

CLINICAL TRIAL PROTOCOL

*Topical timolol treatment for
infantile hemangiomas: a phase II
multicentre randomized clinical
trial*

Final degree project

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Phase II, multicentre, randomized, double-blind placebo-controlled clinical trial to evaluate the efficacy and safety of topical timolol maleate 0,5% solution for the treatment of infantile hemangiomas.

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ACCEPTANCE OF THE INVESTIGATORS

I have read this protocol and I agree to coordinate this clinical trial according to all the stipulations established in it. I accept to fulfil the Declaration of Helsinki, the Good Manufacturing Practice Guide and the pertinent national regulations.

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1. ABBREVIATIONS

IHs	Infantile Hemangiomas
IH	Infantile Hemangioma
US	Ultrasound
MRI	Magnetic Resonance Imaging
HR	Heart Rate
BP	Blood Pressure
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
PE	Physical Examination
ECG	Electrocardiogram
CP	Clinical Photograph
AE	Adverse Events
GLUT-1	Glucose transporter protein-1
VEGF	Vascular Endothelial Growth Factor
bFGF	basic Fibroblast Growth Factor
ERK	Extracellular signal-related Kinases
MAPK	Mitogen-activated Protein Kinases
RRA	RadioReceptor Assays
EMA	European Medicines Agency
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
ISSVA	International Society for the Study of Vascular Anomalies
SPSS	Statistical Package for the Social Science

2. ABSTRACT

Background: Infantile hemangiomas (IHs) are common benign vascular tumours of infancy, although the best approach to their management remains unclear. IHs have a characteristic natural course, with a rapid proliferating phase followed by a spontaneous involuting phase, leaving in many cases residual lesions. The standard approach to uncomplicated IHs is “wait and see” but active intervention may be necessary since they can reach a considerable size and the aesthetic outcome is unpredictable. In addition, IHs can cause psychological distress in affected children and their parents. Recently, topical timolol has emerged as a new therapy option for treating uncomplicated IHs, but literature data are still lacking.

Objective: We aim to evaluate the efficacy and safety of topical timolol maleate 0,5% solution for treating superficial and mixed IHs.

Methods: A phase II, multicentre, randomized, double-blind, placebo-controlled, parallel-group trial will be conducted during an estimated period of 2 years. Infants between 1 and 12 months with a focal, superficial or mixed IH will be recruited and randomly assigned to placebo and treatment groups. Efficacy will be assessed by performing blinded investigator photograph scoring and blinded volume measurements with ultrasound imaging at weeks 0, 1, 2, 3, 4, 8, 12, 16, 20 and 24. Safety will be assessed by measuring timolol in serum at week 4, and measuring heart rate and blood pressure and reporting adverse events at weeks 0, 1, 2, 3, 4, 8, 12, 20 and 24. Follow up will be carried out during 6 months in order to detect rebound.

3. INTRODUCTION

3.1 Vascular Anomalies

Infantile hemangioma (IH) is a benign vascular tumour considered to be the most common tumour of infancy (1,2). It belongs to a group of lesions known as “vascular anomalies”. Based on their endothelial characteristics and clinical history, vascular anomalies can be classified into two groups: vascular tumors –whose main representative is the hemangioma– and vascular malformations (3,4). The importance of this classification lies in allowing a systematic approach to vascular anomalies that correlates predictably with clinical history, disease course, and treatment options (5).

Hemangiomas generally appear shortly after birth and undergo a proliferative phase with rapid growth, followed by a spontaneous involuting phase over several years. Histologically, the proliferating phase is distinguished by endothelial hyperplasia, and the involuting phase exhibits fibrosis and fat deposition, and ultimately subsequent regression (6).

On the other hand, vascular malformations are always present at birth, although not necessarily visible, and do not involute, growing in proportion to the child. Histologically, they do not have increased endothelial cell turnover; instead, they are structural abnormalities of the capillary, venous, lymphatic, or arterial system, depending on the vessel affected (6).

The word “hemangioma” has been used to describe a wide range of lesions, but there is now a consensus that it needs an adjective to constitute an entity (2,5). This work only focuses on “infantile” hemangiomas, but it is convenient to know that other types of hemangiomas much less frequent, such as rapidly involuting congenital hemangiomas (RICH) and noninvoluting congenital hemangiomas (NICH) exist.

3.2 Overview of Infantile Hemangioma

The current estimated incidence of IH is 4 to 10% in infants (2,5,7). The various risk factors include female gender (4:1), prematurity, low birth weight and chorionic villus sampling (1,2,8). IHs are less common in African and Asian races (8). Regarding to the location of IH, the region most commonly affected is the head and neck (60%), followed by the trunk (25%) and extremities (15%) (3).

The pathogenesis of IH is not clearly defined and the origin of hemangioma endothelial cells is still unknown, although several hypotheses exist (1). Hemangioma endothelial cells may represent a clonal expansion of cells in which a somatic mutation in genes that play a significant role in vascular growth or regulatory pathways has occurred. Another hypothesis is that abnormalities in other cell types in the hemangioma's environment such as monocytes, fibroblasts, mesenchymal cells, adipocytes and mast cells, cause normal endothelial cells to undergo aberrant proliferation. It has also been suggested that hemangioma cells could be of placental origin. Immunohistochemical analysis of hemangioma tissue has demonstrated that IHs express markers that are shared by human placenta. Glucose transporter protein-1 (GLUT-1) is expressed by IHs during all phases of its development and it is not expressed by vascular malformations or other vascular tumors and moreover, it is absent in normal vessels of the skin. Another theory is that IHs may arise from

immature endothelial progenitor cells. Despite the frequency of IHs, their pathogenesis remains incompletely understood and it appears that several mechanisms under the control of multiple genes, in addition to local effects, play a role in their development, growth and involution (1).

Morphologically, IHs are classified into superficial, deep and mixed types (1,4). Superficial hemangiomas (50-60%) are located in the superficial dermis, they are bright red in colour and their surface is finely lobulated. Deep hemangiomas (25-35%) are located in the deep dermis and/or subcutis and present as blue-purple masses with minimal or no overlying skin changes. Mixed hemangiomas (25-35%) have both superficial and deep components. The use of the terms “capillary” or “strawberry” to describe superficial IHs or the term “cavernous” to refer to deep IHs must be avoided, since there are no histologic differences between both types and this old terminology only creates confusion (3).

Based on their distribution, IHs can also be classified into focal, segmental, indeterminate and multifocal (4). Focal hemangiomas appear to arise from a single focus whereas segmental hemangiomas involve a broad anatomic region or developmental unit. In some cases it is difficult to classify lesions and they are designated as indeterminate. In multifocal hemangiomas, infants have 5 or more non-contiguous lesions and they are often associated with systemic involvement (8).

The natural history of these lesions is very useful in the diagnosis; therefore, in over 95% of the cases clinical history and physical examination are enough (3). Imaging studies or tissue biopsy with a diagnostic purpose is rarely needed. IHs generally appear within the second week of life although 30% of the cases are present at birth as precursor lesions (9). Premonitory marks include telangiectasias surrounded by a border of pallor, pink macules and blue-bruise like patches, which can even be confused with an injury from child maltreatment (1). IHs have a characteristic natural course, with a rapid proliferating phase followed by a gradual involuting phase that can last several years.

The proliferating phase is characterized by the growth of the hemangioma, showing an intense red colour during the first months, if there is superficial affectation (3). When they have a certain volume, especially deep hemangiomas, palpation reveals a firm consistency and an increase in local temperature. Regarding to the duration of the proliferating phase, Chang *et al.* in their study observed that in most IH growth occurred until 5 months of age

although it could last up to the age of 9 months (10). Deeper IH exhibited a 1-month delay in onset and also showed sustained growth when compared to superficial IH.

