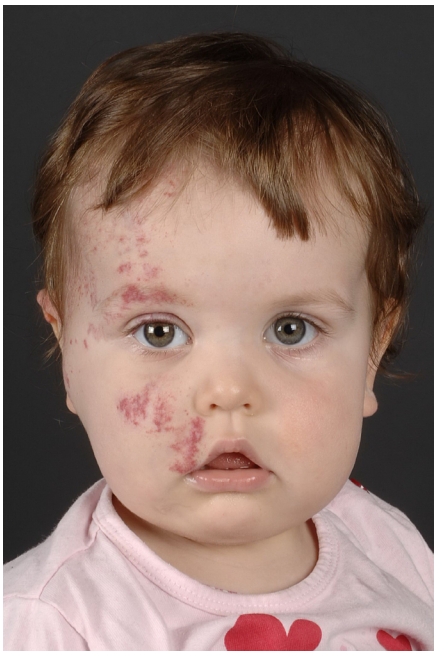

Figure 2. Age 18 months, during propranolol treatment.

yoghurt at night time was started on admission, propranolol was halved and prednisone titrated up to 1 times 1 mg and 1 times 0.5 mg daily (0.15 mg/kg/day) and continued until morning cortisol levels were >0.3 µmol/l (>11 µg/dL). Afterwards propranolol was increased to its original dosage and prednisone was successfully tapered without reoccurrence of adverse events (Figure 2).

Discussion

In 2008 Léauté-Labrèze et al. were the first to observe a spectacular effect of propranolol in treatment of infantile hemangiomas.[1] Propranolol is a well-established and safe drug in the pediatric population and has been not associated with hypoglycemia when prescribed at low dosage (< 4mg/kg/day) to date.[2] It therefore opens a window of opportunities for treatment of infantile hemangiomas.

Glucose homeostasis is maintained by glycogenolysis immediately after feeding and by gluconeogenesis several hours after meals. The hypoglycemic effects of insulin are opposed by the counterregulatory hormones glucagon, growth hormone, cortisol and epinephrine which act in concert by increasing blood glucose concentrations via activating glycogenolytic

enzymes (glucagon, epinephrine); inducing gluconeogenic enzymes (glucagon, cortisol); inhibiting glucose uptake by muscle (epinephrine, growth hormone, cortisol); mobilizing amino acids from muscle for gluconeogenesis (cortisol); activating lipolysis; providing glycerol for gluconeogenesis and fatty acids for ketogenesis (epinephrine, cortisol, growth hormone and glucagon); and inhibiting insulin release and promotion of growth hormone and glucagon secretion (epinephrine). Congenital or acquired deficiencies in one of these counterregulatory hormones rarely result in hypoglycemia. However a concurrent deficiency of several hormones may result in hypoglycemia that is more severe or occurs earlier during fasting.

A number of cases of hypoglycemia during periods of restricted oral intake have been reported in patients treated with propranolol. However, most concern long preoperative fasts.[3,4,5,6,7] Also, a propranolol dosage of over 4 mg/kg/day seems to put the pediatric patient at risk for development of hypoglycemic events.[3,4,6,8,9]

This is the first time that documented symptomatic hypoglycemia is reported in relation to treatment of hemangiomas with propranolol.

Recently Lawley et al. reported on an infant on propranolol with a serum glucose of 48 mg/dl (2.7 mmol/l) during a routine laboratory investigation.[10] Since this infant was symptom free and doing well no dietary changes were made nor were additional serum glucoses measured. This child did not experience a symptomatic hypoglycemic event and it is debatable whether or not a serum glucose of 48 mg/dl should be considered hypoglycemia in a 36 days old infant. In the Netherlands for example the cut-off value for hypoglycemia is 45 mg/dl (2.5 mmol/l).

In our patient hypoglycemia occurred early during fasting presumably due to a concurrent deficiency of the counterregulatory hormones epinephrine and cortisol as a direct result of both beta-blockage by propranolol (acting as a functional deficiency of epinephrine) and iatrogenic adrenal insufficiency due to prednisone use. Since a concurrent deficiency of several counterregulatory hormones is much more likely to result in hypoglycemia than a single deficiency it is most likely that the simultaneous use of prednisone and propranolol resulted in hypoglycemia rather than the use of prednisone alone. This is of great clinical significance given the escalating use of propranolol in the treatment of infantile hemangiomas and its usage to taper prednisone in patients with steroid-dependent hemangiomas. A possible solution to hypoglycemic events in propranolol therapy may be the use of more selective beta-1 agents with low beta-2 activity such as atenolol or metaprolol. However, since the exact working mechanism of propranolol in hemangiomas remains to be elucidated, it is not at all certain that metaprolol will have equally favorable results. For now extreme care should be taken in patients treated with both propranolol and prednisone since they are at increased risk of hypoglycemia.

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5.2

Adverse effects of propranolol when used in the treatment of hemangiomas: a case series of 28 patients

Marlies de Graaf[1], Johannes M.P.J. Breur[2], Martine F. Raphael[3], Marike Vos[1], Corstiaan C. Breugem[4], Suzanne G.M.A. Pasmans[1]

[1] Department of Pediatric Dermatology and Allergology, Wilhelmina Children's Hospital Utrecht.
[2] Department of Pediatric Cardiology, Wilhelmina Children's Hospital Utrecht.
[3] Department of Pediatric Hematology and Oncology, Wilhelmina Children's Hospital Utrecht.
[4] Department of Pediatric Plastic Surgery, Wilhelmina Children's Hospital Utrecht.

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Abstract

Background Infantile hemangioma (IH) is a frequently encountered tumor with a potentially complicated course. Recently, propranolol was discovered to be an effective treatment option.

Objective To describe the effects and side effects of propranolol treatment in 28 children with (complicated) IH.

Methods A protocol for treatment of IH with propranolol was designed and implemented. Propranolol was administered to 28 children (21 girls and 7 boys, mean age at onset of treatment: 8.8 months).

Results All 28 patients had a good response. In two patients, systemic corticosteroid therapy was tapered successfully after propranolol was initiated. Propranolol was also an effective treatment for hemangiomas in 4 patients older than 1 year of age. Side effects that needed intervention and/or close monitoring were not dose dependent and included symptomatic hypoglycemia (n = 2; 1 patient also taking prednisone), hypotension (n = 16, of which 1 is symptomatic), and bronchial hyperreactivity (n = 3). Restless sleep (n = 8), constipation (n = 3), and cold extremities (n = 3) were observed.

Limitations Clinical studies are necessary to evaluate the incidence of side effects of propranolol treatment of IH.

Conclusions Propranolol appears to be an effective treatment option for IH even in the nonproliferative phase and after the first year of life. Potentially harmful adverse effects include hypoglycemia, bronchospasm, and hypotension.

Introduction

Infantile hemangiomas (IH) are benign vascular tumors found in approximately 4% to 10% of white infants.[1] They are characterized by a 3- to 9-month period of rapid growth followed by gradual involution.[2] Historically, prednisone has been used for treatment of complicated IH.[3] However, systemic steroid therapy is associated with numerous potentially serious side effects, including hypertension, growth retardation, intracranial hypertension (when tapering prednisone), osteoporosis, immunosuppression, and a cushingoid appearance.[4] Recently, Léauté-Labrèze et al[5] reported a spectacular response to treatment of IH with propranolol, and this was confirmed in other studies.[6-13]

We describe the results of propranolol treatment and associated side effects in 28 patients with IH.

Patients and methods

Propranolol treatment was administered to 28 children with IH associated with life-threatening potential, functional risk, local complications, or cosmetic disfigurement. A treatment guideline was designed that was based on the known side effects of propranolol and in collaboration with pediatric cardiologists, hematologists, dermatologists, and plastic surgeons. Children younger than 1 month of age and those at risk for development of hypoglycemia, bradycardia and/or hypotension, or infants with other relative contraindications to propranolol were treated in an inpatient clinic (Figure 1). All other children were treated as outpatients. Before treatment was started, an electrocardiogram (ECG) was performed to detect any preexisting cardiac conduction disturbance. Serial photographs of the IH were obtained to evaluate the efficacy of propranolol. The starting dosage was 1 mg/kg/day in 2 or 3 divided daily doses. The dosage was increased to 2 mg/kg/day after a minimum of 5 doses, since stable plasma concentrations of propranolol are established at that time. During treatment the dose was adjusted for increase in weight. In cases in which the clinical response was inadequate, the dose was increased stepwise to 4 mg/kg/day.

Following uneventful introduction of propranolol, inpatients were discharged home on day 5 (or after 10 doses). Outpatients were evaluated after 1, 2, 4, 8 and 12 weeks. At each clinic visit, blood pressure and heart rate were measured, the effect of the treatment was determined, and possible adverse events were documented.

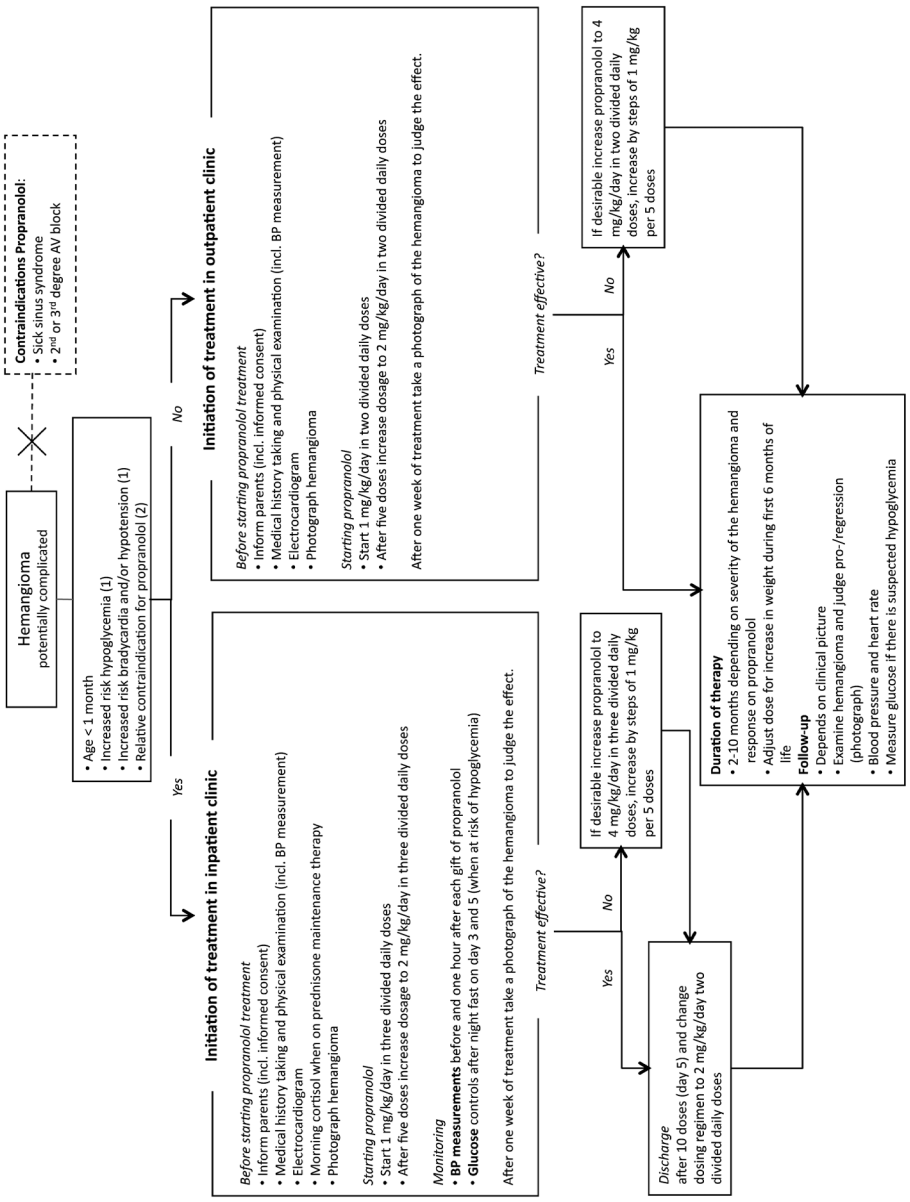

Figure 1. Guidelines for utilization of propranolol in the treatment of (complicated) IH at Wilhelmina Children's Hospital.

(1) For example, prematurity or dysmaturity and/or simultaneous use of prednisone;

(2) Relative contraindications to propranolol: impaired cardiac function (when this is secondary to the hemangioma, appropriate treatment is advisable); Sinus bradycardia, hypotension, first-degree atrioventricular block; asthma; and/or bronchial hyperreactivity;

diabetes mellitus; chronic renal insufficiency.

AV, Atrioventricular; BP, blood pressure.

Results

Patients

Of the 28 patients treated with propranolol, 21 (75%) were female and 7 (25%) were male. One patient had PHACE (Posterior fossa abnormalities, Hemangiomas, Arterial abnormalities, Cardiac anomalies, Eye abnormalities) syndrome; magnetic resonance angiography showed malformations of the cerebral arteries (occlusion of the left internal carotid artery and left vertebral artery, and stenosis of the right internal carotid artery with a dilatation in the neck). Another patient had LUMBAR (Lower body IH and other skin defects, Urogenital anomalies and Ulceration, Myelopathy, Bony deformaties, Anorectal malformations and Arterial anomalies, and Renal anomalies) syndrome. Two patients were previously treated with oral prednisone, 4 with intralesional corticosteroids, 1 with intravenous vincristine, 1 with pulsed dye laser therapy and 1 by surgical debulking of the hemangioma before receiving propranolol. No significant ECG abnormalities were reported.

The median age at the time of initiation of propranolol treatment was 6 months (range, 2 to 43 months).The location of the IH and other details are listed in Table 1.

Effects of treatment with propranolol

A rapid improvement of the IH was observed in every patient. After 1 week all lesions had changed in color from bright red to purple with areas of gray. Considerable softening to palpation was noted. After a remarkable initial response to treatment, the IH continued to regress with respect to both color and thickness.

The maximum dosage of propranolol varied between 1.8 and 4 mg/kg/day. In patients 1, 4, 5, 9, 10, and 20, the duration of treatment varied between 4.5 and 17 months. The remaining patients were still receiving propranolol treatment at the time of writing.

Side effects of treatment of IH with propranolol

Observed side-effects ranged from mild to severe (see Table 1).

Hypoglycemia (n = 2). Patient 4 (Figure 2) had a rapidly growing segmental facial IH obstructing vision and hearing. There was a rapid response to treatment with prednisone 4 mg/kg per day, which was started shortly after birth. Several attempts to taper the dose of prednisone failed because of rebound growth. Propranolol (2 mg/kg/day) was introduced at age 15 months following which prednisone was tapered successfully. Four days after the dose of prednisone was reduced to 0.1 mg/kg/day, her mother found her unresponsive in bed. Blood glucose, measured by paramedics, was 1.7 mmol/L. After a yoghurt drink, the patient became fully alert. The dose of prednisone was increased. Several days later, another hypoglycemic event occurred (blood glucose 1.9 mmol/L). The morning serum cortisol level was found to be undetectable (<0.2 µmol/L) as a result of iatrogenic adrenal insufficiency. Cornstarch in yoghurt at bedtime was given to prevent future hypoglycemic events. Oral

Table 1. Clinical characteristics of the 28 patients*

Patient	Gender	Location of IH	Indication for propranolol	Previous treatment	Age at initiation of propranolol treatment [months]	Age at end of propranolol treatment [months]	Side effects	Maximum dosage propranolol (mg/kg)	Blood pressure before treatment (systolic/ diastolic)	Lowest measured blood pressure during treatment (systolic/diastolic)
1	F	Face (large segmental IH) PHACE syndrome	functional/ rebound prednisone	prednisone	11	28		2.5	96/56 (p50=54)	85/**33** (p50=55)
2	M	Face (periocular area)	functional		5	t	restless sleep, constipation	2		80/**44** (p50=52)
3	F	Face (large segmental IH)	functional	surgical debulking	43	t	Paleness; no muscle tone w/o hypoglycemia	2		92/**50** (p50=57)
4	F	Face (large segmental IH)	functional/ rebound prednisone	prednisone	15	21	hypoglycemia while on propranol and prednisone	2	128/78 (p50=55)	94/63 (p50=55.5)
5	F	Genitals (LUMBAR syndrome)	functional		2.5	14		3		91/64 (p50=53)
6	M	Upperlip and nose	functional		11	t		2	98/61 (p50=51)	86/56 (p50=56)
7	F	Subglottis	functional	intralesional corticosteroids	2.5	t	symptomatic hypotension, reduced intake, vomiting	1.8	120/65 (p50=51)	56/**34** (p50=53)
8	F	Upper eyelid	functional		2	t		3.8	93/47 (p50=51)	84/**46** (p50=50.5)
9	F	Upper eyelid	functional		6.5	11	bronchial hyperreactivity, constipation	2.2	105/65 (p50=52.5)	88/**50** (p50=53)
10	F	Nose	functional		6	14	constipation	2		74/**37** (p50=54) (during sleep)
11	F	Subglottis	functional/ stridor	intralesional corticosteroids	6	t		2	128/68 (p50=52)	74/**46** (p50=54)

Table 1. Clinical characteristics of the 28 patients*

12	M	Upper lip	functional		6	t		3.5	114/64 (p50=53)	84/**54** (p50=55.5)
13	F	Face, neck, thorax, arm	functional	vincristine	32	t	hypoglycemia during reduced intake, restless sleep, nausea	4	90/60 (p50=57)	92/**49** (p50=57)
14	F	Forehead, neck, thorax	functional		7	t	restless sleep	3	121/49 (p50=53)	88/59 (p50=53)
15	F	Cheek, scalp, thorax	cosmetic		19	t	restless sleep	2.4	100/70 (p50=55)	81/**53** (p50=55)
16	F	Eye, ear, thorax	functional	laser	3	t		2.2		60/**34** (p50=51)
17	F	Nose, thorax, shoulder	functional		7	t		2.3	111/69 (p50=53)	88/52 (p50=53)
18	M	Face (parotid area)	functional	intralesional corticosteroids	7	t	malaise	1.9	98/57 (p50=54)	82/**42** (p50=54)
19	F	Subglottis	functional/ stridor	intralesional corticosteroids	2	t	cold extremities	2	74/56 (p50=51)	94/68 (p50=51)
20	F	Ear (external acoustic meatus)	functional		4	8		2.2		100/**43** (p50=52)
21	F	Upper lip	functional		4	t	restless sleep	2.5	133/73 (p50=51)	72/**36** (p50=52.5)
22	M	Lower lip, chin	functional/ diagnostic		6	t	restless during day and night	2.3		100/56 (p50=54)
23	F	Lower lip	functional		9	t	restless sleep, reduced intake	2		61/**49** (p50=54)
24	F	Genitals	functional/ ulceration		8	t		2.2	88/51 (p50=53)	89/76 (p50=55)
25	F	Face (cheek)	diagnostic		10	t		1[a]	107/67	125/65[b]

Table 1. Clinical characteristics of the 28 patients*

26	F	Forehead, right foot	functional	3	t	cold extremities	1[a]	100/65	91/76[b]
27	M	Forehead, abdomen	cosmetic	6	t	bronchial hyperreactivity, cold extremities, restless sleep, diarrhea	1[a]	107/65	85/51[b]
28	M	Nose	functional	3	t	bronchial hyperreactivity	1.8	115/74	75/52[b]

F, Female; IH, infantile hemangioma; M, male; p50, 50th percentile of diastolic blood pressure (diastolic blood pressure level at midpoint of normal range) corrected for age and gender; LUMBAR (syndrome), lower body IH and other skin defects, urogenital anomalies and ulceration, myelopathy, bony deformaties, anorectal malformations and arterial anomalies, and renal anomalies; PHACE (syndrome), posterior fossa abnormalities, hemangioma, arterial abnormalities, cardiac anomalies, eye abnormalities; t, receiving treatment. **Bold typeface** indicates that diastolic blood pressure was below p50.

*Propranolol was administered to 28 children with an IH associated with functional risk (eg, impediment to hearing, breathing, and/or eating), local complications (eg, ulceration), rebound growth of the IH after tapering the dose of prednisone, or cosmetic disfigurement. In two patients, propranolol treatment was started to differentiate between an IH and a vascular malformation.

[a] Just initiated propranolol treatment.

[b] Blood pressure measured only once because of recent initiation of propranolol treatment

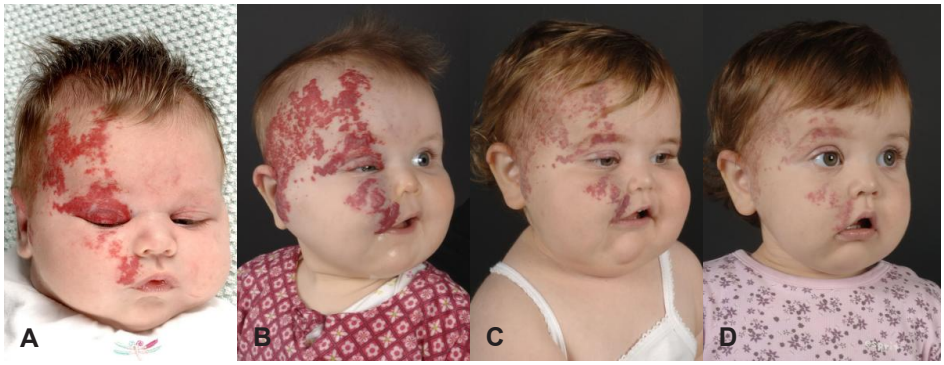

Figure 2. Patient 4. A, Age 4 weeks, no treatment. B, Age 33 weeks, after the first course of prednisone treatment had been stopped. C, Age 15 months, 3 weeks after starting propranolol. D, Age 18 months, during propranolol treatment. Published with the permission of parents.

prednisone was tapered to 0.05 mg/kg/day and continued until the morning serum cortisol was greater than 0.3 µmol/L. The propranolol dosage was reduced as well, but shortly afterwards the IH showed rebound growth. The original dose (2 mg/kg/day) was resumed without a recurrence of hypoglycemia.

Patient 13 suffered from pathological food refusal. While taking propranolol for treatment of IH, she was hospitalized for a hunger provocation test to increase her motivation to eat in a controlled fashion. After a prolonged period of fasting, she became less responsive and the serum glucose was 2.7 mmol/L. Propranolol was discontinued for the remaining duration of the hunger provocation test.

Bronchial hyperreactivity (n = 3). Patients 9, 27, and 28 suffered from bronchial hyperreactivity associated with a viral infection after initiation of propranolol. None had a history of bronchial hyperreactivity. Propranolol was discontinued in all 3 patients with rapid resolution of wheezing. In patients 27 and 28, propranolol was successfully restarted afterwards.

Hypotension (n = 16, of which 1 is symptomatic). During a routine clinic visit, patient 7 was observed to have very cold extremities with prolonged capillary refill. Her blood pressure was 56/34 mmHg (50th percentile [p50] for diastolic blood pressure at age 7.5 months = 53 mm Hg). Because of this low blood pressure, the propranolol dosage was maintained below 2 mg/kg/day. Most patients showed a decrease in blood pressure; 16 of 28 patients had a diastolic blood pressure below p50 (see Table 1), but only patient 7 had symptoms possibly attributable to hypotension. Propranolol dosage was not adjusted in asymptomatic patients.

Seizure. Five hours after the first dose of propranolol, patient 5 had a staring spell and tonic-clonic movements of her arms and legs. She was unresponsive to her parents during this incident. After 3 minutes she recovered spontaneously. Paramedics transported her to a local hospital where neither the blood pressure nor serum glucose was measured. An electroencephalogram was not performed. Propranolol was restarted while patient 5 was an inpatient at our hospital without further adverse events.

Other side-effects. Parents reported restless sleep in 8 infants (29%), constipation in 3 (11%), and cold extremities in 3 patients (11%).

Discussion

Efficacy

Propranolol is a lipophilic, nonselective beta-blocker, available since 1964 and widely used in pediatric cardiology. There has been limited experience of propranolol for treatment of IH and the mechanism of action is poorly understood.[5,6] The therapeutic effect is thought to originate from a vasoconstrictive effect on the capillaries in IH. Propranolol also decreases expression of vascular endothelial growth factor and fibroblast growth factor and induces apoptosis of capillary endothelial cells.[6,8,14] Another postulated mechanism is that beta-blockers may induce apoptosis by blocking IH GLUT-1 receptors.[7]

Propranolol was an effective treatment for IH in 4 infants over 1 year of age (patients 3, 4, 13, and 15). Propranolol, started at age 11 and 15 months respectively, allowed successful withdrawal of prednisone in two steroid-dependent infants (patients 1 and 4) with progressive regression of the IH.

Treatment of patient 1 and another child with PHACE syndrome, reported previously, suggests that propranolol may be used in patients at risk for cerebral ischemia due to abnormal cerebral vasculature.[8] Careful clinical observation with frequent blood pressure measurement until stable serum concentrations of propranolol are established is obviously warranted in these children.

Side-effects

Symptomatic hypoglycemia can be a serious complication of propranolol treatment. Nonselective beta-blockers are competitive antagonists of catecholamines at the beta-1 and beta-2 adrenergic receptors. Beta-2 receptor blockade may result in hypoglycemia as a result of decreased glycogenolysis, gluconeogenesis, and lipolysis. Patients taking propranolol may be vulnerable to hypoglycemia during periods of prolonged fasting when counter-regulatory mechanisms may fail. As a result of beta-1 blockade, signs of hypoglycemia such as tachycardia, sweating, and anxiety may be absent.[15]

Although there are no documented cases of serious cardiovascular morbidity or mortality from propranolol,[16] a number of cases of hypoglycemia during periods of restricted oral intake have been reported. Most concern long preoperative fasts.[17-21] A propranolol dosage of over 4 mg/kg/day seems to put the pediatric patient at risk for development of hypoglycemic events.[17,18,20,22,23] However, hypoglycemia in patients 4 and 13 appeared to be unrelated to the dose of propranolol.

Patient 4 had a normal oral intake, and additional testing of blood and urine was negative for disorders of carbohydrate or fatty acid metabolism. Undetectable morning cortisol levels were most likely due to adrenal insufficiency from prednisone therapy. When the blood glucose is low, counter-regulatory hormones (glucagon, growth hormone, cortisol, and epinephrine) act in concert by increasing blood glucose concentrations.[24] When a concurrent deficiency of several hormones exists (epinephrine by beta-blockade and cortisol by adrenal insufficiency), hypoglycemia may occur, especially during episodes of fasting. Therefore extreme care should be taken when propranolol is initiated in patients receiving corticosteroid therapy.

Propranolol treatment was associated with a decrease in blood pressure. One patient experienced cold extremities and a prolonged capillary refill time. However, serious sequelae suggestive of organ hypoperfusion (such as loss of consciousness) due to hypotension were not reported.

One patient probably experienced a seizure after the first dose of propranolol. A possible explanation for this seizure could be hypoglycemia, but diagnostic investigations were not performed. Hypoglycemia has never been reported in healthy infants at the propranolol dosage used in this case. The fact that propranolol was restarted without any adverse effects makes a causal relationship between propranolol and the seizure-like incident highly unlikely.

In 11% of patients (3/28), propranolol had to be discontinued due to bronchial hyperreactivity during viral infections. Bronchial hyperreactivity is a direct effect of non-beta selectivity of propranolol, resulting in bronchospasm due to pulmonic beta2-blockade.

The use of a non-selective lipophilic beta-blocker results in several other reported side effects. Restless sleep probably is a direct result of the lipophilic character of propranolol, which allows it to cross the blood brain barrier.[25]

Previous reports of propranolol treatment of IH did not comment on or reported limited side effects.[5-13] A possible explanation for this difference may be our multidisciplinary approach in which patients are frequently evaluated and closely monitored in the outpatient clinic by a pediatrician, a pediatric dermatologist, and/or a pediatric plastic surgeon. However, information from a case series has limitations and further clinical studies are necessary to determine the incidence of these adverse effects.

A solution to many of the side effects of propranolol therapy may be the use of more selective beta-1 antagonists such as metoprolol, which, at low dosage, have little beta-2 activity; thus, in theory, they bear a lower risk of inducing hypoglycemia and bronchospasm. Treatment with a hydrophilic beta-1 antagonist such as atenolol may prevent side effects, such as restless sleep. However, it is not yet known if these selective beta-blockers will have efficacy that is equal to propranolol.

Our study confirms the impressive results of propranolol as a treatment for IH. It seems to be a more effective and safer therapeutic drug than systemic corticosteroids. Its use may be

expanded to treatment of IH after the first year of life. Because of potentially harmful side effects, including hypoglycemia, bronchospasm, and hypotension, these patients are preferably treated in a multidisciplinary setting by physicians knowledgeable about the effects and side effects of propranolol.

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5.3

Reply to: How "unsafe" is propranolol when used in the treatment of infantile hemangioma?

Marlies de Graaf[1], Johannes M.P.J. Breur[2], Martine F. Raphael[3], Corstiaan C. Breugem[4], Suzanne G.M.A. Pasmans[1]

[1] Department of Pediatric Dermatology and Allergology, Wilhelmina Children's Hospital Utrecht.
[2] Department of Pediatric Cardiology, Wilhelmina Children's Hospital Utrecht.
[3] Department of Pediatric Hematology and Oncology, Wilhelmina Children's Hospital Utrecht.
[4] Department of Pediatric Plastic Surgery, Wilhelmina Children's Hospital Utrecht.

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To the Editor: We thank Dr Prashanth for his critical comments. Indications for treatment are changing. Whereas prednisone treatment was indicated in case of airway obstruction, ulceration, or functional impairment, propranolol is now also used in case of aesthetic risk.[1] The exact working mechanism of propranolol is still unknown and long term side effects are unclear.

The aim of our article was to increase the awareness of possible side effects associated with propranolol treatment. So far only case reports of side effects in the treatment of infantile hemangioma with propranolol have been described but they are not scarce.[2-7] However until to date data on side effects of this therapy in IH are lacking. This could be an explanation why only few side effects of the treatment with propranolol are reported. Recently Hogeling et al[8] reported in their randomized controlled trial side effects, including bronchiolitis, gastroenteritis, cold extremities and sleep disturbance.