The involuting phase starts around 9 to 12 months of age (10). As it is a continuous process it is hard to delimit the end of the proliferation phase and the beginning of the involution. The hemangioma slowly decreases in size, turning the initial bright red coloration into a grey tonality while firm consistency decreases. In addition, small and medium telangiectasic vessels of a reddish-violet coloration become more evident. The process of involution starts in the middle of the lesion and progresses to the periphery. Ultimately, an atrophic skin with numerous telangiectasias can be seen. In deep hemangiomas a progressive reduction of the volume of the lesion will be observed. If during the proliferating phase, skin expands significantly, it is rare that it returns to normality, observing at the end of the involuting phase redundant skin as well as the presence of drainage vessels of different calibres (3).

In general terms, it is estimated that 30% of hemangiomas involute by 3 years of age, 50% by 5 years and 70% by 7 years (1,9). It is estimated that it is less than 50% the percentage of hemangiomas that regress without leaving any residual lesion (11). Therefore, involution does not mean complete disappearance of IH as it is commonly thought. Only some IHs involute completely, while many may leave residual lesions such as de- or hyperpigmentation, telangiectasias, atrophy, scarring, fibrofatty tissue and laxity (11).

With regard to complications, ulceration is the most common one, occurring in up to 10% of all IHs (1,2). Most bleeding episodes are minor and can be controlled with firm pressure. Ulceration is more common on the lip, the neck and the anogenital region, but may occur at any location; and it is also associated within large, mixed and segmental IHs (2). In addition to causing pain, ulcers increase the risk of infection and result in scarring with textural change of the affected area. Another complication is large IHs; they may distort normal tissues, interfere with normal function and lead to significant long-term complications because of residual masses. In addition, high-output congestive heart failure may complicate the course of large IHs. There is a greater risk of this life-threatening complication in visceral IHs (1). There are also regionally significant IH (2). Periocular hemangiomas are often associated with ophthalmologic complications, such as amblyopia, strabismus and astigmatism. Deep and mixed IHs located on the nasal tip can distort the underlying cartilage and leave significant fibrofatty residua. IHs located on the pinna may ulcerate and become infected and IHs on the external auditory canal may cause conductive hearing loss.

Anogenital IHs are often complicated by ulceration and infection, and affected infants often experience painful urination and defecation (1).

IHs affect mostly the head and neck, which are visible locations. Craniofacial disfigurement in general has long been recognized as associated with negative psychosocial consequences. A critical review of studies on the psychosocial impact of IHs on children and their families concluded that specific IH-related psychosocial problems appear to exist, especially in parents of children with IHs, and in children over 4-5 years of age (11). Emotions in parents due to an IH may include panic and disbelief, fear of stigmatization and name calling when their child starts school, distress, feelings of loss, a sense of isolation, and a guilt or self-blame. In addition, one study showed that children with IHs considered others valued them less compared to their healthy controls (11).

Some IHs, depending on the location or extent, may be associated with extracutaneous involvement, and must be ruled out with the appropriate radiologic studies (2). Infants with large segmental hemangiomas on the face are at risk for PHACES syndrome (Posterior fossa anomalies, Hemangiomas, Arterial anomalies, Coarctation of aorta and Cardiac defects, Eye abnormalities, Sternal clefting and Supraumbilical raphe) (4,5). In a similar way, segmental IHs in the perineal region may be associated with LUMBAR syndrome (Lower body hemangioma, Urogenital anomalies and ulceration, Myelopathy, Bony deformities, Anorectal and arterial malformations and Renal anomalies) (4,5). Laryngeal involvement with subsequent airway obstruction can occur if IH are present on the lower facial or the “beard” distribution (8). Infants with multiple cutaneous IHs constitute another group which is at risk for visceral involvement, especially the liver, making it the most common extracutaneous site. Other sites of involvement in multiple IHs include the central nervous system, lungs, kidneys and eyes (8). Raised levels of iodothyronine deiodinase have been demonstrated in large proliferative IHs, which can lead to hypothyroidism. The majority of reported cases have been associated with hepatic hemangiomatosis; consequently, it has been recommended that children with large cutaneous IH or hepatic hemangiomatosis undergo evaluation of thyroid function (1).

Most cases of IH can be diagnosed clinically, making imaging unnecessary. However, when imaging is used, it is important to choose the modality based on the specific lesion and clinical situation (5). Ultrasonography (US) and magnetic resonance imaging (MRI) are the two most efficient modalities for imaging IHs (2,5). US is used for initial screening because it is a relatively simple, non invasive, and does not require sedation in children (5). It must

include gray-scale, color Doppler, and spectral Doppler tracings to evaluate vascularity and determine types of vessels present (5). US is useful for distinguishing a deep hemangioma from other entities, because it shows high flow vessels (2). MRI is the study of choice when US has not been concluding or when documentation of the extent of larger lesions or the presence of associated anomalies is needed (2).

3.3 Management of Infantile Hemangioma

The best approach to the management of IHs remains controversial and needs to be individualized (1,3,8). Treatment will depend on the following factors: distribution of the lesion (focal/segmental), type of hemangioma (superficial/deep/mixed), phase of the lesion, size and location, presence or absence of ulceration, associated systemic involvement and psychosocial distress of the parents or child (3,8).

Systemic corticosteroids have been the mainstay of treatment for complicated IHs for several decades (12). Their mechanism of action is not entirely clear, although it is postulated to have an inhibitory effect on the production of vascular endothelial growth factor A (VEGF-A) (8). Dosage recommendations, duration of therapy and tapering schedules vary widely and no single standard exists. Initial dosages of prednisone (or its equivalent) of 2-3 mg/kg/day are most commonly used (9). Treatment is usually maintained at these doses until cessation of growth or shrinkage occurs, and is followed by a gradual taper. It is noteworthy the serious adverse effects that can occur in children receiving corticosteroids, including cushingoid facies, decreased growth rate, personality changes, gastrointestinal symptoms, hypertension and immunosuppression (12).

During decades, no alternatives were available for treating complicated IHs until the recent discovery of the beta-blocker propranolol in IH treatment. The efficacy of propranolol was accidentally discovered by Dr Léauté-Labrèze *et al.*, when in 2008 observed regression of IHs in two children who were being treated with propranolol for cardiologic diseases (13). The first child had a nasal superficial IH and when obstructive hypertrophic cardiomyopathy developed, the patient was started on propranolol. The day after the initiation of treatment, the IH changed from red to purple, and it softened. The second child had a plaque IH with subcutaneous component in part of the face involving the orbit; despite corticosteroid treatment, the IH continued to enlarge. When the patient developed increased cardiac output, treatment with propranolol was initiated. Seven days later, the IH improved in volume and colour and the child was able to open his eye spontaneously (13).

This surprising finding brought great progress in the treatment of IH. Ever since, several studies describing its therapeutic efficacy and side effects have been published, and propranolol, has been widely used off-label until relatively recently (8). In April 2014, the European Medicines Agency (EMA) approved Hemangiol® (propranolol hydrochloride oral solution) and it became the first and only drug to be approved for the treatment of “proliferating infantile hemangioma requiring systemic therapy”: 1) life- or function-threatening IH, 2) ulcerated IH with pain and/or lack of response to simple wound measures and 3) IH with a risk of permanent scars or disfigurement (14).

While propranolol has long been known and used in cardiology, its use in infants had not been properly studied and there was no pharmaceutical form approved for paediatric use. The efficacy and safety of propranolol in infants has been demonstrated in a randomized, controlled, multicentre, double blind, multidose, adaptative phase II/III study aimed to compare four regimens of propranolol (1 or 3 mg/kg/day for 3 or 6 months) to placebo (14). Treatment was administered to 456 subjects (401 Propranolol at a dose of 1 or 3 mg/kg/day for 3 or 6 months; 55 Placebo). Patients (71.3% female; 37% aged 35-90 days old and 63% aged 91-150 days old) presented a target hemangioma on the head in 70% and majority of the infantile hemangiomas were localized (89%). Treatment success was defined as complete or nearly complete resolution of the target hemangioma, which was evaluated by blinded centralized independent assessments made on photographs at week 24. The regimen 3 mg/kg/day during 6 months (selected at the end of the phase II part of the study) presented 60.4% of success versus 3.6% in the placebo arm (p value < 0.0001). 11.4% of patients needed to be re-treated after treatment discontinuation (14).