We believe the temporal association suggests that the side effects reported in our article were related to propranolol. Before treatment with propranolol the patients did not experience bronchial hyperreactivity during viral infections. After stopping the treatment the bronchial hyperreactivity disappeared, and after reintroduction of propranolol the bronchial hyperreactivity reoccurred. Furthermore, the bronchial hyperreactivity was unresponsive to supportive care.

Blood pressures were measured before the start of treatment (baseline blood pressure) and 1, 2, 4, 8 and 12 weeks after the start of treatment (at least twice per visit on the arm). Hypotension was defined as blood pressure below p5 (5^{th} percentile corrected for age), or when symptoms of hypotension occurred simultaneous with a significant drop in blood pressure.

Hypoglycemia is a well-documented side effect of propranolol treatment. In both patients (patient 4 and 13) with hypoglycemia there were predisposing factors for developing hypoglycemia (prednisone usage and reduced oral intake respectively). Although not reported, other causes of hypoglycemia in patient 13 were ruled out during admission.[4]

In summary, there is general consensus on the spectacular results that may be achieved with propranolol in treatment of infantile hemangioma and indications for treatment are shifting. However, we would like to emphasize that every physician treating a benign condition with medication should be fully aware of both the effects and side effects of the treatment initiated. We should remain vigilant for unwanted side effects and consider safer alternatives such as selective beta-blockers.[9,10]

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5.4

Reply to: Treating hemangioma of infancy with beta-blockers: is there really a risk of hypotension?

Marlies de Graaf[1], Martine F. Raphael[2], Corstiaan C. Breugem[3], Suzanne G.M.A. Pasmans[1], Johannes M.P.J. Breur[4]

[1] Department of Pediatric Dermatology and Allergology, Wilhelmina Children's Hospital Utrecht.
[2] Department of Pediatric Hematology and Oncology, Wilhelmina Children's Hospital Utrecht.
[3] Department of Pediatric Plastic Surgery, Wilhelmina Children's Hospital Utrecht.
[4] Department of Pediatric Cardiology, Wilhelmina Children's Hospital Utrecht.

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To the Editor: With great interest we have read the comments of Janmohamed et al. The authors are absolutely right to define hypotension as a blood pressure below the fifth percentile corrected for age and gender. In our article we do not define hypotension. However, we agree that our subheading 'hypotension', under which we discuss the effect of propranolol on blood pressure, can easily lead to the misunderstanding that we define hypotension as a diastolic blood pressure below the 50th percentile. This of course is incorrect and was never our intention. The goal of reporting blood pressures before and after initiation of propranolol solely was to report our observation that propranolol does lower blood pressure. We fully agree with the authors that hypotension only rarely occurs. In our series only patient 7 developed symptomatic hypotension after initiation of propranolol with a blood pressure of 56/34 mm Hg (fifth percentile = 68/34 mm Hg corrected for age and sex (Table 1a and 1b)).[1] Most blood pressure reference reports only provide percentiles for 50th and up. There are hardly any reports on normal values for blood pressure below the 50th percentile. Therefore, we specifically use blood pressure reference values adapted from the Second Task Force on Blood Pressure Control in Children, National Heart, Lung, and Blood Institute, since they also provide fifth percentile values in young children (prepared by Dr. B. Rosner).[2]

Blood pressures were obtained with a Dinamap (GE Medical Systems, Tampa, FL). Age appropriate sized blood pressure cuffs were used on the arm. The average of 3 blood pressure measurements was obtained. The large majority of patients were awake at the time of blood pressure measurement; we did not wake up patients to obtain blood pressures, however.

In conclusion, we fully agree with Janmohamed and colleagues that hypotension is rarely encountered during treatment of infantile hemangiomas with propranolol. On the other hand we would like to emphasis that every doctor treating a benign condition with medication should be fully aware of potential side effects of this treatment and should be actively looking for their occurrence and for safer alternatives such as selective beta-blockers (like atenolol).[3]

Table 1a. Normal blood pressure readings for boys

Systolic blood pressure percentile					Diasystolic blood pressure percentile				
Age	**5th**	**50th**	**90th**	**95th**	**Age**	**5th**	**50th**	**90th**	**95th**
Normal bloodpressure readings for boys									
1 day	54	73	87	92	**1 day**	38	55	68	72
3 days	55	74	89	93	**3 days**	38	55	68	71
7days	57	76	91	95	**7days**	37	54	67	71
1 mo	67	86	101	105	**1 mo**	35	52	64	69
2 mo	72	91	106	110	**2 mo**	33	50	63	66
6 mo	72	90	105	109	**6 mo**	36	53	66	70
1 yr	71	90	105	109	**1 yr**	39	56	69	73
2 yr	72	91	106	110	**2 yr**	39	56	68	72
3 yr	73	91	107	111	**3 yr**	39	55	68	72
4 yr	74	93	108	112	**4 yr**	39	56	69	72
5 yr	76	95	109	113	**5 yr**	40	56	69	73
6 yr	77	96	111	115	**6 yr**	41	57	70	74
7 yr	78	97	112	116	**7 yr**	42	58	71	75
8 yr	80	99	114	118	**8 yr**	43	60	73	76
9 yr	82	101	115	120	**9 yr**	44	61	74	78
10 yr	84	102	117	121	**10 yr**	45	62	75	79
11 yr	86	105	119	123	**11 yr**	47	63	76	80
12 yr	88	107	121	126	**12 yr**	48	64	77	81
13 yr	90	109	124	128	**13 yr**	45	63	77	81
14 yr	93	112	126	131	**14 yr**	46	64	78	82
15 yr	95	114	129	133	**15 yr**	47	65	79	83
16 yr	98	117	131	136	**16 yr**	49	67	81	85
17 yr	100	119	134	138	**17 yr**	51	69	83	87
18 yr	102	121	136	140	**18 yr**	52	70	84	88

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Table 1b. Normal blood pressure readings for girls

Systolic blood pressure percentile					Diasystolic blood pressure percentile				
Age	**5th**	**50th**	**90th**	**95th**	**Age**	**5th**	**50th**	**90th**	**95th**
Normal bloodpressure readings for girls									
1 day	46	65	80	84	**1 day**	38	55	68	72
3 days	53	72	86	90	**3 days**	38	55	68	71
7days	60	78	93	97	**7days**	38	54	67	71
1 mo	65	84	98	102	**1 mo**	35	52	65	69
2 mo	68	87	101	106	**2 mo**	34	51	64	68
6 mo	72	91	106	110	**6 mo**	36	53	66	69
1 yr	72	91	105	110	**1 yr**	38	54	67	71
2 yr	71	90	105	109	**2 yr**	40	56	69	73
3 yr	72	91	106	110	**3 yr**	40	56	69	73
4 yr	73	92	107	111	**4 yr**	40	56	69	73
5 yr	75	94	109	113	**5 yr**	40	56	69	73
6 yr	77	96	111	115	**6 yr**	40	57	70	74
7 yr	78	97	112	116	**7 yr**	41	58	71	75
8 yr	80	99	114	118	**8 yr**	43	59	72	76
9 yr	81	100	115	119	**9 yr**	44	61	74	77
10 yr	83	102	117	121	**10 yr**	46	62	75	79
11 yr	86	105	119	123	**11 yr**	47	64	77	81
12 yr	88	107	122	126	**12 yr**	49	66	78	82
13 yr	90	109	124	128	**13 yr**	46	64	78	82
14 yr	92	110	125	129	**14 yr**	49	67	81	85
15 yr	93	111	126	130	**15 yr**	49	67	82	86
16 yr	93	112	127	131	**16 yr**	49	67	81	85
17 yr	93	112	127	131	**17 yr**	48	66	80	84
18 yr	94	112	127	131	**18 yr**	48	66	80	84

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6.1

Atenolol a promising alternative for propranolol in the treatment of hemangiomas

Martine F. Raphael[1], Marlies de Graaf[2], Corstiaan C. Breugem[3], Suzanne G.M.A. Pasmans[2], Johannes M.P.J. Breur[4]

[1] Department of Pediatric Hematology and Oncology, Wilhelmina Children's Hospital Utrecht.
[2] Department of Pediatric Dermatology and Allergology, Wilhelmina Children's Hospital Utrecht.
[3] Department of Pediatric Plastic Surgery, Wilhelmina Children's Hospital Utrecht.
[4] Department of Pediatric Cardiology, Wilhelmina Children's Hospital Utrecht.

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To the Editor: In this issue of the Journal, we report our experience with propranolol as an effective treatment for infantile hemangiomas (IH).[1] Despite the good results, two patients had to discontinue propranolol treatment because of adverse effects. We hypothesized that the use of a hydrophilic, selective beta-1 blocker could avoid these side effects. We present the preliminary results of the first patients treated with atenolol for IH.

Patient 1 presented with a nose tip IH (Cyrano nose) for which propranolol treatment was started at age 3 months. Because of severe bronchial hyperreactivity necessitating hospital admission for oxygen therapy and bronchodilator medications and because of hypotension with diastolic blood pressure around the fifth percentile for age, propranolol was repeatedly discontinued and dosage could not be raised to 2 mg/kg per day. During propranolol treatment, an improvement in volume and color was observed. At age 9 months, treatment with atenolol was started (first 7 days 0.5 mg/kg per day, thereafter 1 mg/kg per day). Atenolol was well tolerated and no bronchial hyperreactivity occurred. Blood pressures remained above the 50th percentile. The hemangioma responded to atenolol (Figure 1) and is currently in regression after 2.5 months of therapy.

Patient 2 is a 3½-month-old boy with an ulcerating sacral hemangioma for which ulcer excision was performed and propranolol treatment initiated. During propranolol treatment the boy had problems falling asleep and was restless while sleeping. Discontinuation of propranolol resulted in a normal sleeping pattern. At age 5 months propranolol was restarted at a lower dose of 1 mg/kg per day. The hemangioma responded well, but the side effects reoccurred. Sleep disturbance responded well to cessation of propranolol. Atenolol was subsequently started at age 9 months (first 7 days 0.5 mg/kg per day, thereafter 1 mg/kg per day). No side effects occurred. Follow-up at the age of 10½ months showed further regression of the hemangioma (Figure 2).

Propranolol, a lipophilic nonselective beta blocker, has been introduced as an effective treatment for IH.[2] The effect of propranolol might be attributed to beta-2 blockage in the endothelial cell resulting in vasoconstriction, inhibition of angiogenesis, and induction of apoptosis.[3] Despite excellent results, we observed serious side effects.[1] We hypothesized that the use of a hydrophilic beta-1 antagonist could avoid the adverse events observed during propranolol therapy. Hydrophilic beta blockers, which appear at low concentrations in brain tissue, are less likely to produce central nervous system-related side effects (nightmares and hallucinations) than lipophilic beta-blockers, which occur at higher concentrations in the brain.[4] In addition, atenolol is less likely to produce pulmonary side effects.[5]

Therefore atenolol was started during hospital admission in two patients who had to discontinue propranolol due to side effects. Follow-up visits for effects and side effects were frequently performed by experienced dermatologists and pediatricians in the outpatient clinic. These visits included obtaining medical history and physical examination with monitoring of blood pressure and heart rate. Serum glucose values were obtained during the first week of treatment. Both patients tolerated atenolol very well and no adverse events occurred. Fur-

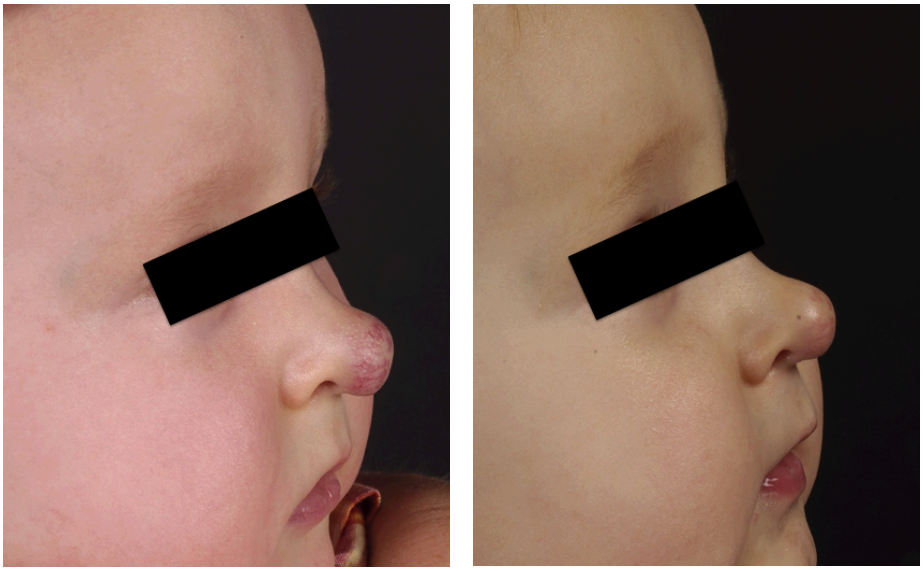

Figure 1. A, One month after stopping propranolol treatment and at start of atenolol treatment. B, 2.5 months after starting atenolol treatment.

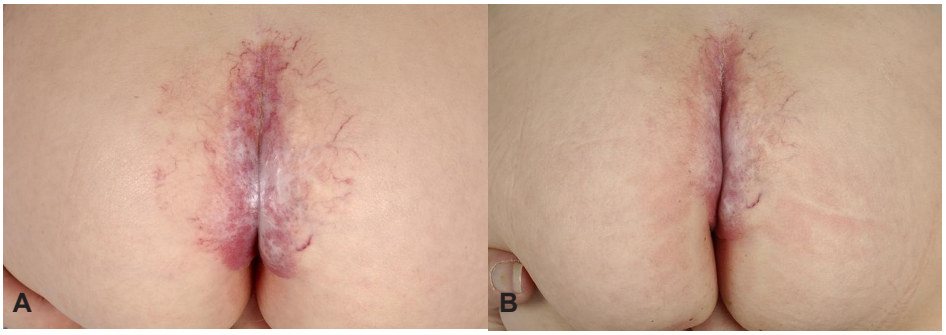

Figure 2. A, One month after stopping propranolol treatment and 1 week before start of atenolol treatment. Scars after excision of ulceration are visible. B, One month after start of atenolol treatment.

thermore, the hemangiomas responded well on atenolol therapy, although maybe slightly slower, as seen in patient 1.

A possible explanation for the observed effect is the limited beta-2 blocking potential of atenolol.[6] This may also explain why the spectacular discoloration of the IH in the early phase of therapy (early vasoconstriction) was not observed.[7] Another explanation for the effect is that we observed the natural course of IH in two patients. However, the change in clinical course after initiation of atenolol makes this unlikely. Finally, there may be currently unknown pathways through which beta blockers mediate their effect on IH.

A randomized controlled clinical trial should be conducted to prove the equal efficacy and better tolerance of atenolol compared with propranolol.

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6.2

Treatment of infantile hemangiomas with atenolol: comparison with a historical propranolol group

Marlies de Graaf[1], Martine F. Raphael[2], Corstiaan C. Breugem[3], Mirjam J. Knol[4], Carla A.F.M. Bruijnzeel-Koomen[1], Moshe Kon[3], Johannes M.P.J. Breur[5], Suzanne G.M.A. Pasmans[1,6]

[1] Department of Pediatric Dermatology and Allergology, Wilhelmina Children's Hospital Utrecht.
[2] Department of Pediatric Hematology and Oncology, Wilhelmina Children's Hospital Utrecht.
[3] Department of Pediatric Plastic Surgery, Wilhelmina Children's Hospital Utrecht.
[4] Julius Centre for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht.
[5] Department of Pediatric Cardiology, Wilhelmina Children's Hospital Utrecht.
[6] Current affiliation: department of Pediatric Dermatology, Erasmus University Medical Center Rotterdam.

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Abstract

Propranolol, a lipophilic non-selective beta-blocker, has proven to be effective in the treatment of infantile hemangioma (IH). However, several side effects have been reported. Atenolol, a hydrophilic selective beta-1 blocker, could be an alternative and associated with fewer side effects.

Thirty consecutive patients with IH were treated with atenolol between June 2010 and May 2011. The therapeutic effect was judged by clinical assessment and quantified by using a Visual Analogue Scale (VAS) and the Hemangioma Activity Score (HAS). Side effects were also evaluated. The atenolol cohort was compared with a previously described cohort of 28 patients treated with propranolol between July 2008 and December 2009.

Clinical involution was present in 90% (27/30) of the IH treated with atenolol. Mild side effects occurred in 40% (12/30) of these patients and severe side effects occurred in 3% (1/30). Compared with the previously described cohort treated with propranolol, mild side effects occurred in 50% (14/28) and severe side effects in 25% (7/28) of the patients (p=0.04). Quantitative improvement of the IH in the atenolol group (n=27) showed no significant difference in either the VAS score or the HAS compared to the propranolol group (n=24).

This study indicates that atenolol is effective in the treatment of IH. Compared with a historical control group treated with propranolol, the effects of atenolol seems to be similar and less frequently associated with severe side effects. Randomized clinical trials are necessary to evaluate the efficacy and safety of atenolol treatment in IH.

Introduction

Infantile hemangiomas (IH) are benign vascular tumors found in approximately 4-10% of Caucasian infants.[1,2] IH can impede the function or development of neighboring structures or organs necessitating treatment.[3]

Léauté-Labrèze et al. and others reported an impressive therapeutic response to propranolol, a lipophilic non-selective beta-blocker, in the treatment of IH.[4-15] Although the treatment of IH with propranolol has shown spectacular results, side effects, like hypoglycemia, bronchial hyperreactivity, hyperkalemia, and diarrhea, have been reported.[16-20)] We hypothesized that the use of a hydrophilic, selective beta-1 blocker could prevent the side effects attributable to the beta-2 activity and lipophilicity of propranolol.[20,21] The current report describes the efficacy and side effects of atenolol in 30 patients with IH. These results were compared with a previously described cohort of patients treated with propranolol.[20]

Patients and methods

Patients

Atenolol was administered as standard treatment to 30 consecutive children with IH. All IH were either potentially (life-)threatening, or had functional risk, local discomfort, or cosmetic disfigurement. This study has been received by the ethical committee of the University Medical Center Utrecht and it has not been a subject to review. The parents of the patients received written information about the effects and side effects of the treatment and they gave their consent before starting the treatment. All data was analyzed anonymously.

Patients presented at the Centre for Congenital Vascular Anomalies of the Wilhelmina Children's Hospital, University Medical Center Utrecht, the Netherlands, between June 2010 and May 2011. All patients were treated as outpatients and only admitted when indicated (e.g., age <1 months, increased risk of side effects and pain due to ulceration (requiring surgery)). Before commencing treatment, patients were screened for contra-indications and an electrocardiogram (ECG) was performed to detect any pre-existing cardiac conduction disturbances. Patients were evaluated after approximately 2, 8 and 20 weeks. During each visit, body weight (kg), blood pressure (BP, mmHg, measured with a Dinamap), and heart rate (beats/min) were measured and digital photographs were made. During the treatment period, atenolol dosage was adjusted for weight gain. Blood glucose levels were measured only when indicated (in case of clinical signs of hypoglycemia, age <1 months, prematurity/dysmaturity and during admission). The clinician determined the clinical involution of the IH and side effects were documented and evaluated. Furthermore, parents were asked to complete a questionnaire about the efficacy and side effects of the atenolol treatment. All side effects were evaluated during the first 12 months of treatment.

The starting dosage of atenolol was 0.5 mg/kg/day (once daily). After one week of treatment the atenolol dosage was increased to 1 mg/kg/day. If clinical response was inadequate the atenolol dosage was gradually increased to a maximum of 3 mg/kg/day.
A previously described cohort of 28 consecutive children treated with propranolol (average dosage 2 mg/kg/day) between July 2008 and December 2009 was used as a historical control group.[20] This means that the time period, rather than the physician, defined treatment allocation to propranolol or atenolol.
The data of the atenolol group were compared with the historical propranolol group.

Efficacy assessment

Clinical assessment of efficacy.

The efficacy of atenolol (n=30) treatment was assessed by determining the clinical involution (color change, softening to palpation, reduction in size) at the time of visit in the outpatient clinic.
The same was done in the case of patients treated with propranolol (n=28). In case of non-cutaneous IH, additional investigations (ultrasound and/or magnetic resonance imaging (MRI)) were performed to assess efficacy.

Quantitative assessment of efficacy.

In addition to the clinical assessment, efficacy was quantified by two blinded clinical-investigators using digital photographs. These photographs were performed prior to the treatment (baseline) and after the start of treatment at 2-8 weeks (t1) and 11-24 weeks (t2). The primary 'end'point was change in the appearance of IH as evaluated on a visual analog scale (VAS). The VAS uses a 100-mm scale on which -100 represented a doubling in the size and extent of the IH, 0 represented no change/baseline and +100 represented complete disappearance.[22] The investigators were asked to mark on the VAS the changes in the size, color and extent of the IH, comparing the photographs of baseline, t1 and t2. To make the evaluation of efficacy more objective, the Hemangioma Activity Score (HAS)[23] was used to score the proliferative activity of the IH. Both investigators scored the photographs of baseline, t1 and t2. The change (ΔHAS) was calculated from the differences between baseline and t1 and baseline and t2. The greater the ΔHAS, the better the therapeutic effect. When both investigators assessed the IH differently (difference in VAS and/or HAS score) they came to a consensus in order to get one final score.
The non-cutaneous IH could not be scored because of lack of clinical photographs in five patients (*n*=1 for atenolol and *n*=4 for propranolol) and therefore these were excluded in the analysis of this quantitative efficacy of atenolol. Patients in the atenolol group who were previously treated with propranolol were also excluded.

Analyses

Baseline characteristics of the atenolol group and the historical propranolol group were compared with a chi-squared test. First, the percentage of patients with clinical involution of the IH was compared between the two treatment groups with a chi-squared test. Second, *t*-tests were used to calculate the difference in efficacy between the propranolol and atenolol group for both VAS and ΔHAS at t1 and t2. Third, because the photographs were not taken at exactly the same time points for all patients and some photographs of t2 were missing, a linear mixed model was used where time was modelled as a continuous variable. The model included treatment group, time and the interaction between time and treatment. Furthermore, we adjusted for age and indication for treatment, because these variables differed between the treatment groups. The correlation between the VAS and HAS was calculated.

Results

Patients

Table 1 shows detailed characteristics of the 30 patients treated with atenolol. In all these patients the involution/improvement of the IH was clinically determined and side effects were evaluated. The median age at the time of initiation of atenolol treatment was 6.4 months (range 1.5 to 30). No significant ECG abnormalities were reported. The maximum dosage of atenolol varied between 1–3 mg/kg/day (average 1.2 mg/kg/day, mean 1.0 mg/kg/day). I average duration of treatment was 11.5 months (0.5-28 months).

Data of the atenolol group were compared with the historical propranolol group. Detailed characteristics of the 28 patients treated with propranolol were reported earlier.[20]

To quantify the improvement of the IH, patient 4, 9, and 11 of the atenolol group were excluded because of previous treatment with propranolol (which had to be stopped due to side effects) or non-cutaneous location of the IH. The atenolol patients previously treated with propranolol were not included in the propranolol group.

Of the historical propranolol group, patients 7, 11, 18, and 19 were excluded because of non-cutaneous location of the IH. Table 2 shows the baseline characteristics of the 27 patients in the atenolol group and the 24 in the propranolol group. There was no statistically significant difference between gender distribution, location of the IH, characteristics of the IH (localized/nodular, segmental, indeterminate, multifocal) or therapeutic indication for both patient groups (all $p>0.05$). Although not significant, the atenolol group contained more patients with ulceration (30% vs 4%). The patients treated with atenolol were significantly younger compared to the patients treated with propranolol ($p=0.01$). Digital photographs at t2 were missing (because of logistical problems and/or patient no show) in three patients in the atenolol group and in three patients in the propranolol group.

Table 1. Detailed characteristics of the 30 patients treated with atenolol

Patient	Gender	Location of IH	Characteristic of IH	Indication for atenolol treatment	Previous treatment	Age at initiation of atenolol treatment (mo)	Age at end of atenolol treatment (mo)	Side effects	Maximum dosage atenolol (mg/kg)
1	F	Face (segmental IH) PHACE syndrome	segmental	functional		1.5	10		3
2	F	Buttock	localized/nodular	ulceration		5	5.5		1
3	F	Neck	indeterminate	ulceration		3	4		1
4[a]	*M*	*Groin and upper leg*	*indeterminate*	*functional*	*propranolol*	*7*	*8*	*(transient) restless sleep*	*1*
5	F	Preauricular	localized/nodular	functional		2	12		1
6	M	Chest	indeterminate	ulceration		5	12		1
7	F	Knee	indeterminate	ulceration		4	19		1
8	F	Cheek (large IH in parotid area)	localized/nodular	functional		3	[b]		2
9[a]	*F*	*Cheek*	*localized/nodular*	*functional*	*propranolol*	*26*	*54*		*1*
10	F	Face (segmental IH) PHACE syndrome	segmental	functional		3	20	constipation	2
11[a]	*M*	*Sternal intraossal IH*		*functional*		*30*	*42*	*diarrhea*	*1*
12	F	Orbita	localized/nodular	functional		7	19	(transient) restless sleep	1.5
13	F	Buttock	localized/nodular	ulceration		4.5	9		2
14	M	Lower eyelid	localized/nodular	functional		2	15	low diastolic BP	1
15	F	Chin	localized/nodular	functional		4	23	diarrhea, (transient) restless sleep	1.5
16	F	Eye and orbita	localized/nodular	functional		4	16	constipation	1
17	F	Cheek	localized/nodular	functional		1.5	15	(transient) restless sleep	2
18	F	Cheek	localized/nodular	cosmetic		4	26	(transient) restless sleep	1.5
19	F	Cheek	localized/nodular	functional		5	12	(transient) restless sleep	1
20	F	Eye	localized/nodular	functional		3	18		1.5
21	F	Lower eyelid	localized/nodular	functional		3.5	12		1
22	F	Back	localized/nodular	ulceration		4	9	(transient) restless sleep	1.5

Table 1. Detailed characteristics of the 30 patients treated with atenolol

23	M	Hand	indeterminate	functional	8	14	(transient) restless sleep	1
24	M	Ear	indeterminate	ulceration	2	15		1.6
25	F	Scalp	localized/nodular	ulceration	6	19		1
26	M	Forehead, scrotum, thorax	localized/nodular	cosmetic	8	17		1
27	F	Lower lip (back)	localized/nodular	functional	5	16		1
28	M	Upper eyelid	localized/nodular	functional	2	17		2
29	M	Forehead	localized/nodular	cosmetic	7	26		1.5
30	F	Hand, upper leg	indeterminate	functional	1.5	17		1

PHACE syndrome (Posterior fossa abnormalities, Haemangiomas, Arterial abnormalities, Cardiac anomalies, Eye anomalies).

[a] To quantify the improvement of the infantile haemangiomas (IH) patient 4, 9, and 11 were excluded because of previous treatment with propranolol or non-cutaneous location of the IH.

[b] still on atenolol treatment.

Table 2. Baseline characteristics of the patients in the atenolol and the historical propranolol group.

		Atenolol n=27	(%)	Propranolol n=24[a]	(%)	p-value
Gender	Male	7	26	6	25	0.94
	Female	20	74	18	75	
Location IH	Face and neck	21	78	22	92	0.17
	Other parts of the body (except face)	6	22	2	8	
Characteristic IH	Localized/nodular	19	70	19	79	0.36
	Segmental	2	8	3	13	
	Indeterminate	6	22	2	8	
	Multifocal (5 or more IH)	0	0	0	0	
Indication of treatment	Functional	16	59	20	83	0.07
	Ulceration	8	30	1	4	
	Cosmetic	3	11	2	8	
	Diagnostic	0	0	1	4	
Age at initiation of treatment	1-6 months	23	85	12	50	0.01
	6-12 months	4	15	8	33	
	>12 months	0	0	4	17	

For the quantified assessment of the improvement of the infantile hemangiomas (IH) patients with non-cutaneous IH and patients in the atenolol group who were previously treated with propranolol were excluded.

[a] Historical propranolol group.[20]

Efficacy of atenolol

In the atenolol group 27 out of 30 patients (90%) showed clinical involution at t1, at 2-8 weeks after start of treatment. Figure 1a and 1b show examples of two patients treated with atenolol.

Clinical assessment of efficacy compared with propranolol (atenolol n=30, propranolol n=28).

Two patients (patients 2 and 3) with an ulcerated IH showed insufficient response after two weeks of atenolol treatment (1 mg/kg/day), with respect to ulceration and pain, and the ulcer was excision. Patient 3 did not respond to treatment with propranolol 2 mg/kg/day as well. Patient 1, with a segmental IH in the face affecting her right eye, initially responded well on atenolol treatment. However, the effect on the IH of the upper eyelid of the right eye was insufficient and surgical debulking was inevitable.

In the historical propranolol group all patients (100%) showed clinical involution (color change, softening to palpation and reduction in size) at t1 (p=0.09).

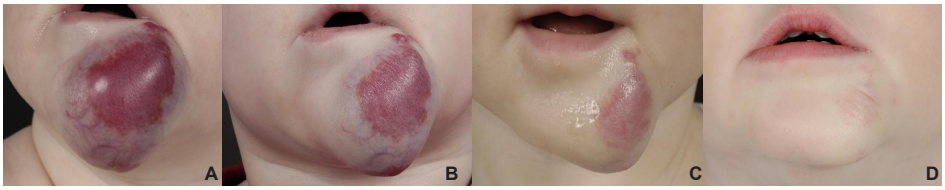

Figure 1a. Patient 15.
A, baseline (before treatment). B, t1: 5 weeks after start of atenolol treatment (age 5 months). C, t2: 19 weeks after start of atenolol treatment (age 8.5 months). D, 16 months after start of atenolol treatment (age 20 months). Photograph D was not included in the study.