Propranolol is a non-selective beta-adrenergic antagonist, which competitively inhibits β_1 - and β_2 - receptors with the same affinity. The striking effect of propranolol on IHs can be attributed to three potential mechanisms of action: vasoconstriction, inhibition of angiogenesis and induction of apoptosis (15). They correspond to early (change in colour), intermediate (growth arrest) and long-term (tumor regression) clinical observations. Vasoconstriction is due to the β_2 inhibitory effect of propranolol, which decreases the release of the vasodilator transmitter nitric oxide. Vasoconstriction of the supplying capillaries induces a reduction of blood flow, which is associated with a visible change in colour of the hemangioma. These are early effects, and can be observed within 1-3 days after the onset of therapy. Inhibition of angiogenesis is due to a downregulation of proangiogenic factors (VEGF, bFGF and matrix metalloproteinases) and to an inhibition of proangiogenic cascades (ERK/MAPK cascade) causing the intermediate effects of growth arrest. Long-term effects of

propranolol are characterized by induction of apoptosis in proliferating endothelial cells, and result in tumor regression (15).

Propranolol has a negative inotropic and chronotropic effect on the heart. Cardiovascular events reported during clinical studies were asymptomatic. It was observed a decrease of heart rate (about 7 bpm) and of systolic blood pressure (less than 3 mmHg) following drug administration (14). Isolated cases of symptomatic bradycardia and hypotension have been reported in literature. The most serious side effect is hypoglycemia. Blood sugar decreases observed during clinical studies were asymptomatic, although related events like hypoglycemic seizure have been reported. Hyperkalemia has been reported in the literature in few patients with large ulcerated hemangioma. The most common adverse reactions (occurring in 10% of the patients) are sleep disorders, aggravated respiratory tract infections, diarrhea, and vomiting (8,14,16). Sleep disorders correspond to insomnia, poor quality of sleep and hypersomnia. Concerning the lower respiratory tract infections such as bronchitis or bronchiolitis, an aggravation of symptoms (including bronchospasm) has been observed due to the bronchoconstrictive effect of propranolol. Diarrhea was frequently reported and seems to be dose dependent (14).

When comparing the efficacy of propranolol versus corticosteroids, there are only a few studies that have compared the efficacy of these two drugs. A multicenter retrospective analysis concluded that propranolol therapy was more effective and had a better safety profile than oral corticosteroids; therefore, propranolol should be considered a first-line agent in the treatment of IH (12). Nowadays, propranolol has completely replaced corticosteroids and it has become the standard in treatment of complicated IH.

In general, it is widely accepted that active intervention is needed in function-threatening IH (ocular, ear, nasal tip, and genitalia), life-threatening IH (airway lesion), disfiguring large facial IH, ulcerated IH and when there is associated systemic involvement (8).

However, there is no consensus if treatment is necessary in the remaining majority of the cases that can be defined as uncomplicated. The natural tendency of IH towards a spontaneous regression has resulted in "passive" approach being the most widespread, only waiting for the involution to take place (3). Nowadays, a slightly different approach, which has been termed "active non-intervention", is more appropriate (1,8). It consists of education to the parents about the natural course, explanation of the treatment options and anticipatory guidance. Nevertheless, the incomplete involution in many cases, together with the therapeutic advances, is encouraging a change into an actual active approach in the management of uncomplicated IH (3).

Recently, following the example of propranolol, topical timolol has been reported to be a good therapy option for uncomplicated IH. Topical timolol maleate solution is a non-selective beta-blocker that was approved in 1978 for the treatment of glaucoma and has been safely used as a first-line therapy for pediatric glaucoma for more than 30 years (17,18). Although many reports on systemic propranolol have been published, only a few deal with the local application of beta-blockers (19–29).

In 2010, Guo and Ni first revealed successful outcomes following the use of topical timolol maleate 0,5% solution in the treatment of a 4-month-old infant with a superficial IH on the upper eyelid (19). Subsequently, timolol has been used for off-label treatment of IH and several studies have suggested its clinical efficacy and safety. However, to date, there have been relatively few studies on topical timolol treatment for IH, and the majority of these are case reports and case series.

Chakkittakandiyil et al conducted a retrospective cohort study to investigate the efficacy and safety of topical 0,5% or 0,1% timolol maleate gel-forming solution. The primary endpoint was change in the appearance of IH as evaluated using a visual analog scale (VAS). All patients except one improved, with a mean improvement of $45 \pm 29.5\%$. Predictors of better response were superficial type of hemangioma, 0,5% timolol concentration, and duration of use longer than 3 months (20,22).

Semkova and Kazandjieva described the preliminary results of a prospective study, which evaluated the efficacy and safety of topical 0,1% timolol gel for patients with IH. The patients were evaluated at 4-week intervals using the physician's Global Assessment Score (GAS), the mean change was an 85% improvement from baseline and complete clearance was achieved in four children. The treatment was more effective for plaque than for nodular lesions, and for proliferating than for involuting lesions. They concluded that timolol is a very effective and relatively safe treatment for small, localized, superficial IHs (24).

In a case series Moehrle et al treated 11 IHs with 0,5% timolol gel using a standardized occlusive dressing. In all infants topical timolol was associated with growth arrest and a reduction in redness and thickness within the first 2 weeks. Seven hemangiomas showed almost complete resolution, and four became much paler and thinner (25).

Yu et al performed a prospective study to evaluate the short-term efficacy and safety of timolol in the treatment of superficial IHs in Chinese infants. Patients were divided into two groups: treatment (101 patients) and observation (23 patients) and the results were categorized into three classes compared with baseline photographs: class 1 (ineffective),

class 2 (controlled growth) and class 3 (promoted regression). Four months following the initiation of timolol treatment, the overall response was class 1 in 8 patients (7,9%), class 2 in 36 patients (35,6%) and class 3 in 57 patients (56,4%). Among the patients in the observation group, there were 15 class 1 patients (65,2%), 7 class 2 patients (30,4%) and only one class 3 patient (4,3%) (26).

In 2013, the safety and efficacy of topical timolol has been studied in a blinded, randomized, placebo-controlled trial in the setting of small, superficial focal IHs in infants aged 5 to 24 weeks. The medication was dispensed in a ratio of 1:1 as placebo or timolol maleate 0,5% gel. Parents were instructed to apply 1 drop twice daily for 24 weeks. Efficacy was periodically assessed by performing blinded volume measurements and blinded investigator photograph scoring. The authors observed significant colour change at week 24, significant reduction in volume by >5% at weeks 20 and 24 and significant reduction in proportional growth from week 16 onward in the treatment group compared to placebo. The authors suggested that 2 drops per day application of topical timolol maleate 5% gel is safe and effective therapy for IH that does not require systemic medications (29).

In reference to timolol pharmacodynamics, no studies have been published about the subject. Timolol maleate, like propranolol, is a non non-selective beta-adrenergic antagonist, hence they might share the same mechanisms of action on IH: vasoconstriction, inhibition of angiogenesis and induction of apoptosis (15).

The specific pharmacokinetics of timolol maleate solution are not well defined. In order to reach therapeutic drug concentrations in deeper skin layers, effective drug permeation across the uppermost skin barrier, the stratum corneum, is required. One study evaluated the skin permeation of β -blockers for topical drug delivery and pointed the lipoidal pathway as the main permeation mechanism, suggesting thus, the possibility of topical treatment of IH using β -blockers (30).