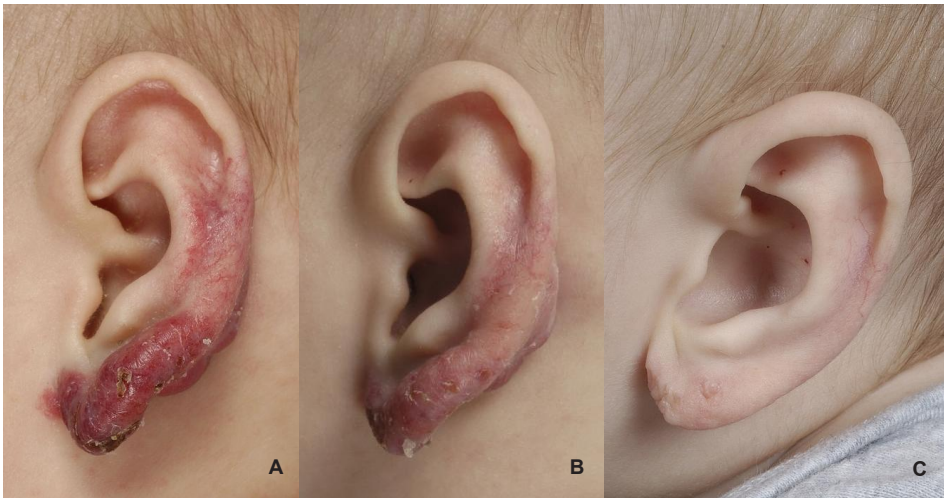

Figure 1b. Patient 24.
A, baseline (before treatment). B, t1: 4 weeks after start of atenolol treatment (age 3 months). C, t2: 20 weeks after start of atenolol treatment (age 7 months).

Quantitative assessment of efficacy of atenolol (n=27) compared with the historical propranolol group (n=24).

The scores of both VAS and HAS for the quantitative improvement of the IH are shown in Figure 2(a and b). Figure 2a shows the VAS scores of both treatment groups and Figure 2b shows the difference in scores between baseline and t1 and between baseline and t2 (ΔHAS) for both treatment groups. Both scores at t1 were slightly higher in the propranolol group and at t2 the VAS score was almost equal in both groups and the ΔHAS was slightly higher in the atenolol group. However, these differences were statistically not significant (all $p>0.05$). The average time of the first photograph taken for atenolol was 3.0 weeks (range 2-6) and for the second photograph 14.9 weeks (range 11-20). For propranolol the average time of the photographs was respectively 3.9 weeks (range 2-8) and 14.9 weeks (range 11-24).
The interaction between treatment and time was not significant in the linear mixed model for both scores (VAS $p=0.44$ and HAS $p=0.32$), which means that the trend over time with re-

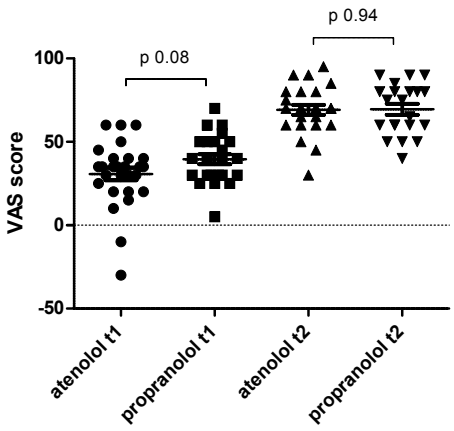

Figure 2a. VAS scores of the efficacy of atenolol and propranolol.
The efficacy of atenolol and propranolol was scored on a Visual Analogue Scale (VAS) at t1 and t2. P-values show no significant ($p<0.05$) difference between both drugs.

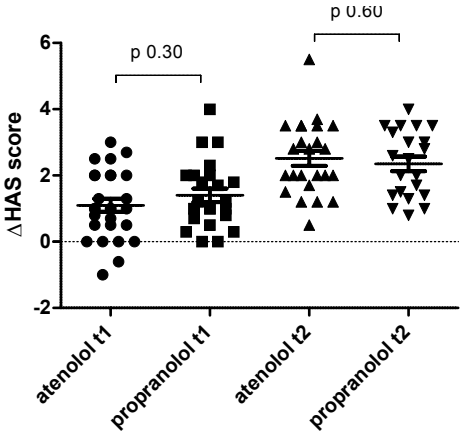

Figure 2b. ΔHAS scores of the efficacy of atenolol and propranolol.
The efficacy of atenolol and propranolol was scored with the Haemangioma Activity Score (HAS) at t1 and t2 and ΔHAS (difference between baseline and t1 and baseline and t2) was calculated. P-values show no significant ($p<0.05$) difference between both drugs.

spect to the scores of the IH did not differ between the treatment groups. Before adjustment for baseline characteristics the VAS score was slightly higher in the propranolol group but statistically not significant (p=0.44). The ΔHAS was the same in both groups (p=0.88). After adjustment for age and indication for treatment, the VAS score was higher in the historical propranolol group and the ΔHAS was higher in the atenolol group. Both differences were statistically not significant (respectively p=0.34 and p=0.39).
The VAS and HAS showed a good correlation at t1 and t2 of respectively 0.58 and 0.59 ($p<0.001$).

Side effects of atenolol

All atenolol patients (n=30) showed a decrease in BP. Only patient 14 once showed a diastolic BP below the 5th percentile for age (BP 66/29, 5th percentile (p5) for diastolic pressure at age 2 months = 33 mmHg) during treatment (pre-treatment BP 84/51 (50th percentile)). Serious signs suggestive of organ hypoperfusion (such as loss of consciousness) were not observed and finally the dosage of atenolol was increased in this patient without showing a low BP. All other patients showed BP above the p5 for age and were asymptomatic, although some of the parents reported cold extremities. Eight patients suffered from (transient) restless sleep (patient 4, 12, 15, 17, 18, 19, 22, and 23). Patient 4 was previously treated with propranolol, which was stopped because of bronchial hyperreactivity and restless sleep. During atenolol

treatment the patient again suffered from restless sleep. After cessation of atenolol treatment, the patient regained a normal sleeping pattern. The other patients suffered from mild and transient restless sleep.

Other side effects reported by parents were constipation in two patients (7%) and diarrhea in two patients (7%). Infection as a cause of diarrhea was not excluded.

None of the patients suffered from hypoglycemia or bronchial hyperreactivity.

The side effects of atenolol (*n*=30) were compared with the side effects of the historical propranolol group (*n*=28).[20] Table 3 summarizes the side effects in both treatment groups. Severe side effects (hypoglycemia, bronchial hyperreactivity and hypotension) occurred in 3% (1/30) of patients treated with atenolol and in 25% (7/28) treated with propranolol (p=0.04). Mild side effects (restless sleep, constipation and diarrhea) occurred in 40% (12/30) of patients treated with atenolol and in 50% (14/28) of patients treated with propranolol (p=0.44).

Table 3. Side effects in patients treated with atenolol compared with the historical propranolol group.

	Atenolol n=30 (%)	Propranolol n=28 (%)[a]
Severe side effects		
Hypoglycemia	-	2 (7)
Bronchial hyperreactivity	-	4 (14)
Hypotension	1 (3)	1 (4)
Mild side effects		
Restless sleep	8 (27)	11 (39)
Constipation	2 (7)	3 (11)
Diarrhoea	2 (7)	-

Some patients had multiple side effects.

Hypotension means a diastolic blood pressure below the 5th percentile for age.

[a] Historical propranolol group.[20]

Discussion

Since the report of Léauté-Labrèze et al., the treatment of IH with beta-blockers has become the treatment of choice.[4,24,25] As far as we know, only one randomized controlled trial (RCT) has proven the effectiveness of propranolol.[(26)] Nevertheless, there seems to be a general agreement that propranolol is effective in IH treatment and studies now focus on optimal treatment regimen and on beta-blockers with a more favorable balance between efficacy and side effects.[21,25,27-30] The results of this study confirm that atenolol is effective in the treatment of IH. Moreover, when compared to a historical control group, atenolol seems to be as effective as propranolol but appears associated with fewer side effects.

Atenolol is a hydrophilic, selective beta-1 blocker and therefore is not associated with side effects attributable to beta-2 activity and lipophilicity seen with propranolol. It has a terminal

half-life of 6-8 hours and therefore has to be administered only once daily, which may improve patient compliance.[31,32]

Itinteang et al.[33] suggested that propranolol acts via the renin-angiotensin system in regulating accelerated involution of proliferating IH by decreasing renin production in the kidneys. As the kidneys predominantly express beta-1 receptors, the renin-angiotensin-aldosterone system (RAAS) is most likely the missing link in understanding the working mechanism of both beta-blockers and angiotensin-converting enzyme (ACE) inhibitors in the treatment of IH.[30] Another explanation, for the effect of atenolol in the treatment of IH, besides currently unknown mechanisms, could be the limited beta-2 blocking potential of atenolol.[34]

Atenolol treatment was clinically effective in 27 patients (90%). Two patients (patient 2 and 3) did not respond after two weeks of treatment with atenolol with respect to pain and ulceration. Besides a low starting dose it is possible that atenolol treatment was started too late and/or discontinued too early. Quantitative comparison of the efficacy of atenolol and propranolol using a historical study group showed no significant difference (all $p>0.05$).

Although rare, symptomatic hypoglycemia can be a serious complication of propranolol treatment. In our previous described cohort treated with propranolol, two patients with hypoglycemia were reported, of which one with adrenocortical suppression due to steroid withdrawal, and 3 patients who had to discontinue propranolol treatment due to bronchial hyperreactivity.[20] In the group of patients treated with atenolol, no hypoglycemia or bronchial hyperreactivity was observed and even a patient in whom propranolol had to be discontinued due to bronchial hyperreactivity responded well to atenolol treatment. This confirms our hypothesis that the use of a hydrophilic beta-1 antagonist reduces beta-2 receptor blockade and subsequently decreases the risk of hypoglycemia and pulmonary side effects.[35-38] Atenolol is theoretically less likely to produce central nervous system (CNS)-related side effects, such as nightmares and hallucinations, compared to lipophilic beta-blockers.[39,40] However, studies in children are lacking. Eight of the patients treated with atenolol suffered from restless sleep, suggesting that most probably atenolol (despite its hydrophilicity) can cross the blood-brain barrier in high-enough concentrations to induce CNS-related side effects.[39] In most of the patients the restless sleep was very mild and transient.

This is the first study comparing two different beta-blockers. The patients in the atenolol group were new consecutive patients treated with atenolol. These patients were compared to a historical control group (consecutive patients treated with propranolol). The decision to treat the patients with either propranolol or atenolol was only based on the period in time and not on patient characteristics, which reduces the chance of confounding. Differences that might have influenced the results between the atenolol and propranolol group were that the former were younger, were less frequently seen, and were treated once/day instead of twice. On the one hand, because of the young age of the patients in the atenolol group, the chance that the effect was not due to the treatment but to the natural involution of the IH is unlikely. On the other hand a younger age may be associated with a better response

to treatment. Therefore we corrected for age in the linear mixed model. The efficacy in both patient groups was quantified by the same blinded investigators, differences in baseline characteristics were adjusted in the statistical analyses, and the improvement of the IH was scored as objective as possible.

Propranolol and atenolol have been used extensively by pediatric cardiologists for many years. However, there are still many unanswered questions for the usage in treating IH. Hard data is lacking about the preferred age to initiate treatment of IH, the optimal dosage, the duration of treatment, and the criteria for discontinuing treatment.

It is unknown whether the long-term outcome of the treatment with beta-blockers for cosmetic indications is favorable above the natural course. Data is also lacking about possible side effects of long term treatment of healthy children with beta-blockers. However, propranolol seems to reduce subsequent memory for both new and previously learned emotional material in healthy adults.[41] More prospective long-term clinical studies about the response rate and side-effects in the treatment of IH with beta-blockers are necessary.

Conclusion

This study shows that atenolol is effective in the treatment of IH. Compared with a historical cohort of patients treated with propranolol, atenolol seems to have a similar effect on IH. Furthermore atenolol seems to be less frequently associated with potentially (life-)threatening side effects. Further clinical studies are necessary to confirm the described effects and safety of atenolol.

Acknowledgement

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6.3

Response from the authors of 'Treatment of Infantile Hemangiomas with Atenolol: comparison with a historical propranolol group'

Marlies de Graaf[1], Martine F. Raphael[2], Corstiaan C. Breugem[3], Mirjam J. Knol[4], Carla A.F.M. Bruijnzeel-Koomen[1], Moshe Kon[3], Johannes M.P.J. Breur[5], Suzanne G.M.A. Pasmans[1,6]

[1] Department of Pediatric Dermatology and Allergology, Wilhelmina Children's Hospital Utrecht.
[2] Department of Pediatric Hematology and Oncology, Wilhelmina Children's Hospital Utrecht.
[3] Department of Pediatric Plastic Surgery, Wilhelmina Children's Hospital Utrecht.
[4] Julius Centre for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht.
[5] Department of Pediatric Cardiology, Wilhelmina Children's Hospital Utrecht.
[6] Current affiliation: department of Pediatric Dermatology, Erasmus University Medical Center Rotterdam.

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Dear Sir,

With great interest we have read the comments of Ashvin Raju and Roba Khundkar. We are pleased that the authors acknowledge atenolol as a possible alternative to propranolol.

In respect to age adjustment, we included age as a categorical variable (1-6 months, 6-12 months and >12 months) in our model, so linearity between age and efficacy was not assumed. We agree that propranolol was shown to be the more efficacious option with regard to the percentage of patients with clinical involution, but this was not statistically significant (p=0.09).

When confronted with two patients on propranolol that developed side effects, we initiated atenolol treatment.[1] We hypothesized that the use of a hydrophilic, selective beta-1-blocker could be effective and prevent side effects of propranolol.[2] Good results made atenolol our primary drug of choice.

Patients 4 and 9 were excluded for analysis because of previous unsuccessful propranolol treatment and patient 11 because of its non-cutaneous location of IH and inability to assess quantitative outcome. They all responded well to atenolol.

Patient 1 with a periorbital IH revealed minor improvement on atenolol and partial surgical debulking was performed. Patient 2 showed minor improvement on atenolol and because of severe pain due to ulceration, surgical excision was performed. For both patients no propranolol therapy was commenced. Patient 3 did not respond to propranolol after two weeks of atenolol treatment. Subsequently an excision was performed. Ever since, no atenolol failures were seen.

A concurrent deficiency of epinephrine and cortisol as a direct result of both beta blockade by propranolol together with adrenal insufficiency as a result of prednisone use caused hypoglycaemia in one patient.[3] Besides less administration of prednisone therapy in IH, probably beta-1-selectivity of atenolol will also reduce the risk for hypoglycaemia.

This study is a first indication for efficacy and safety of atenolol. We agree that more, well-designed studies are required to clearly delineate the possible differences between these beta blockers.

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7

Discussion

Introduction

The main objective of this thesis is to provide new data to improve diagnosing and treatment of Infantile Hemangiomas (IH) for parents and physicians.
The last decennia several developments have been important for the care for IH (chapter 1). The classification for vascular anomalies by Mulliken and Glowacki has put an end to the confusing nomenclature of vascular anomalies.[1] Moreover, in recent years associated structural anomalies have been identified with certain hemangiomas and recommendations about diagnostics and treatment have been published. The most important clinical improvement was the discovery of the efficacy of beta blocker treatment for IH. This has led to new insights in the pathogenesis and treatment of IH.
In chapter 2.1 and 2.2 we have shown how eHealth can be a helpful tool to improve the knowledge of and (risk) evaluation by parents. Chapter 3 illustrates that eHealth is a potential tool for treatment of IH in secondary care, making IH care more efficient and accessible. Chapter 4 describes associated anomalies of IH in the lumbosacral and perineal region which need to be recognized before proper diagnostic evaluation can be initiated. Chapter 5 presents data on the effect and potential (life-) threatening side effects of propranolol treatment. In chapter 6 it is shown that the selective beta blocker atenolol is effective in the treatment of IH, being associated with less severe side effects compared to propranolol.