Little is known about the percutaneous absorption of timolol.(18) Most of the information regarding systemic absorption of timolol solution is found in the ophthalmology literature; nevertheless, ocular mucosal absorption cannot be compared to absorption through intact skin (18). One study of the systemic absorption of topically applied 5% timolol via 0,2 mg/cm² transdermal patches indicated that plasma concentrations were undetectable in 3 of 4 patients 48 hours after application (29). This finding is reinforced by the fact that no systemic adverse reactions have been reported in previous studies (19–29) with exception of one case of sleep disturbance (in a 4-month-old infant with a 1,5x1,5 cm hemangioma) necessitating discontinuation of timolol (22). However, concern has been voiced regarding

the potential systemic absorption of topical timolol solution and it should be evaluated. Regarding to local side effects, they have only been observed in one case of mild pruritus over the lesion where timolol application was used to treat an 18-month-old female with ulcerated hemangioma associated with PHACE syndrome (21).

3.4 Justification

The treatment of IH represents a significant challenge for physicians. Propranolol is only indicated in the treatment of proliferating IH “requiring systemic therapy”. Whereas the side effect profile of propranolol is favorable in general terms, the potential risk for hypoglycemia, bradycardia and hypotension makes it difficult to justify its use for less severe IH. Timolol is a new and promising medication in the treatment of uncomplicated IH but evidence supporting its efficacy and safety comes from a few case reports and case series and only one RCT. There are yet some aspects that have not been fully elucidated and timolol should be further studied in order to become a first line agent in the treatment of uncomplicated IH.

This will be the first clinical trial conducted in Spanish hospitals to evaluate the efficacy and safety of topical timolol maleate 0,5% solution for treating IH. A more sensitive scoring system with ultrasound imaging incorporating height and depth will be introduced. US imaging will allow us to calculate the volume of IH accurately and also to study the deep component of mixed IH and observe if topical timolol can be effective in treating this type of IH.

In contrast to most of the previous studies, we are going to use a standardized occlusive dressing (VariHesive Extra Fino[®]) which will prevent the medication from leaking. This mode of application has only similarly done in one case series where growth arrest and reduction in redness and thickness was observed within the first 2 weeks, achieving the most rapid therapeutic onset of action with timolol.(25) We therefore, suspect it is the correct mode of application.

The previous RCT observed differences in response depending on the size of the lesion. Lesions $>100\text{mm}^3$ treated with topical timolol maleate gel appeared to have no significant difference in growth compared with lesions of a similar volume in the placebo group at any time point (29). This might be due to a fixed dose of topical timolol being applied regardless of lesion size. In order to prevent this from happening, we will administer different doses according to the size of IH, 1 drop of the solution per 2 cm^2 . With the application of different

doses of timolol maleate solution we aim to estimate the correct dose of use.

Concern has been raised regarding timolol safety since there are no studies of systemic absorption of topical timolol 0,5% solution when applied to intact skin. Therefore, our study will measure blood levels of timolol after application on skin in order to answer this question more precisely. In addition, since we are going to administer higher doses of timolol, it is especially important to monitor its safety. Based on what we know about the systemic absorption of other topical medications, using timolol near or on mucosal surfaces (e.g., eye, mouth, or anus), on thinner skin sites (e.g., perineum), or in areas of hemangioma ulceration may further increase systemic absorption (18).

We further want to highlight the necessity to treat even not complicated IH. The characteristic natural involution of IHs is the reason for the wide acceptance of “active-non-intervention” as the primary approach for the majority of uncomplicated IHs. Nevertheless, a therapy should be indicated since no reliable factors of the possible extent of the expansion and involution exist. In addition, the involuting phase might take years, and in more than half of the cases, there are residual findings.

To date, there are no medications approved for the treatment of uncomplicated IH. We think that timolol could be an effective and safe medication for this subset of IH and it could also be used when parents reject systemic therapy. The major advantages of topical timolol are ready availability, cost, ease of administration and minimal risk of drug-related adverse events.

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5. HYPOTHESIS

Topical timolol maleate 0,5% solution is an effective and safe medication for treating superficial and mixed infantile hemangiomas in infants between 4 weeks and 12 months.

6. OBJECTIVES

6.1 Main objective

Evaluate the efficacy of topical timolol maleate 0,5% solution compared to placebo for treating superficial and mixed infantile hemangiomas in infants between 4 weeks and 12 months.

6.2 Secondary objectives

Evaluate the safety of topical timolol maleate 0,5% solution for treating superficial and mixed infantile hemangiomas in infants between 4 weeks and 12 months.

Establish predictors of a favourable response to topical timolol maleate 0,5% solution in the treatment of superficial and mixed infantile hemangiomas in infants between 4 weeks and 12 months.

7. METHODS

7.1 Study Design

A phase II, multicentre, randomized, double-blind, placebo-controlled, parallel-group trial will be conducted during an estimated period of 2 years.

Three centres from Girona's province will take part in this trial: Hospital Universitari de Girona Doctor Josep Trueta, Hospital Santa Caterina and Hospital de Palamós.

Subjects will be randomized in a 1:1 ratio as timolol maleate 0,5% solution or placebo. Randomization will be performed by the clinical trial pharmacist using SPSS software. A code of allocation will be assigned to each patient and subjects will be attached to this code through the whole trial, having the pharmacist only access to it. Therefore, the sequence of randomization will be securely hidden under this code.

The masking will be double blind; subjects, and investigators will not know treatment allocations.

The estimated time of recruitment is 1 year. Once a patient is enrolled in the trial, the duration of the intervention will be of 6 months. Follow up extension will be carried out for another 6 months in order to detect rebound of IH. Therefore, the total estimated duration of the trial would be of 2 years.

7.2 Eligibility of Patients

7.2.1 Inclusion criteria

- Focal, superficial or mixed, infantile hemangioma diagnosed according to ISSVA classification (4)
- Not requiring systemic therapy or when parents reject systemic therapy
- Age between 4 weeks and 12 months at time of enrolment

7.2.2 Exclusion criteria

- Mucosal or deep infantile hemangioma
- Requiring systemic therapy (8,14):
 - Function-threatening hemangiomas: ocular, nasal tip, ear, genitalia
 - Life-threatening hemangiomas (airway lesion)
 - Ulcerated IH with pain and/or lack of response to simple wound measures
 - IH with a risk of permanent scars or disfigurement
 - Associated systemic involvement
- History of prior treatment for IH, including any medical and/or surgical procedures
- Evidence of short-term regression
- Patients born prematurely who have not yet reached his/her equivalent age
- Any contraindication to Timolol maleate 0,5% solution(31):
 - Hypersensitivity to any component of the product
 - Bronchial asthma or a history of bronchial asthma, or severe chronic obstructive pulmonary disease
 - Sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, cardiogenic shock

7.3 Sample Selection

A consecutive non-probability sampling will be taken on infants diagnosed of IH in any of the participating centres. This is a multicentre trial, in which three centres take part: Hospital Universitari de Girona Doctor Josep Trueta, Hospital Santa Caterina and Hospital de Palamós. The sample recruitment will take place in the dermatology and paediatrics departments of the participating centres. Parents of candidate patients will be asked to participate and an information sheet describing the trial will be given (Annex I). After written informed consent (Annex II) is obtained from the children's parents, infants will be enrolled in the trial.

7.4 Sample Size

The sample size and power calculator GRANMO was used. Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 20 subjects are necessary in first group and 20 in the second to find as statistically significant a proportion difference, expected to be of 0.47 in group 1 and 0.06 in group 2. It has been anticipated a drop-out rate of 20%. The ARCSINUS approximation was used (29).

Although IH is quite common, not all hemangiomas are sent to a dermatologic specialist. Therefore, dermatologists do not see all IH diagnosed. In order to achieve a sample size of 40 patients, we propose a multicenter trial based on the expectations of IH seen per year in the dermatology department. We expect to diagnose within a year at least 20 hemangiomas in Hospital Universitari de Girona Doctor Josep Trueta, 10 in Hospital Santa Caterina and 10 in Hospital De Palamós.

7.5 Variables and measure instruments

7.5.1 Independent variable

Being allocated in the timolol treatment group or in the placebo group.