In this discussion three questions will be addressed. Firstly, the question how to achieve early recognition and referral of high risk IH, will be evaluated based on the data in chapter 2, 3 and 4. Secondly, we will discuss how to improve the quality of care for IH, based on the results of chapter 2 and 3. Finally, the question whether IH should be treated with atenolol instead of propranolol will be answered, based on our findings in chapter 5 and 6.
The first two questions relate to Part I of this thesis *Care for Infantile Hemangioma*. The last question relates to Part II of this thesis *Cure for Infantile Hemangioma*.

Part I Care for Infantile Hemangiomas

1. How to achieve early recognition and referral of high risk IH?

In the "Centre for Congenital Vascular Anomalies Utrecht" (CAVU) in the Wilhelmina Children's Hospital in Utrecht, we often see patients who develop complications from IH which could have been prevented by early referral. Twenty-four percent of patients with IH experience complications, like ulceration, bleeding, functional impairment, life-threatening risk, or

cosmetic risk (mainly due to deformities).[2] Early recognition and presentation of high risk IH is important to prevent complications, to diagnose possible associated anomalies, and to initiate early treatment.
In our opinion, the main reason of late recognition and presentation of IH at risk for complications is a lack of knowledge among parents and (primary) care providers. Other reasons, such as waiting times, might be a contributing factor as well.[3]

A lack of knowledge leading to late recognition and referral of high risk IH by parents may be explained by psychosocial factors and difficulties in accessing appropriate care. The development of an IH shortly after birth may induce feelings of guilt or uncertainty, since parents are often subjected to comments, questions and unsolicited advice from friends, family and complete strangers.[4-7] People may stare, ignore or avoid a child with an IH.[4] This might influence appropriate help-seeking behavior. Furthermore, some parents experience difficulties in getting access to appropriate care.[6,8] These factors might contribute to late referral of IH with an increased risk for complications.

A lack of knowledge by primary care providers may be explained by difficulties in diagnosing IH and recognizing complications and risk for associated anomalies. In practice, it can be difficult to make an accurate diagnosis in a neonate presenting with a vascular anomaly. Vascular tumors and vascular malformations may resemble IH and, despite the classification of Mulliken and Glowacki[1], not all physicians are using the same nomenclature in diagnosing vascular anomalies. This may lead to confusion and misinterpretation of diagnosis.
Furthermore, due to recent developments with respect to diagnosis and treatment of IH, not all primary care providers are aware of the most recent guidelines. For diagnostic evaluation of IH in the perineal and lumbosacral region guidelines are even lacking. Complications, like ulceration, are sometimes not recognized as a complication requiring referral to an expert specialist.
Since propranolol has shown its efficacy in IH, more IH are treated now as compared to a few years ago and a gradual shift to more cosmetic indications is occurring.[9,10] Some primary care providers are not aware of this new treatment option for IH replacing the former 'wait and see' policy in some cases.

We hypothesized that improvement of knowledge of both parents and care providers may prevent late recognition and referral of high risk IH. Care for IH starts with parents actively seeking information and help for their child. Since parents are increasingly becoming active participants in the decision making process in clinical practice[11,12], we designed a strategy to involve parents in the discussion about the optimal care of their child ('from victim to expert').
Since it is known that parents frequently use the internet as a source for health information about their children[13,14], eHealth is a helpful tools to increase knowledge and involve parents

in the treatment of their child. Parents especially use the internet to look for complementary information, to get a second opinion, to complement the information provided by their physician or to confirm what they are already thinking.[15] Our new eHealth intervention for IH (www.aardbeivlek.nl) meets these needs (chapter 2). The e-learning module gives information about IH and via e-consultation parents can get a second opinion. Our results have shown that the use of this eHealth intervention increased parent's knowledge about (risk) evaluation of IH. In chapter 2.2 the positive attitude of parents towards the eHealth intervention for IH has been shown. The advantage for parents is that the information is always available; they can search for information when it suits them, and it is possible for them to be anonymous in their contact with professionals.[16] Chapter 2.2 has shown that parents are compliant to the advice of the dermatologist given via the second opinion of the e-consult. The e-consult may also lead to a faster referral to a specialized center.

eHealth interventions can also be used to improve the knowledge of physicians. Studies have demonstrated that online health communities can be used to exchange medical experience and knowledge and to increase knowledge of participants thereby improving adherence to guideline recommendations.[17,18] In chapter 3 we have described an example of an eHealth intervention to increase the knowledge on IH of secondary care providers. Eventually, this might lead to early recognition of IH at risk for complication development or IH that require additional diagnostic evaluation.

IH located in the perineal / lumbosacral region may be a sign of an underlying syndrome. In order to develop a guideline for diagnosis and treatment of these IH we systematically reviewed the literature (chapter 4). This new guideline will be helpful in diagnosing LUMBAR syndrome (*Lower body IH and other skin defects, Urogenital anomalies and Ulceration, Myelopathy, Bony deformaties, Anorectal malformations and Arterial anomalies, and Renal anomalies*).

2. How to improve the care for IH?

Patient-centered care instead of disease-centered care supported by eHealth

Previously, the physician-patient relation in healthcare was characterized by a disease-centered model with an emphasis on the evaluation and treatment of diseases rather than the evaluation and treatment of patients.[19,20] However, the physician-patient relation is changing and clinical care today is guided by norms of shared decision making rather than benevolent paternalism and authority of the physician.[21] Healthcare is becoming more patient-centered care instead of disease-centered care. The role of the physicians is changing "from experts who care for patients to enablers who support patients to make decisions".[22]

eHealth might be a tool to support the changing physician-patient relation in health care. The Personal Health Record (PHR) of the Hemangioma Treatment Plan (HTP) in the pediatric Skin House (www.huidhuis.nl) (chapter 3) is an example. The parents of children with IH

themselves are the administrators of the PHR of their child. Parents can authorize physicians, involved in the care of their child, to get access to the PHR. The PHR can be used by physicians to advice and monitor treatment, and to communicate about existing problems with each other, with the parents, and vice versa. Parents are able to directly get in contact with their physician and to ask questions (e-consultation). Chapter 2.1 has shown that parents can be actively involved in diagnosing and evaluating the IH of their child by using the e-learning module of www.aardbeivlek.nl. Chapter 2.2 and 3 have shown that the acceptance and usability of both eHealth interventions by parents is high.

However, eHealth tools may also have disadvantages. Information provided by online eHealth interventions is presented within a limited context. This may result into a misunderstanding of medical information and might disrupt collaborative relationships between patients and physicians.[23] The accuracy of information of eHealth tools may be overestimated by patients and in case a clinical visit is required, they may use the tool instead.[23] Furthermore, physicians and patients may lack interest in using the internet or lack confidence in their perceived skills to use the internet.[16]

However, internet is implemented in many institutions as a way to increase the efficiency of their support to patients and a way to reduce the pressure on daily work.[16] In addition, studies have shown that internet can also be used to increase the collaboration with patients, to reach a wider audience and to cut organizational costs.[24-26]

An essential element of patient-centered care is active participation of both physicians and parents. Physicians must provide sufficient information and involve parents in their decision making. The patients must understand that it is their responsibility to take joint responsibility for the decisions and therapeutic strategies agreed with their physicians, and accept the results of these decisions.[19]

For successful implementation of eHealth interventions active participation is also imperative.[27] Conceptual frameworks for the implementation of complex interventions in everyday work have been developed, like the Normalization Process Theory (NPT).[28,29] This sociological theory is based on four propositions: "the ways that people make sense of the work of implementing and integrating a complex intervention (coherence); how they engage with it (cognitive participation); enact it (collective action); and appraise its effects (reflexive monitoring)".[29] Based on the NPT, an eHealth Implementation Toolkit (e-Hit) has been developed.[30] Topics in the e-Hit are context (national and local policy culture, resources and risks), the intervention (impact on clinical practice, ease of use and cost-effectiveness) and workforce (impact on work flow; education and training and relationships between different professional groups).[30] Our pilot study in chapter 3 has shown that for successful implementation of our eHealth intervention we have to pay attention to some of the topics of the e-HIT, like context (achieving organizational/local support), intervention (resolving technical problems), and workforce (training of regional physicians).

Furthermore, the implementation of eHealth and e-learning in the care for IH will incur costs. Health insurances do already reimburse the implementation of eHealth in some fields of medicine. However, there is still no funding for the care provided through the eHealth interventions.

It is likely that eHealth for IH will probably be cost-effective. Early referral of IH at risk for complications to specialized centers will prevent irreversible damage. Furthermore, unnecessary referrals of uncomplicated IH might be prevented. Parents are more likely to get the right care in the right place. This will eventually for example result in fewer doctors consultations and less absence from work.

Organizing the care for Infantile Hemangioma

Another way of improving the organization of the care for IH is implementing the concept of organized stepped care.[31] Organized stepped care is developed for and currently used in the treatment of chronic diseases.[31] It is the concept of increasing the intensity of professional input, starting with primary care and ending with specialist care.[31] The care can be multidisciplinary and is individualized according to the preferences and progress of the patient.[31] Since IH can last for several years it can be seen as a chronic disease. Furthermore, the fact that not all IH need pharmacological treatment and treatment should be started at the right time and adequately fits exactly within the concept of stepped care.[32] Effective stepped care asks for active participation of parents which fits in the concept of patient-centered care.[31]

So how can we position the care and cure for IH in the context of organized stepped care and a patient-centered model? Nowadays most complicated IH are treated in multidisciplinary expert teams. However, in our opinion, not only specialists from different disciplines, e.g. dermatology, pediatrics, and (plastic) surgery, should be involved, but also physicians from different sectors of the health care system, e.g. primary, secondary, and tertiary care providers. Primary care providers have to inform the parent about the diagnosis of IH and should consider whether the 'watch and wait' policy is justified. Especially in the first weeks there should be a frequent follow-up of the patient.[33] Primary care providers have to assess the indication for additional diagnostic procedures, and when uncertain they should refer the patient or consult a specialist (for example via the HTP in the pediatric Skin House). Secondary care providers take up the account of the 'chronic' care for the patient with a high risk IH. They screen for associated anomalies, take care of complications like ulceration, follow the effect of treatment and evaluate the adverse effects. Tertiary care providers are responsible for more complicated cases, like non-responders to treatment, rare complications, and associated anomalies (in case of PHACE and LUMBAR syndrome). Furthermore, they may support primary and secondary care providers using a digital PHR, like the HTP of the pediatric Skin House (chapter 3). For example, it may occur that a patient with PHACE syndrome is treated for her IH by the pediatrician in a nearby hospital (secondary care) and for the follow-up of

complications of PHACE syndrome the patient is seen by a multidisciplinary expertise center in an University hospital (tertiary care).
Organized stepped care requires higher levels of cooperation, coordination and communication between specialist care, care management, primary care, and patients than generally exist.[31] Hereby, the PHR of the HTP can be a helpful tool since all physicians and the patient can view the digital file of the patient in the PHR and, if necessary, communicate with each other. The results of our pilot study (chapter 3) have shown that the PHR may be feasible, although improvements for successful implementation are required. Furthermore, the role of the primary care provider needs to be evaluated.

Conclusions

Healthcare is becoming more patient-centered in which patients play a more active role in making decisions. Our eHealth interventions (chapter 2.1, 2.2 and 3) could play an important role in facilitating this patient-centered care and in the efficient organization of the care for IH. It can be used to involve parents in the care for IH by improving their knowledge. After completing an e-learning module parents are able to correctly diagnose an IH and most parents are able to assess the risk of complications and the need for (urgent) specialized care. By using eHealth to exchange medical experience and knowledge, the knowledge of care providers can also be increased. The involvement of both parents and secondary care providers in the care for IH by using eHealth, might result in earlier recognition and presentation of high risk IH.

Future studies

Future studies have to confirm that increasing knowledge leads to early presentation, prevention of complications and adequate treatment of high risk IH. Furthermore, clinical studies should provide additional information about IH in the lumbosacral and perineal region to come to a consensus about their diagnostic approach and to define the diagnostic criteria for LUMBAR syndrome.
The PHR of the Hemangioma Treatment Plan can be used not only in the care for IH but also in the care for other (chronic) diseases. After optimizing the HTP, especially the professional part, future studies have to evaluate the effect of implementation. This will facilitate the implementation of other treatment plans in the PHR of the pediatric Skin House. Furthermore, the cost-effectiveness of the use of eHealth in the care for IH has to be investigated.
Although organized stepped care strategies are potentially an effective way to organize integrated health care services, little is known about whether stepped care programs function well in practice.

Part II Cure for Infantile Hemangioma

3. Why treating IH with atenolol instead of propranolol?

Since the discovery in 2008 that propranolol, a lipophilic non-selective beta blocker, has effect on IH, numerous articles have been published. Currently, propranolol is the most commonly used beta blocker for the treatment of IH. So far, only one randomized controlled trial has proven the efficacy of propranolol.[34] Nevertheless, propranolol is the first choice in the treatment of IH and the first consensus guideline was published recently.[9] The recommendations of the consensus guideline are mostly based on expert opinions and observational studies. Our treatment protocol of beta blockers for IH (chapter 5.2 and 6.2) was mainly consistent with this consensus guideline. The consensus guideline recommends a target dose of propranolol of 2 mg/kg/day (1 to 3 mg/kg/day) divided into 3 times daily.[9] However, the duration of treatment is not mentioned in the guideline and varies mostly between 9 and 18 months in the literature.[9,35-37]

The working mechanism of propranolol in the treatment of IH is not completely understood. It is thought to originate from vasoconstriction of capillaries and induced apoptosis of capillary endothelial cells resulting in an anti-angiogenic effect. Furthermore, the renin-angiotensin-aldosterone system (RAAS system) is suppressed leading to inhibition of proliferating endothelial progenitor cells (see chapter 1). In chapter 5 we have shown that treatment of IH with propranolol, due to its beta 2-blocking effect, can be associated with side effects, like hypoglycemia and bronchial hyperreactivity. In our clinic we had to stop treatment with propranolol in two patients suffering from severe bronchial hyperreactivity. Since a hydrophilic β1-selectieve beta blocker might not induce these side effects we subsequently initiated treatment with the β1-selective beta blocker atenolol. Both patients did not show bronchial hyperreactivity again and atenolol proved to be effective for their IH (chapter 6.1). Due to this observation we started a clinical study (chapter 6.2) to measure the efficacy and observe side effects of atenolol.

A possible explanation for the working mechanism of atenolol in IH is that it induces accelerated involution of the IH by acting on the beta-1 receptors in the kidneys and thereby decreasing renin production via the RAAS system, leading to inhibition of proliferating endothelial progenitor cells .[38] Furthermore, it has been demonstrated that the expression of β1-adrenoceptor mRNA is high in IH and IH-derived stem cells.[39] Another explanation for the effect of atenolol in the treatment of IH, may be its limited beta-2 blocking potential.[40] However, the exact working mechanism of both propranolol and atenolol remains unclear.