7.5.2 Dependent variables

7.5.2.1. *EFFICACY VARIABLES*

Primary endpoint

- *Reduction of red colour of hemangioma*

In order to evaluate it a blinded physician will score digital photographs at weeks 0, 1, 2, 3, 4, 8, 12, 16, 20 and 24 using a descriptive scale of colour of the IH:

1. Bright red colour
2. Light red colour
3. Grey colour
4. Normal skin colour with or without residual telangiectasia

Efficacy will be defined as reduction of red colour of hemangioma until normal skin colour with or without residual telangiectasia.

High-resolution colour photographs will be always taken by the same investigator, using the same digital camera and tripod, at 30 cm and perpendicular to the hemangioma in the same position and conditions of light.

Secondary endpoints

- *Reduction of volume of hemangioma*

It will be evaluated by ultrasound studies at weeks 0, 1, 2, 3, 4, 8, 12, 16, 20 and 24.

Efficacy will be defined as reduction of at least 25% of volume of hemangioma compared to baseline measurements.

Ultrasound studies will be performed by an experienced musculoskeletal radiologist, with a HD15 Ultrasound System (Philips healthcare) using a lineal-array high-frequency (5-12MHz) transducer. Gray scale images of the soft-tissue abnormalities will be obtained in transvers and longitudinal planes. Lesions will be measured in three dimensions (length, width and thickness). A copious amount of gel or a gel pads will be used over the surface of the most superficial lesions and compression will be avoided in those lesions because this may result in a false thinning.

- *Rebound growth*

During follow up period rebound growth will be assessed at weeks 32, 40 and 48.

Rebound will be defined as an increase in redness using the same scale or an increase in volume of at least 25% measured by US.

7.5.2.2 SAFETY VARIABLES

- *Timolol serum level*

It will be measured at 1 month into therapy. A blood test will be performed when 1 month of therapy has been completed to all patients. Timolol concentrations will be analysed only in patients on timolol using a sensitive radioreceptor assay (RRA).(32) The radioreceptor assay is a competitive binding assay technique in which the binder is a tissue receptor (β_1 and β_2 adrenergic RRA from rat tissue). The positive substances, tracers and receptors must be prepared and loaded into a cell harvester. The samples are then washed, measured and the radioactivity is analysed on a gamma counter. These specialized systems are not available in our hospital; therefore, we will send the samples to Vall d'Hebron and they will be able to do it.

- *Heart rate and blood pressure (systolic blood pressure and diastolic blood pressure)*

They will be measured at baseline and at every visit using an automatic device (OMRON 705 validated).

Bradycardia is defined below the following limits(14):

Age	0-3 months	3-6 months	6-12 months	1 year-3years
Heart rate (beats/min)	100	90	80	70

Hypotension is defined below the following limits(14):

Age	0-3 months	3-6 months	6-12 months	1 year-3 years
Blood pressure (SBP/DBP)(mmHg)	65/45	70/50	80/55	90-55

- *Presence of systemic adverse events*

Any systemic adverse event associated with the treatment will be reported and documented by parents in a personal data collection sheet (Annex III: Safety data collection sheet)

- *Presence of local adverse events:*

Skin irritation will be evaluated by visual scoring according to the adapted Frosch and Kligman scale. (Erythema score was excluded since the IH is already red)

1. Scaling

- 0) Absent
- 1) Fine
- 2) Moderate
- 3) Severe with large flakes

2. Fissures score

- 0) Absent
- 1) Fine cracks
- 2) Simple or multiple broader fissures
- 3) Wide cracks with haemorrhage or weeping

7.5.3 Covariates

- *Gender:* male/female
- *Age*
- *Phase of IH:* proliferation/ early involution
- *Site of lesion:* head and neck/ trunk/ extremities
- *Type of IH:* superficial/mixed
- *Volume of IH*
- *Dose of timolol*

7.6 Procedures and data collection

A study scheme is provided next page in order to facilitate the comprehension of the sequence of procedures and data collection.

All infants diagnosed of IH and not requiring systemic therapy will be approached by paediatricians and dermatologists at the participating centres and will be referred to the coordinating centre (Hospital Universitari Dr Josep Trueta). In the selection visit, the inclusion and exclusion criteria will be checked, and if the patient is candidate, the option of entering into the trial will be given along with the information sheet. After written informed consent is obtained from the children's parents, infants will be enrolled in the trial. The same day randomization will take place, and patients will be allocated in the treatment group or in the placebo group.

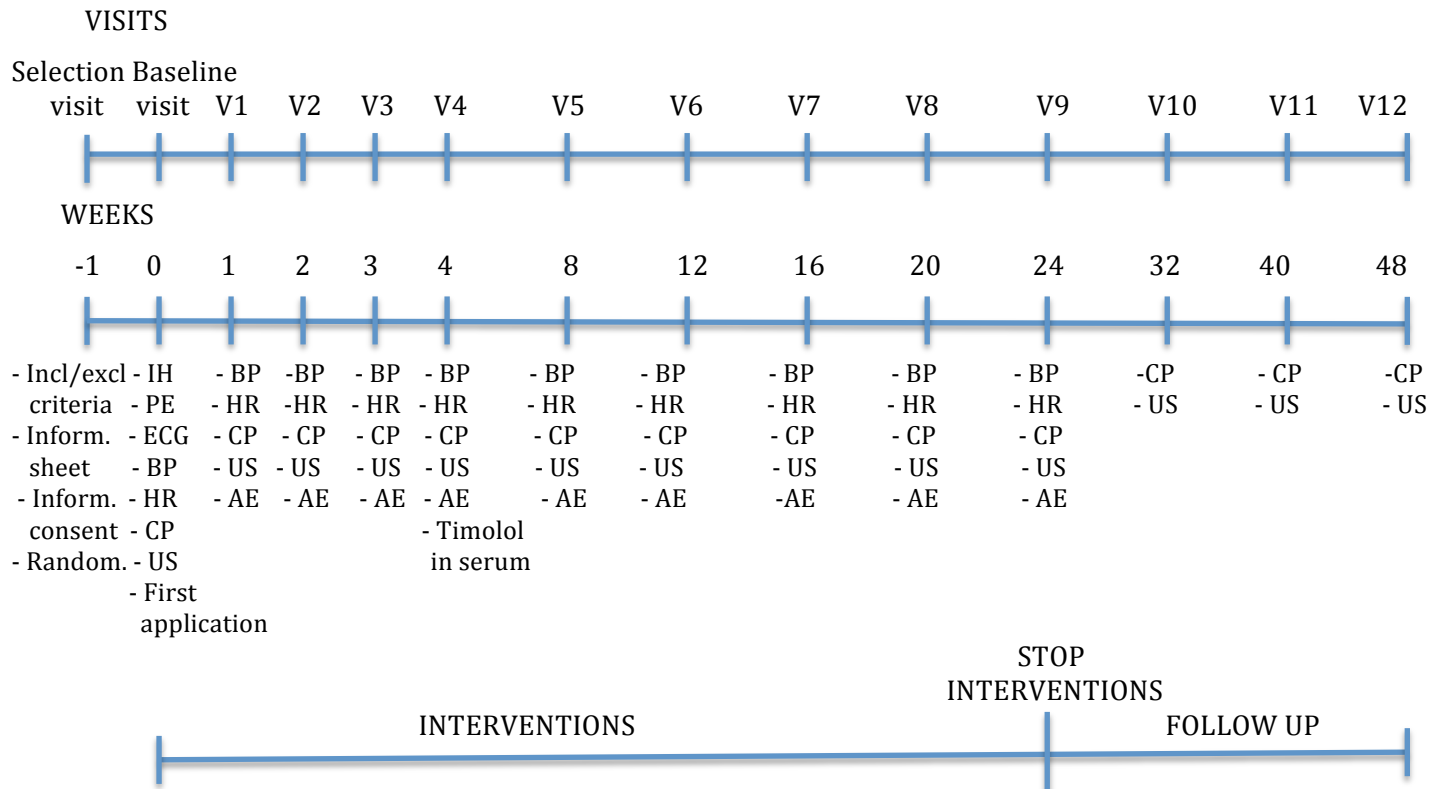
In the baseline visit, screening will include a clinical description of the IH, respiratory and cardiac physical examination (PE), an ECG, heart rate (HR) and blood pressure (BP) measurements, a clinical photograph (CP) and a basal ultrasound (US). In the baseline visit, both interventions will be dispensed in the pharmacy department by the clinical trial pharmacist and the first application of treatment will take place in the outpatient department. Heart rate and blood pressure will be measured just before application and 30 min after application. Heart rate and blood pressure measurements will be compared with age-related reference ranges. Parents will be informed about the possible adverse events (AE) associated to the treatment and a safety data collection sheet will be handled in order to document any adverse event that could occur.

Repeat blood pressure and heart rate measurements, as well as clinical photographs and US will be performed at weeks 1, 2, 3, 4, 8, 12, 16, 20 and 24 after commencement of study treatment (V1, V2, V3, V4, V5 and V6, V7, V8 and V9). In addition, any adverse event will be reported. A blood test to measure timolol will be performed once the patient completes 1 month of treatment (V4). All this information will be collected in the database.

During the trial, proliferation of the lesion, risk of ulceration, developing signs of early ulceration, or parental desire to start systemic therapy will result in withdrawal from the trial and institution of systemic medications. Subjects' withdrawal from the trial will not be replaced.

At week 24, interventions will be ceased. Post-trial follow up will be carried out by performing clinical photographs and US at weeks 32, 40 and 48 (V10, V11 and V12).

Study scheme:



7.7 Interventions

7.7.1 Treatment group

Topical timolol maleate 0,5% solution will be given to patients allocated in the treatment group. The medication used will be *TIMOFTOL[®] 5 mg/ml ophthalmic solution*. According to its safety data sheet it contains 6,8 mg of timolol maleate, equivalents to 5 mg of timolol in 1 ml. It is a clear and colourless solution. It is packed in a translucent bottle with a dropper and it contains 3 mL of solution per bottle. There is 0,05 mL in one drop, and it contains a dose of 0,25 mg of timolol.

This medication will be acquired by the pharmacy of the hospital and the clinical trial pharmacist will put a single tag for the number code of the patient on the bottle. The clinical trial pharmacist will be the only one who dispenses the medication to the patient.

Parents will be instructed to apply 1 drop of the solution per 2 cm² onto the surface of the hemangioma, to gently rub it in using a fingertip, and immediately after, to cover it using a standardized occlusive dressing (VariHesive Extra Fino[®]). Skin must have been previously washed with soap and water. This process will be performed twice a day (morning and evening)

7.7.2 Placebo group

A placebo solution will be given to patients allocated in the placebo group. It is compounded with the excipients found in the medication. The inactive ingredients are: monobasic sodium phosphate dihydrate, dibasic sodium phosphate dodecahydrate, sodium chloride, disodium edetate dehydrate, sodium hydroxide and water for injection. Benzalkonium chloride 0,01% is added as preservative.(31)

This solution will be put in an identical dispensing bottle and it will be only dispensed by the clinical trial pharmacist. Parents will be instructed to apply it in the same way.

7.8 Statistical Analysis

Data will be introduced in the database (Access 2014) and statistical analysis will be performed using SPSS software.

Categorical variables will be presented as percentages of the global group and of every centre. Continuous normally distributed variables will be presented as means and standard deviations and continuous non-normally distributed variables will be presented as medians and interquartile range.

Categorical variables will be analysed using the Chi-square test. For continuous normally distributed variables, the t-student will be used; and for continuous non-normally distributed variables, the Mann-Whitney U test will be used.

A multivariate analysis will be performed using a Cox proportional hazards model to evaluate the contribution of covariates (gender, age, phase of IH, site of lesion, type of IH, volume of IH, dose of timolol).

In this trial, the choice of analysis set will be intention-to-treat analysis. (ITT). The method of handling missing data will be last observation carried forward (LOCP).

8. ETHICAL ASPECTS

Research Ethics Committee of each participating centre will evaluate the project and approval must be obtained. Children's parents will be informed about the interventions and an information sheet will be given. Written informed consent must be obtained from children's parents before entering into the trial. AEMPS must also authorise the clinical trial.

This clinical trial follows the Ethical Principles for Medical Research Involving Human Subjects according to the Declaration of Helsinki developed by the World Medical Association. It is also carried out in line with the Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients developed by the International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use.

It will be conducted under the normative framework of these laws:

Ley 29/2006 de 26 de julio, de garantías y uso racional de los medicamentos y productos sanitarios

- *RD 223/2004 de 6 de febrero: ensayos clínicos con medicamentos*
- *RD 1591/2009 de 16 de octubre y 1616/2009 de 26 de octubre: investigación con productos sanitarios*

The information will be confidential, guaranteeing the anonymity of the patients involved in the study under the Organic Law of Data Protection 15/1999. The clinical documents will be preserved to demonstrate the validity of the study and the integrity of the collected data. The principle files must be determined at the beginning of the study, kept during the course of the trial, and preserved in conformity with the pertinent regulations.

This clinical trial has an insurance to take the responsibility towards its members if any adverse event is suffered because of our study.

As it is now recommended, the clinical trial will be registered in EUDRA-CT and also in ClinicalTrials.gov (<http://clinicaltrials.gov>)

If an ethical reflection had to be done, we should ask ourselves why placebo was given instead of a known effective medication such as propranolol. Our justification for not doing so is that propranolol is only indicated for complicated IH. We want to compare if giving a topical medication is more effective than the actual approach of uncomplicated IH, which is active-non-intervention.

9. LIMITATIONS

One study limitation is that interventions will be applied by the parent's patients under our instructions. We therefore do not know if they will do it correctly and if the exact dose we ordered will be administered. This can interfere in our results.

Although numbers are sufficient to compare blood pressure and heart rate between the groups, there are insufficient numbers to exclude rare and idiosyncratic adverse events.

In order to avoid a selection bias, losses and withdrawals will be handled with the method of last observation carried forward (LOCP). One limitation is that this method could give a biased estimate of the treatment effect and underestimate the results. Nevertheless, we prefer a conservative estimate of how well the patient would have done if they had remained in the study.

Secondary outcomes have an exploratory nature, and must be confirmed in a study ad hoc.

10. WORK PLAN

Investigators: Mireia Seguí (MS), Laura Marquès (LM)

Collaborators: Elda Balliu (radiologist, RX), paediatricians (PE) and dermatologists (DE) from Hospital Doctor Josep Trueta, Hospital Santa Caterina and Hospital de Palamós, pharmacist (PH), laboratory (LA), statistician (ST) and monitoring of the trial consultant (MC).

The trial has been designed in six phases:

1. **Coordination phase** (1 month): all staff. An organizing meeting of all the team will be held initially. It aims to check that the protocol has been fully understood and to make sure that it is going to be followed as planned. The timeline will be examined and the methods of data collection will be shared in the database, which will be set in the coordinating centre. The team will discuss among them the most suitable communication system that will be used through the trial.
2. **Field work** (18 months): PE, DE, MS, LM, PH, RX, LA. Non- probability sampling will be performed in the participating centres. Recruitment is expected to be achieved within 1 year. Once a patient is enrolled in the trial the intervention will last 6 months. Study variables will be collected.
Course of action on each patient:
 - A) Every patient diagnosed of IH not requiring systemic therapy will be approached at the participating centres and will be referred to the coordinating centre for the selection visit.
 - B) Interview at the coordinating centre: explanation again of the purposes of the study, provision of the information sheet and signature of the informed consent. Baseline screening, dispensing the medication/placebo and explanation to the parents the application.
 - C) Collection of the study variables at the coordinating centre.
3. **Follow up** (18 months): MS, LM, RX. It will be carried out after 6 months of inclusion.
4. **Data collection:** (24 months): MS, LM, RX, LA, MC. Data will be entered in the database simultaneously with the trial development. Regularly, a quality control of data will be performed in order to monitor its evolution.