Side effects of beta blockers in the treatment of Infantile Hemangioma

Physicians treating children with IH should be aware of the potential risks of the treatment. Looking back at the history of the treatment of children with IH (chapter 1), propranolol is associated with relatively few side effects. Both propranolol and atenolol have been used for decades by cardiologists in the treatment of hypertension and supraventricular tachycardia, also in children. However, the treatment of IH mostly involves healthy children and therefore side effects cannot be ignored. We believe it is important to prevent the occurrence of side effects in the treatment of healthy infants with beta blockers as much as possible. Therefore, physicians should actively inform their patients about the recognition of side effects. Although most side effects will not lead to modification of the treatment, adjustment of dosage and (temporally) discontinuation of treatment should be considered.

Hypoglycemia is the most common serious side effect of the treatment of IH with propranolol. Hypoglycemia during propranolol treatment is often associated with poor oral intake, concomitant use of prednisone, infection, and/or an extremely high dose (>4mg/kg/day) (chapter 5.1 and 5.2).[9,41] Non-selective beta-blockers, like propranolol, are competitive antagonists of catecholamines at beta-1 and beta-2 adrenergic receptors. Beta-2 receptor blockade may result in hypoglycemia as a result of decreased glycogenolysis, gluconeogenesis, and lipolysis. Therefore patients taking propranolol may be vulnerable to hypoglycemia in periods of prolonged fasting or reduced oral intake. As a result of beta-1 blockade, signs of hypoglycemia such as tachycardia, sweating, and anxiety may be absent.[42] We have observed hypoglycemia in two patients treated with propranolol, of which one had adrenocortical suppression due to steroid withdrawal and the other developed hypoglycemia after a prolonged period of fasting (chapter 5.2). Due to the beta-1-selectivity of atenolol the risk of hypoglycemia is likely to be reduced. In our cohort of IH patients treated with atenolol hypoglycemia was not observed (chapter 6.2). However, since the decrease in the administration of oral prednisolon for the treatment of IH, the risk of hypoglycemia during propranolol use is small, as long as low dosages are prescribed (<4 mg/kg/day). Routine screening of serum glucose during propranolol treatment is therefore not recommended by the consensus guideline.[9]

Bronchial hyperreactivity, described as wheezing, bronchospasm, or exacerbation of asthma/bronchitis, is a well-known side effect of propranolol and results from its direct blockade of pulmonary beta-2 receptors. Therefore, bronchial asthma is a contraindication for propranolol treatment. We have observed bronchial hyperreactivity in the setting of an acute viral illness in three patients on propranolol treatment (chapter 5.2). Temporary discontinuation and even cessation of propranolol treatment was needed (chapter 5.1 and 6.1). Bronchial hyperreactivity was not seen during treatment with atenolol, not even in the patients who were suffering from bronchial hyperreactivity during propranolol treatment. This can be explained by the beta-1 selectivity of atenolol.

Bradycardia and hypotension are common side effects of the treatment with both non-selective and selective beta blockers. Cardiovascular contraindications to beta blocker treat-

ment are cardiogenic shock, sinus bradycardia, hypotension, heart block, and heart failure (chapter 5.2).[34] Symptomatic hypotension was observed in one of the patients of our cohort IH patients treated with propranolol (chapter 5.2). In our cohort treated with atenolol one patient showed asymptomatic hypotension (chapter 6.2). Both patients did not show serious signs suggestive of organ hypoperfusion (such as loss of consciousness) and treatment could be continued. Based on the pharmacodynamics of propranolol and atenolol a difference in the occurrence of hypotension is not likely.

Other reported side effects, like cold extremities, sleep disturbance, and diarrhea, are observed during both propranolol and atenolol treatment (chapter 5.2 and 6.2).[9] Mostly side effects are mild and transient.

In summary, physicians should be aware of the potential side effects of beta blocker treatment for IH. However, probably only bronchial hyperreactivity will influence the course of treatment. Due to the beta-1-selectivity of atenolol the risk of hypoglycemia and bronchial hyperreactivity is likely to be reduced when compared to propranolol.

Vigilance during the treatment with beta blockers

Although beta blocker treatment for IH seems to be relatively safe, indications should be carefully weighed against the benefits and disadvantages of the intervention on a case by case basis.

A relative contraindication for the treatment with beta blockers is children with food allergy at risk of anaphylaxis. Children with food allergy may have anaphylactic reactions needing intervention with epinephrine. Anaphylaxis in children taking beta blocker treatment, both propranolol and atenolol, may be more difficult to treat since the beta stimulating effect of epinephrine may be blocked by the beta blocker.[43] Most children treated for IH are very young and in general food allergy is not yet manifest at that age. However, clinicians should be aware of the potential effect of beta blocker treatment on the efficacy of epinephrine, especially in atopic children.

Physicians must be aware of the possible risk of topical treatment with timolol or propranolol. For superficial IH, which are cosmetically disturbing, topical timolol or propranolol, both non selective beta blockers, are sometimes initiated. However, it has been suggested that the application of topical timolol leads to systemic absorption, thereby possibly causing systemic side effects.[44] Other studies suggest that propranolol is approximately ten times more permeable than timolol across the Human Epidermal Membrane.[45] However, the clinical relevance of these findings are unclear since no systemic side effects of topical treatment with timolol or propranolol have been reported so far.[46-49]

Beta blocker treatment in patients with PHACE syndrome (*Posterior fossa malformations, Hemangiomas, Arterial anomalies, Cardiac anomalies, and Eye abnormalities*) should be carefully weighed. Most children with PHACE have a segmental IH in the face for which treatment is often indicated. PHACE syndrome is characterized by arterial anomalies of the head and

neck and acute ischemic stroke is a known complication.[50] Children with PHACE are believed to be at higher risk for stroke development in case of severe, long-segment narrowing or non-visualization of major cerebral or cervical arteries with co-existing inadequate collateral circulation (defined on magnetic resonance imaging).[51] Also other possible risk factors for stroke in PHACE syndrome have been described, such as cardiac malformations, sickle cell anemia, chromosomal aberrations, neurocutaneous syndromes, trauma, drugs or infections.[52,53] However, the exact etiology of the increased risk of stroke in PHACE syndrome is unknown.[53] Theoretically, the risk of stroke might be increased by propranolol treatment due to its blood pressure lowering effect and attenuating flow through absent, occluded, narrow, or stenotic vessels.[54] Non-selective beta blockers, like propranolol, increase the variability in systolic blood pressure to a greater degree than selective agents, and labile blood pressure is a known risk factor for stroke.[55] This is an argument to choose for treatment with a selective beta blocker, like atenolol, instead of propranolol when treating PHACE syndrome patients. Until now two cases of acute ischemic stroke in PHACE syndrome patients, during the treatment with propranolol, have been reported.[51] Both patients were concomitantly on oral steroid treatment and had severe arteriopathy. However, it has been shown that the use of propranolol does not cause cerebral hypoperfusion[53] and safe use of propranolol treatment in PHACE syndrome patients has been described as well (chapter 5.2).[50,56,57] Metry et al.[57] initiated propranolol in 32 patients with PHACE and only one patient developed a change in neurologic status during treatment (mild right hemiparesis that improved during propranolol treatment). However, given the sample size, they could not exclude the possibility that propranolol could augment the risk of stroke in their population.[57] Clinical trials assessing the safety of the use of both propranolol and atenolol are lacking. In case of a severe IH in a PHACE syndrome patient it is recommended to thoroughly investigate the possible cerebrovascular anomalies.[50,57] The potential benefits of treatment must be weighed against the risks of starting beta blocker treatment. It is recommended to start with the lowest possible dose, followed by a slow upward dosage titration under close clinical observation (inpatient hospitalization in high risk infants), and to minimize abrupt changes in systolic blood pressure by dosing 3 times daily.[9,57] In addition to the latter the use of atenolol, instead of propranolol, might be considered since atenolol increases the variability in systolic blood pressure to a lesser extent than propranolol.

In summary, physicians should be cautious when starting beta blocker treatment in patients at risk for anaphylactic reactions and in patients with PHACE syndrome.

Ethics in the treatment of Infantile Hemangioma with beta blockers

There are no Food and Drug Administration (FDA)-approved indications for any beta blocker usage (including propranolol and atenolol) in pediatric patients in the United States.[9] The same applies to the Netherlands and this means that the use of propranolol and atenolol for children with IH is off-label. Off-label use of drugs in treating the pediatric population is

not rare and ranges from 10% to 79%.[58-60] For years it was considered unethical or impossible to perform clinical trials of new drugs in children. As a result many drugs used for treating children are insufficiently documented regarding dosing, efficacy and safety. Off-label use of medications in children may often represent rational, evidence-based therapy in adults and it does not mean improper, unethical or illegal use, nor does it mean the drug is contraindicated.[54]

When treating children with off-label medication, like beta blockers for IH, ethical dilemmas are faced, like (1) providing treatment based on experience rather than evidence but in the best interest of the patient, and (2) withholding that treatment because of a lack of available safety and efficacy data.[54] We have developed multidisciplinary protocols, based on the available literature, for the treatment of IH with propranolol and atenolol. Prior to treatment we have informed parents (verbally and in writing) about the off-label use of beta blockers, and informed consent was given before the start of treatment. In this way, off-label prescription of medication in the pediatric population can be done with good intentions and in good trust, and in the best interest of the child.

Since most studies in IH are done with propranolol FDA-approval for propranolol might be achieved in near future. This could implicate that other treatment options for IH, like atenolol, will become less frequently prescribed.

Long-term outcome of the treatment with beta blockers with regard to cosmetic outcome and long-term side effects is unknown. It is unknown if the long-term outcome for cosmetic indications is favorable when compared to the natural course. Bauland et al.[61] found that there is no correlation between the growth pattern of an IH and the risk for a residual lesion. Based on these data it might be doubtful whether beta blockers will influence the residual lesion since they influence the growth of the IH.

Furthermore, data are lacking about possible side effects of long-term treatment of healthy children with beta-blockers. However, it has been reported that propranolol reduces subsequent memory for both new and previously learned emotional material in healthy adults.[60] Due to its hydrophilic character atenolol is less likely to cross the blood brain barrier and may therefore reduce the chance of this potential serious side effect. At this moment, the clinical relevance of this possible effect on memory for children treated with propranolol for IH is unclear.

Another ethical dilemma in the treatment of children with IH is that some parents "claim" treatment. They might be worried about the cosmetic consequences of the IH and they are eager for intervention. Physicians are often asked: 'could you please just cut the IH out?'. In some cases a cosmetic indication for treatment is doubtful (e.g. a large IH on the forehead). In those cases the advantages and disadvantages of treatment with beta blockers must be thoroughly discussed with the parents.

Conclusions

Every physician treating IH should be fully aware of both the effects and side effects of propranolol. In our opinion, safer alternatives, such as selective beta blockers like atenolol, must be considered. Our study does not prove that atenolol is superior to propranolol with respect to effectiveness. However, atenolol has possible advantages compared to propranolol: 1) less side effects: hypoglycemia and bronchial hyperreactivity were not observed during atenolol treatment due to its beta-1 selectivity; 2) due to its hydrophilic character atenolol crosses the blood brain barrier to a lesser extent, which reduces the risk of short- and long-term side effects of the brain; 3) atenolol increases the variability in systolic blood pressure to a lesser extent than propranolol and this might reduce the risk of stroke in PHACE syndrome patients. Another advantage of atenolol is that it has to be administered only once daily, due to its terminal half-life of 6-8 hours, which may improve patient compliance.[63,64]

For these reasons atenolol is the first choice of treatment for children with a high risk IH.

Future studies

Further clinical studies are necessary to confirm our data concerning clinical outcome and safety of atenolol treatment for IH. The safety of atenolol treatment for patients with PHACE syndrome has to be proven as well.

Since beta blockers might act via the RAAS system[38], other drugs blocking the RAAS system, like ACE inhibitors, may be effective in the treatment of IH. Indeed captopril has been described as effective in the treatment of IH.[65] However, ACE inhibitors are associated with potential serious side effects, like renal impairment or failure, especially in young children.[66] This makes ACE inhibitors an unattractive alternative in the treatment of IH. Furthermore, rapamycin, a calcineurin inhibitor, has been suggested as a treatment option for IH.[67] Rapamycin is used in the treatment of kaposiform hemangioendothelioma and has anti-vasculogenic activity.[68] The efficacy and their role in the treatment of IH has yet to be proven.

Future studies should also provide clarity about the best treatment regimen and the long term outcome of the treatment with beta blockers. Despite the recent recommendations by a consensus team, no systematic strategy currently exists to identify (long term) effects and (long term) side effects of beta blocker therapy in infants with IH.[9] Future clinical trials probably will adjust the guidelines and give clarity about cardiovascular monitoring, dosage regimen and duration of treatment. Futhermore, consensus about the position of topical beta blocker treatment is needed. Finally, another challenge is to elucidate the exact etiology of IH in order to explain the working mechanism of beta blockers, or vice versa.

Epilogue

This thesis includes primarily patient-centered research. We performed observational research instead of randomized clinical trials. We started with identifying needs of patients and problems in daily practice: eHealth was developed to involve parents in the care for IH and atenolol was used to reduce side effects. Thereby, our clinical observations tested the validity of our hypothesis for individual patients.

In the past, cases have shown to be very useful for showing the unexpected and signaling a new truth[69], like the discovery of the efficacy of propranolol for IH.[70] Our case reports and case series may not provide the strongest level of evidence, but were the "first line of evidence" of eHealth for IH and the efficacy of atenolol.[71,72] Data for future research can be generated by collecting patient data with the help of eHealth tools. The new insides provided by this thesis might lead to improvement of the care for IH and new ideas for future research.

Final conclusions

The following general conclusions can be drawn from this thesis:

- Parents were able to correctly diagnose and evaluate an IH after completing an e-learning module. E-learning by parents could result in earlier presentation and treatment of high risk IH.
- Parents showed a high compliance to the advice of the dermatologist given via our web-based eHealth intervention. This high compliance might be positively influenced by the good acceptance and usability of the eHealth intervention and might result in timely presentation and treatment of children with high risk IH in specialized centers.
- E-learning and an online PHR could be used to optimize the care for IH.
- All children with a large (≥2.5 cm) midline or segmental IH in the lumbosacral and perineal region should be thoroughly investigated in a multidisciplinary team to exclude LUMBAR syndrome.
- Propranolol, a non-selective beta blocker, is effective in the treatment of IH, but is associated with potentially harmful side effects, including hypoglycemia and bronchial hyperreactivity.
- Atenolol, a selective beta blocker, is effective in the treatment of IH and seems to be less frequently associated with potentially harmful side effects.

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8

Summary/Samenvatting

Summary

Infantile hemangiomas (IH) are common benign vascular tumors, that become visible shortly after birth, and have an unique growth pattern. Most IH have an uncomplicated course and a general 'wait and see' policy is often justified. However, 24% of the patients with IH experience complications, like ulceration, bleeding, functional impairment, life-threatening risk, or cosmetic risk of which 38% need treatment. Nowadays complicated IH can be treated with beta blockers. An active approach and diagnostic evaluation is also necessary in case of a segmental IH which can be associated with congenital malformations.
Correct initial diagnosis and timely referral of patients at risk of complications is important, since early intervention may prevent complications.