- 5. Data analysis** (5 months): MS, LM, ST. Once interventions are completed, all data collected in the database will be analysed using the appropriate statistical test. After follow up is over another statistical analysis will be performed.
- 6. Publication of results** (7 months): MS, LM. The results will be interpreted and conclusions will be drawn. The corresponding articles will be written and findings will be ultimately published.

The timeline is provided in Annex IV

11. AVAILABLE MEANS TO CARRY OUT THE PROJECT

Although the recruitment will take place at three hospitals, all the procedures and data collection will be performed in Hospital Universitari de Girona Dr. Josep Trueta, which will provide the medical offices for the examination of patients. This will allow us the use of the basic materials such as office furniture and stretchers. The electrocardiograph and the devices to monitor blood pressure will also be accessible in the medical offices. The investigators will be in charge of performing the data extraction and data collection during visits.

The ultrasound system is available in the radiology department and we count on a radiologist's kindly collaboration for measuring the volume of IH. We also rely on the pharmacy department for storing and dispensing the medication. The laboratory department of Vall d'Hebron will analyse timolol concentrations in serum with the radioreceptors we will provide them.

In addition, the suitable informatics equipment and the necessary computer programs are available for the trial development.

12. BUDGET

There is a strong need to hire FROSST laboratories services for the manufacturing, preparation, packaging and shipping under the optimal conditions of the medication and placebo. The dispensing bottle of timolol maleate medication and placebo will be sold at 1,73€ per unit. It is estimated that each patient will use an amount of 15 bottles. ($1,73 \times 15 = 25,95$). And there are 40 patients ($25,95 \times 40 = 1038$). This summed up with the shipping expenses, will result in 1.100€ to hire the laboratory services.

We will also need to acquire β_1 and β_2 adrenergic radioreceptor assays (RRA) in order to measure timolol in serum. The company XenoTech has given us a quote of 3.000€ for the preparation and shipping of the RRA. To measure these RRA, it is needed specialized systems, which are not available in our hospital. Therefore, we will send the samples to Hospital Vall d'Hebron by urgent messenger services, and its laboratory services will determine the concentrations of timolol in serum. Hiring MRW messenger services will cost 19,03 € per sample. We will send in total 20 samples ($19,03 \times 20 = 380,6$ €). In addition, samples must be preserved cold; thus we will buy a dry ice kit (solid Carbon Dioxide- CO_2). (98€)

Another service worthwhile hiring is the statistician. We expect that 100 hours are needed to analyse all data, and it will be paid 35/hour ($100 \times 35 = 3.500$ €).

This project cannot be carried out without hiring monitoring of the study services. A monitor will be in charge of the quality control of data and of the elaboration of periodical reports at the beginning and end of the trial. The monitor is estimated to cost 5.000 €.

Although we already have most of the needed infrastructure for the correct development of the trial we must buy an appropriate camera and tripod for taking good quality clinical photographs.

Regarding to consumables, the occlusive dressing (VariHesive Extra Fino[®]) will be required to cover the medication. It costs 6'92 € per unit, and every patient will need approximately 4 units ($6,92 \times 4 \times 40 = 1107,2$ €)

Other necessary expenses for the correct development of the clinical trial are insurance (2.300€), AEMPS authorisation application (1.500€), and publication and diffusion expenses (1.000€)

It is very important that the three centres are well-coordinated and communicated in order to do the sample recruitment. For this reason, a coordination meeting will be held at the beginning of the trial. It will cost 200€. In addition, the investigators should go to the 21st ISSVA congress, where they will learn interesting and relevant things for the trial. It is expected to cost 3.000 €

REQUESTED BUDGET	
1. Hiring services	Euros
- Hiring FROSST laboratories for preparation, packaging and shipping under the optimal conditions of the medication and placebo	1.100
- Hiring XenoTech services for acquiring RRA	3.000
- Hiring MRW messenger services for sending samples to Hospital Vall d'Hebron	380,6
- Dry ice kit	98,49
- Hiring statistician services	3.500
- Hiring monitoring of the study services	5.000
2. Inventoriable materials	
- Canon EOS 500 Camera	700
- Tripod	50
3. Consumable materials	
- VariHesive Extra Fino [®]	1.107,2
4. Insurance	2.300
5. AEMPS authorisation application form	150
6. Publication and diffusion expenses	1.000
7. Travel and meal expenses	
- Coordination meeting	200
- Investigator meetings (21 st ISSVA Congress)	3.000
TOTAL	21.586,29

13. IMPACT OF THE PROJECT

IH is the most common tumour of infancy, with an estimated incidence of 4 to 10% in infants. Thus, if this clinical trial demonstrates the efficacy and safety of topical timolol in the treatment of uncomplicated IH, many infants might benefit of it. It can help to minimize the risk of cosmetic disfigurement and other complications and we can also prevent psychological distress for affected children and their parents. The innovation of including a more sensitive scoring system with US imaging and the measurement of the systemic absorption of topical timolol will help us in order to publish results in international journals with impact factor. We also expect that the European Medicines Agency and the AEMPS take into consideration this medication in order to be approved for the use of IH treatment.

14. ANNEXES

ANNEX I: HOJA DE INFORMACIÓN AL PACIENTE

TÍTULO DEL ENSAYO CLÍNICO

“Ensayo clínico fase II, aleatorizado, doble ciego, controlado con placebo, para evaluar la eficacia y seguridad del maleato de timolol al 0,5% en solución en pacientes con hemangioma infantil”

Versión 1 fecha 11 de Noviembre de 2014

Esto es un ensayo clínico

Los ensayos clínicos incluyen únicamente a los pacientes que deseen participar. Por favor, tómese su tiempo para llegar a una decisión.

Invitación a participar en el estudio

Este documento está destinado a los padres o tutores de los niños con hemangioma infantil, y hoy se les invita a participar en este proyecto de investigación. Su participación es totalmente voluntaria, depende de usted si decide que su hijo/a participe o no en este estudio. Le rogamos lea de forma completa este formulario de consentimiento informado y tómese su tiempo para tomar una decisión. Le animamos a hablar con su médico de cabecera, su familia y/o amigos antes de decidir. Usted puede cambiar su decisión y retirar el consentimiento en cualquier momento, sin que por ello se altere la relación con su médico ni se produzca perjuicio alguno en el tratamiento de su hijo/a.

Este estudio ha sido aprobado por el Comité Ético de Investigación Clínica correspondiente y la Agencia Española del Medicamento y Productos Sanitarios, de acuerdo a la legislación vigente, el Real Decreto 223/2004, de 6 de febrero, por el que se regulan los ensayos clínicos con medicamentos.

Introducción

Los hemangiomas infantiles (HI) son tumores vasculares benignos con una incidencia del 4 al 10% en niños. Se caracterizan por la existencia de dos fases evolutivas a lo largo de su historia natural. La fase proliferativa se caracteriza por un crecimiento llamativo de la lesión durante los primeros 6 meses de vida. La fase de involución comienza a partir del año de vida y se caracteriza por una reducción progresiva del tamaño del hemangioma, junto a un

cambio del color hacia tonos más grisáceos. En términos generales se calcula que el 30% de los hemangiomas involucionan a los 3 años de edad, el 50% a los 5 años y el 70% a los 7 años. Sin embargo, involución no quiere decir desaparición completa del hemangioma. Se estima que no llega al 50% el porcentaje de hemangiomas que se resuelven sin dejar ninguna secuela.

La tendencia natural de los hemangiomas hacia una involución espontánea ha motivado que la actitud terapéutica más extendida sea “pasiva” controlando el crecimiento y permaneciendo a la espera de que la involución tenga lugar. Sin embargo, la involución incompleta en muchos casos, junto a los avances terapéuticos, está motivando un cambio hacia una actitud más “activa” y temprana en el abordaje de estas lesiones. Recientemente, el maleato de timolol tópico ha surgido como una nueva opción para el tratamiento del hemangioma infantil no complicado con resultados prometedores.

Descripción de la investigación

Este estudio desea determinar la eficacia del tratamiento con maleato de timolol tópico en pacientes con HI. Para ello se realizará un ensayo clínico que consiste en la administración aleatoria del fármaco o placebo. La aleatorización asegura la asignación de los participantes a uno de los dos grupos, teniendo la misma probabilidad de ser asignados a un grupo o a otro.

El estudio se empezará realizando una historia clínica, una exploración física minuciosa y se medirán la tensión arterial y la frecuencia cardíaca. También se le tomará una fotografía y se le realizará una ecografía del área a tratar.

Posteriormente, se realizará la entrega del tratamiento para cada paciente. Consiste en aplicar 1 gota de la solución por cada 2 cm² en la superficie de la lesión, frotar suavemente con la yema del dedo e inmediatamente tapar el hemangioma con un apósito. La primera aplicación tendrá lugar en la consulta, para que pueda aprender la correcta aplicación.

En las siguientes semanas se realizarán las sucesivas visitas. En cada visita se medirán las constantes vitales y se hará una fotografía y una ecografía de la lesión (visitas 0,1,2,3,4,5,6,7,8 y 9) y en la visita 4 también se realizará un análisis de sangre para medir las concentraciones del fármaco.

A la semana 24, finalizará la fase de tratamiento. A continuación se llevará a cabo un periodo de seguimiento durante 6 meses. Para ello se realizarán tres visitas (visitas 10, 11 y 12) en las que se realizará una fotografía y una ecografía.

Beneficios esperados y tratamientos alternativos

Los HI regresan por si solos, pero tardan años en hacerlo. Con este fármaco, se espera en un plazo de 24 semanas máximo, una mejoría tanto del color como del volumen del hemangioma. Asimismo, cabe decir que existen otros fármacos con eficacia probada, pero con mayores efectos adversos, como es el propranolol.

Información adicional

El ensayo supone la recogida de datos contenidos en el historial médico del niño, y que están relacionados con la enfermedad. Es muy importante que la información recogida sea correcta y, de vez en cuando, puede verificarse con el historial médico. El acceso a la información personal quedará restringido al médico del estudio/colaboradores, autoridades sanitarias (Agencia Española del Medicamento y Productos Sanitarios), al Comité Ético de Investigación Clínica y personal autorizado por el promotor, cuando lo precisen para comprobar los datos y procedimientos del estudio, pero siempre manteniendo la confidencialidad de los mismos de acuerdo a la legislación vigente. Toda la información será estrictamente confidencial y su identidad nunca será revelada. Usted tiene el derecho de acceder a esta información en todo momento. El promotor cumplirá con todas las leyes vigentes en el lugar en que se hayan recabado os datos, incluida la Ley española 15/99 de Protección de Datos de Carácter Personal, es decir, el paciente tiene el derecho de acceso, cancelación y rectificación de los datos que sean considerados personales, así como a conocer la identidad del responsable del tratamiento de los mismos o su representante para lo cual deberá dirigirse a su médico de estudio.

Los datos recogidos para el estudio estarán identificados mediante un código, su médico del estudio/colaboradores podrán relacionar dichos datos con usted y con su historia clínica. Toda la información referente a usted que salga del hospital irá identificada con este código, de forma que su identidad no será revelada.

Solo se transmitirán a terceros y si procediese a otros países los datos recogidos para el estudio que en ningún caso contendrán información que le pueda identificar directamente, como nombre y apellidos, iniciales, dirección, nº de la seguridad sociedad, etc. En el caso de que se produzca esta cesión, será para los mismos fines del estudio descrito y garantizando

la confidencialidad como mínimo con el nivel de protección de la legislación vigente en nuestro país.

Seguro del estudio

El promotor del estudio ha suscrito un Seguro de Responsabilidad Civil que cubre los daños que usted pudiera sufrir como consecuencia de su participación en este ensayo, de acuerdo con la legislación vigente (R.D. 223-2004).

Otra información relevante

Cualquier nueva información referente al fármaco/procedimientos utilizados en el estudio y que pueda afectar a su disposición para participar en el estudio, que se descubra durante su participación, le será comunicada por su médico lo antes posible. Si usted decidiera, por ello, revocar el consentimiento para participar en este estudio, no se añadirán datos nuevos a la base de datos y, podrá exigir la destrucción o anonimización de todas las muestras que pudieran permanecer identificables previamente retenidas. Cuando acabe su participación recibirá el mejor tratamiento disponible y que su médico considere el más adecuado para su enfermedad.

También debe saber que puede ser excluido del estudio si el promotor o los investigadores del estudio lo consideran oportuno, ya sea porque dicha decisión médica sea la más beneficiosa para usted a juicio de su médico, por motivos de seguridad, porque así sea ordenado por las autoridades sanitarias o porque su médico considere que no está cumpliendo con los procedimientos establecidos. En cualquiera de los casos, usted recibirá una explicación adecuada del motivo que justifique su retirada del estudio.

Personas de contacto

Si usted da su consentimiento de participación en este ensayo, se le proporcionará un número de teléfono en el hospital mediante el cual puede ponerse en contacto a cualquier hora si se siente enfermo o si tiene más preguntas. Se le informará también al pediatra del niño de su participación en este ensayo y lo que esto implica, si usted está de acuerdo.

Por favor, tómese su tiempo para deliberar esta información y no dude en hacer más preguntas a su médico si cualquier cosa no esta clara. Tiene el derecho de guardar una copia de este documento después de firmarlo usted y su médico.

ANNEX II: CONSENTIMIENTO INFORMADO

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Yo, (nombre y apellidos),
como madre/padre/tutor de legal de, (nombre y apellidos).....
He podido hacer preguntas sobre el estudio.
He recibido suficiente información sobre el estudio.
He leído la hoja de información que se me ha entregado
He hablado con el Dr.

Comprendo que la participación es voluntaria.

Acepto voluntariamente que mi hijo/hija participe en el ensayo clínico y autorizo el uso de la información relacionada con el ensayo y para los fines especificados en la investigación.

Asimismo, comprendo que puedo retirarlo/la del estudio:

1. Cuando quiera
2. Sin tener que dar explicaciones
3. Sin que repercuta en sus cuidados médicos

Entiendo que recibiré una copia firmada de este consentimiento informado.

Firma del participante: _____

Fecha: _____

Nombre del médico: _____

Firma del médico: _____

Fecha: _____

ANNEX III: Safety data collection sheet

HOJA DE RECOJIDA DE POSIBLES EFECTOS ADVERSOS									
Código del paciente:									
Persona responsable:									
Marque con una cruz en la casilla correspondiente ante la aparición de cualquiera de los siguientes síntomas en el niño.									
(Semanas)	1	2	3	4	8	12	16	20	24
Trastornos del sueño									
Infecciones del tracto respiratorio									
Náuseas/vómitos									
Diarrea									
Otros:									

ANNEX IV: Timeline

Investigators: Mireia Seguí (MS), Laura Marquès (LM)

Collaborators: Elda Balliu (radiologist, RX), paediatricians (PE) and dermatologists (DE) from Hospital Doctor Josep Trueta, Hospital Santa Caterina and Hospital de Palamós, pharmacist (PH), laboratory (LA), statistician (ST) monitoring of the trial consultant (MC).

TASKS	STAFF	2015												2016												2017			
		J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A
Coordination phase	All																												
Sample recruitment	PE, DE, MS, LM																												
Interventions	PH, MS, LM																												
Follow up	MS, LM, RX																												
Data collection	MS, LM, RX, LA																												
Quality control of data	MC																												
Data analysis	MS, LM, ST																												
Publication	MS, LM																												