Part I Care for Infantile Hemangioma

In order to ensure timely referral of high-risk IH, it is important for parents and healthcare professionals to have knowledge about IH and risk factors for developing complications. E-learning is widely used to increase knowledge and parents frequently use the internet as information source regarding the diagnosis and treatment of the disease of their child. We have developed an eHealth intervention (http://www.aardbeivlek.nl) to teach parents about IH, consisting of an e-learning module and an e-consult. In chapter 2.1 we show that this eHealth intervention can be a helpful tool to improve the knowledge of parents. After completing an e-learning module parents were able to correctly diagnose the IH of their child and to evaluate the risk of complications, the need for evaluation by a specialist and the urgency for specialized care. Furthermore, the parents showed a high compliance (86%) to the advice of the dermatologist given via the e-consult (chapter 2.2). This high compliance might be positively influenced by the good acceptance and usability of the eHealth intervention and might result in timely presentation and treatment of children with high risk IH in specialized centers.

Since beta blockers became first choice treatment for IH, the number of patients eligible for treatment is increasing. Currently, treatment of IH with beta blockers is mainly reserved for expert centers. Waiting times at expert centers are lengthening. This, together with the sometimes long travel distances for the parents, points out the need for development of a more efficient and accessible way to provide care for children needing treatment for IH. Therefore, we have developed an eHealth intervention: the Hemangioma Treatment Plan (HTP) to treat IH in regional hospitals with online support from an academic doctor (http://www.huidhuis.nl). This HTP eHealth intervention consists of a digital interactive platform of information, treatment and expertise about IH, including an online Personal Health Record (PHR). The

aim of this HTP eHealth intervention is efficient and easily accessible care for children with IH by making disease knowledge, treatment protocols and the online PHR easily available for both parents and healthcare providers. Chapter 3 shows that the eHealth intervention is considered feasible, especially by parents. Improvement with respect to technical problems, training of regional doctors and achieving organizational support might be needed for successful implementation in the future.

Most IH do not require further examination. However, some IH are associated with underlying congenital malformations or are part of a syndrome. IH in the lumbosacral and perineal region can be associated with anomalies, like intraspinal-, urogenital-, and anorectal malformations. In chapter 4 we systematically reviewed the literature in order to develop a guideline for diagnosis and treatment of these IH. This new guideline will be helpful in diagnosing LUMBAR syndrome (*Lower body IH and other skin defects, Urogenital anomalies and Ulceration, Myelopathy, Bony deformaties, Anorectal malformations and Arterial anomalies, and Renal anomalies*)

Part II Cure for Infantile Hemangioma

In 2008, the efficacy of propranolol in the treatment of complicated IH has been discovered and propranolol became the primary treatment of choice. Propranolol is a lipophilic, non-selective beta blocker. Due to the beta-2 blockade, treatment with propranolol can be associated with side effects, like hypoglycemia, bronchial hyperreactivity, and hypotension. In chapter 5 we discuss the efficacy and safety of the treatment of IH with propranolol. Chapter 5.1 reports a case of hypoglycemia during propranolol treatment in a child on steroid maintenance therapy. In a cohort patients treated with propranolol we experienced more side effects, especially hypoglycemia and bronchial hyperreactivity, leading to (temporarily) discontinuation of the treatment (chapter 5.2).

Atenolol is a hydrophilic, selective beta-1 blocker. We hypothesized that the use of atenolol could prevent the side effects attributable to the beta-2 activity and lipophilicity of propranolol. Chapter 6.1 shows that atenolol is effective in the treatment of two patients who were suffering from bronchial hyperreactivity during propranolol treatment. In chapter 6.2 we compare a cohort IH patients treated with atenolol with the previously described cohort treated with propranolol (chapter 5.2). This study shows that the effects of atenolol seem to be similar and less frequently associated with severe side effects.

Every physician treating healthy IH patients with beta blockers should be aware of the potential harmful side effects. Due to its selectivity atenolol has advantages above propranolol,

especially with respect to side effects. Therefore, atenolol is our first choice treatment for complicated IH.

The following general conclusions can be drawn from this thesis.

- Parents were able to correctly diagnose and evaluate an IH after completing an e-learning module. E-learning by parents could result in timely referral and treatment of high risk IH.
- Parents showed a high compliance to the advice of the dermatologist given via our web-based eHealth intervention. This high compliance might be positively influenced by the good acceptance and usability of the eHealth intervention.
- E-learning and an online PHR could be used to optimize the care for IH.
- All children with a large (≥2.5 cm) midline or segmental IH in the lumbosacral and perineal region should be thoroughly investigated in a multidisciplinary team to exclude LUMBAR syndrome.
- Propranolol, a non-selective beta blocker, is effective in the treatment of IH, but is associated with potentially harmful side effects, including hypoglycemia and bronchial hyperreactivity.
- Atenolol, a selective beta blocker, is effective in the treatment of IH and seems to be less frequently associated with potentially harmful side effects.

Samenvatting

Infantiele hemangiomen (IH), ook wel aardbeivlekken genoemd, zijn goedaardige vasculaire tumoren. Ze komen voor bij ongeveer 10% van de Nederlandse kinderen. IH worden kort na de geboorte zichtbaar en hebben een specifiek groeipatroon. De meeste IH hebben een ongecompliceerd beloop en het beleid is dan ook in het algemeen afwachtend. Een deel van de IH vraagt echter om een actieve aanpak. Een kwart van de kinderen met een IH ontwikkelt complicaties en bij een derde daarvan is een interventie nodig. Voorbeelden van complicaties zijn ulceratie, bloedingen, cosmetische schade, destructie van onderliggend weefsel (bijvoorbeeld op de neus), functionele problemen of bedreiging van het leven (bijvoorbeeld door een IH in de keelholte). In het verleden behandelde men gecompliceerde IH soms langdurig systemisch met prednison, maar sinds 2008 zijn bètablokkers (propranolol) de behandeling van eerste keus. Een actieve aanpak is ook wenselijk wanneer verdere diagnostische evaluatie is aangewezen, zoals bij segmentale IH die geassocieerd kunnen zijn met andere aangeboren afwijkingen.
Het stellen van de juiste diagnose en tijdige verwijzing van patiënten met een verhoogd risico op complicaties is belangrijk, omdat complicaties bestreden of voorkomen kunnen worden door tijdige behandeling.

Deel I Zorg voor Infantiele Hemangiomen

Voor tijdige verwijzing van patiënten met een hoogrisico IH is het belangrijk dat zowel zorgverleners als ouders voldoende kennis hebben van IH en van de risicofactoren voor het ontwikkelen van complicaties. E-learning ('online opleiden') kan worden ingezet om deze kennis te vergroten. Ouders gebruiken het internet veelvuldig als informatiebron voor de diagnose en behandeling van de aandoening van hun kind. Daarom hebben wij een eHealth interventie (www.aardbeivlek.nl) ontwikkeld voor ouders met een kind met een aangeboren vaatafwijking. Dit online hulpmiddel bestaat uit een e-learning module en e-consult en leert ouders om de diagnose hemangioom te stellen en risico's op complicaties te herkennen. In hoofdstuk 2.1 laten wij zien dat deze eHealth interventie een belangrijk hulpmiddel kan zijn om de kennis van ouders over IH te vergroten. Na het voltooien van de e-learning module blijken ouders in staat te zijn om het IH van hun kind correct te diagnosticeren en kunnen zij het risico op complicaties, de noodzaak voor evaluatie door een IH specialist en de urgentie goed inschatten. Daarnaast volgen de ouders het advies, dat de dermatoloog via het e-consult geeft, veelal op (compliance van 86%) (hoofdstuk 2.2). Deze hoge compliance kan positief beïnvloed zijn door de goede acceptatie en bruikbaarheid van de eHealth interventie en kan ertoe leiden dat kinderen met een verhoogd risico op complicaties tijdig worden gezien in gespecialiseerde centra.

Sinds bètablokkers de eerste keus behandeling voor IH zijn, is het aantal patiënten dat in aanmerking komt voor behandeling flink gestegen. Op dit moment vindt de behandeling van IH met bètablokkers voornamelijk plaats in gespecialiseerde centra en met het hoge aanbod van patiënten nemen de wachttijden toe. Daarnaast moeten ouders soms lange afstanden reizen. Efficiëntere en beter bereikbare zorg voor kinderen met IH is daarom noodzakelijk. Om die reden hebben wij opnieuw een eHealth interventie ontwikkeld: het Hemangioom Behandel Plan (HBP, onderdeel van www.huidhuis.nl). Deze interventie kan gebruikt worden om IH in perifere ziekenhuizen te behandelen met online ondersteuning door een academische IH expert. Het HBP omvat een digitaal interactief platform bestaande uit een online persoonlijk medisch dossier (personal health record (PHR)) en informatie over de behandeling van IH. Het doel van deze HBP eHealth interventie is het realiseren van efficiënte en goed bereikbare zorg voor kinderen met een IH. Kennis van de aandoening, behandelprotocollen en de online PHR zijn gemakkelijk toegankelijk voor zowel ouders als zorgverleners. Hoofdstuk 3 laat zien dat met name ouders de eHealth interventie goed werkbaar vinden. Succesvolle implementatie van eHealth kan plaatsvinden na het oplossen van enkele technische problemen, training van perifere zorgverleners en het verbeteren van de ondersteuning vanuit de organisatie.

De meeste IH behoeven geen nadere diagnostiek. Sommige IH kunnen echter geassocieerd zijn met onderliggende aangeboren afwijkingen of onderdeel zijn van een syndroom. IH ter hoogte van het onderste deel van de wervelkolom en in het genitale gebied (lumbosacrale en perineale regio) kunnen geassocieerd zijn met afwijkingen van de wervelkolom, het inwendige bekken en de genitaliën (LUMBAR syndroom). In hoofdstuk 4 hebben wij de literatuur over deze IH kritische beoordeeld en zijn we tot een richtlijn voor het diagnosticeren en behandelen van deze IH gekomen.

Deel II Behandeling van Infantiele Hemangiomen

In 2008 is de effectiviteit van propranolol voor de behandeling van gecompliceerde IH ontdekt. Propranolol is een lipofiele, niet-selectieve, bètablokker. Door de beta-2 blokkade kan de behandeling met propranolol gepaard gaan met bijwerkingen, zoals verlaagde bloedsuiker (hypoglycemie), verhoogde reactiviteit van de luchtwegen (bronchiale hyperreactiviteit) en verlaagde bloeddruk (hypotensie). In hoofdstuk 5 bediscussiëren wij de effectiviteit en veiligheid van de behandeling van IH met propranolol. Hoofdstuk 5.1 rapporteert een patiënt, met prednison onderhoudsbehandeling, die tijdens de behandeling met propranolol een hypoglycemie ontwikkelde. In een cohort patiënten, behandeld met propranolol, zagen wij meer bijwerkingen, met name hypoglycemie en bronchiale hyperreactiviteit (hoofdstuk 5.2). Door deze bijwerkingen moest de behandeling met propranolol soms (tijdelijk) gestaakt worden.

Atenolol is een hydrofiele, selectieve beta-1 blokker. Wij veronderstelden dat het gebruik van atenolol de bijwerkingen van propranolol, door de beta-2 activiteit en lipofiliteit, zou kunnen voorkomen. Hoofdstuk 6.1 laat zien dat twee patiënten, die last hadden van bronchiale hyperreactiviteit tijdens de behandeling met propranolol, effectief zijn behandeld met atenolol. In hoofdstuk 6.2 hebben wij een cohort IH patiënten, behandeld met atenolol, vergeleken met het eerder beschreven cohort behandeld met propranolol (hoofdstuk 5.2). Deze studie toont dat atenolol vergelijkbaar effectief is en minder vaak ernstige bijwerkingen laat zien.

Elke arts, die gezonde IH patiënten behandelt met bètablokkers, moet zich bewust zijn van de potentieel schadelijke bijwerkingen. Door zijn selectiviteit heeft atenolol voordelen boven propranolol, met name met betrekking tot bijwerkingen. Daarom is atenolol onze eerste keus behandeling voor gecompliceerde IH.

Naar aanleiding van de bevindingen, beschreven in dit proefschrift, hebben we de volgende algemene conclusies getrokken.

- Met behulp van onze e-learning module zijn ouders in staat het IH van hun kind correct te diagnosticeren en risicofactoren te evalueren. E-learning voor ouders zou kunnen resulteren in tijdige verwijzing en behandeling van hoogrisico IH.
- Ouders volgen het advies, gegeven door de dermatoloog via onze eHealth interventie, veelal op (hoge compliance). Deze hoge compliance kan positief beïnvloed zijn door de goede acceptatie en bruikbaarheid van de eHealth interventie.
- E-learning en een online PHR kunnen worden gebruikt om de zorg voor IH te optimaliseren.
- Alle kinderen met een groot IH (≥2,5 cm) in de lumbosacrale en perineale regio moeten worden onderzocht door een multidisciplinair team om onderliggende geassocieerde afwijkingen uit te sluiten.
- Propranolol, een niet-selectieve bètablokker, is effectief in de behandeling van IH, maar kan potentieel gevaarlijke bijwerkingen geven.
- Atenolol, een selectieve bètablokker, is effectief in de behandeling van IH en lijkt minder vaak potentieel gevaarlijke bijwerkingen te geven (in vergelijking met propranolol).

9

Dankwoord
List of publications
Curriculum Vitae

Dankwoord

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List of publications

This thesis

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Curriculum Vitae

Marlies de Graaf werd op 8 februari 1981 geboren in het Academisch Ziekenhuis te Utrecht. Na het behalen van haar gymnasiumdiploma aan het St Bonifatiuscollege te Utrecht in 1999, startte zij met de studie psychologie aan de Universiteit van Maastricht. Na het succesvol afronden van haar propedeuse psychologie werd zij ingeloot voor de studie geneeskunde aan dezelfde universiteit. In haar vierde jaar heeft zij aan de Universiteit van Stellenbosch in Zuid-Afrika haar wetenschappelijke stage gelopen. Daar verrichtte zij onderzoek naar schisis en geassocieerde aandoeningen.

Na het behalen van haar artsexamen in augustus 2006, is zij gaan werken als arts niet in opleiding tot specialist op de afdeling kindergeneeskunde/neonatologie van het Meander Medisch Centrum te Amersfoort. In 2007 is zij aangenomen als arts-assistent klinisch onderwijs op de afdeling dermatologie van het Universitair Medisch Centrum Utrecht. In april 2008 is zij daar begonnen met de opleiding tot dermatoloog onder leiding van prof. dr. Carla Bruijnzeel-Koomen en dr. Vigfús Sigurdsson. In het vierde jaar van haar opleiding heeft zij een deel van haar perifere stage gelopen aan het Regional Dermatology Training Center in Moshi, Tanzania, onder leiding van prof. H. Grossmann en prof. J. Masenga.

Tijdens haar opleiding deed zij onderzoek naar het optimaliseren van de zorg voor kinderen met hemangiomen in het Centrum voor Aangeboren Vaatafwijkingen Utrecht (oprichters prof. dr. Suzanne Pasmans en dr. Corstiaan Breugem), Wilhelmina Kinderziekenhuis. De bevindingen van dit onderzoek hebben geleid tot dit proefschrift.

Sinds februari 2013 werkt zij als staflid dermatologie in het UMC Utrecht.