# Protocol for Treatment of superficial Haemangioma with Topical Timolol 0.5%

# Background and Rationale

Infantile haemangioma (IH) is the most common benign tumour of infancy, affecting 4-10% of children1 with a preponderance for female, Caucasian, and premature infants2. It is characterised by rapid proliferation during infancy3 (proliferative phase), with up to 80% reach maximal size by 3 months of age2,4,5. It then undergoes spontaneous involution over the next 1-5 years (involuting phase), with ongoing improvement up to 10 years of age (involuted phase) 4,5 often leaving a fibrofatty residuum.

Most IHs do not require active treatment as they involute spontaneously over time. However, up to 10-15% of IH require intervention during infancy because they cause complications2, such as visual and airway obstruction, ulceration, bleeding, and permanent disfigurement1,6. Following spontaneous involution, approximately 50% of the lesions will leave a blemish, and half of these will require treatment. IH can be assessed using the Haemangioma Severity Scale and the Hemangioma Dynamic Complication Scale, which assess both severity and complications of IH7. Evaluation of treatment outcomes can similarly be assessed, using tools such as the Achauer system8. This system assess improvement of IH based on changes in colour, texture and volume8.

Previous treatments for IH include high-dose oral corticosteroids, interferon, vincristine, surgical excision, and pulsed-dye laser treatment3,5,7, often in combinations. Oral propranolol is now the mainstay treatment for problematic proliferating IH4,9 since it was serendipitously discovered to cause accelerated involution of IH in 200810. Proposed mechanisms of action of propranolol include vasoconstriction10,11, induction of endothelial cell apoptosis11, inhibition of angiogenesis3, and modulation of the renin-angiotensin system3.

We have demonstrated that oral propranolol at 1.5–2 mg/kg/day is an effective and safe treatment for problematic proliferating IH4,5. Known side effects of propranolol in children include bradycardia, hypotension, hypoglycaemia, bronchodilation and sleep disturbances6,5. Complications of propranolol treatment of IH have been reported in up to 31% of patients in a large meta-analysis12, and therefore its use is restricted to problematic IHs. Indications for treatment of IH at our Vascular Anomalies Clinic (VAC) include: threat to life or function such as obstruction of the airway and orbit, ulceration, or permanent tissue distortion. These patients require treatment for an average of 14.5 months4,5. However, many of the remaining 85-90% of IH lesions can cause permanent cosmetic blemish, affecting the skin and/or leaving subcutaneous fatty residuum following spontaneous involution7,9. Earlier treatment (during the early

proliferative phase) has been shown to result in better outcomes and reduced short and long-term complications3,13.

Multiple studies have shown the effectiveness of topical propranolol14–16 and topical timolol3,14,16,17 for the treatment for superficial IHs with minimal side effects. Timolol maleate is a topical β-blocker that has been used for the treatment of glaucoma in the paediatric population for over 30 years3. Each drop of 0.5% timolol is estimated to contain 0.25mg of timolol, which is thought to be equivalent to 2 - 8 mg of oral propranolol hydrochloride18. However, it is assumed that the systemic absorption is lower than this amount when applied to intact skin15, and published data suggests that the systemic absorption of timolol gel-forming solution is less than the standard timolol maleate solution19. Despite this, there remains concerns around systemic absorption of topical β-blockers, especially when used on large IHs, those near mucosal surfaces, or when ulceration is present14. However, in a meta-analysis assessing topical timolol treatment for superficial IH, the only side effect noted was sleep disturbance in one infant16. There are also case reports of successful treatment of small ulcerated IH with topical timolol, with no side effects20,21. Research is yet to define the optimal duration of topical treatment of IH, with studies treating patients from 24 weeks up to 10 months, or until satisfactory improvement was noted16. The best outcomes for topical timolol are seen in patients with superficial IH who used the 0.5% timolol solution for a period of at least three months17.

# Hypothesis

0.5% topical timolol gel is efficacious in the treatment of superficial IHs.

# Aim

To investigate the efficacy of 0.5% topical timolol gel for the treatment of superficial IHs.

# Study Design

# This is a prospective interventional study assessing the effectiveness of 0.5% topical timolol gel in the treatment of superficial IHs.

**Duration of Study**

The study will take 3 years to recruit a sufficient sample size.

# Methods

The patients will be recruited from the Wellington sub-region and reviewed at the VAC at Hutt Hospital. The patients will be referred by midwives, general practitioners, obstetricians, paediatricians and other specialists. Patients will be entered into the study according to the inclusion and exclusion criteria below.

**Inclusion Criteria**

* Infants referred with a superficial IH(s) in the cosmetic sensitive areas (face and neck), perineum, buttock and axilla, who are not suitable for oral propranolol treatment.

**Exclusion Criteria**

* Premature infants (less than 6 weeks corrected gestational age)
* IH on or near mucosal surface such as the eye, mouth and anus
* Any single lesion larger than 90mm2 (e.g., 3x3cm)
* Multifocal IHs with a total surface area of more than 90mm2
* IH with ulceration >1x1cm
* IH with thickness >3mm
* Subcutaneous IH
* Any infants with contraindication to β-blocker use, e.g.:
  + Cardiac disease including: 2nd or 3rd degree atrioventricular heart block, bradycardia, cardiac failure, cardiogenic shock and congenital heart disease
  + Congenital hyperthyroidism
  + Hypersensitivity to any components of the medication
* Weight <3.5kg
* >10 months old
* Premature infants with a history of apnoea or chronic lung disease

**Informed Consent**

Eligible participants will be identified through the VAC at Hutt Hospital. Parents/caregivers of eligible patients will be provided with a Participant Information Sheet (Appendix 1), Patient Consent Form (Appendix 2) and Instruction of the Use of Topical Timolol (Appendix 3).

If the parents/caregivers agree for the child to participate, he/she will be asked to return the signed consent form.

Participants who identify themselves as Maori will be given the opportunity to involve whanau care services when the trial is explained and during the informed consent process. The study team recognises that Te Reo Maori is for some patients their preferred language and translation from Whanau Care Services and/or the patient's whanau will be offered where this is the case. Participants are welcome to bring whanau to all appointments.

**Data Collection**

Data to be collected prospectively includes:

Patient demographics:

* Sex
* Ethnicity
* Obstetric history (any maternal or antenatal complications)
* Gestation at birth
* Mode of delivery (vaginal delivery, forceps delivery, Ventouse delivery, or elective or emergency Caesarean section)
* Birthweight
* Requirement for and duration of stay of neonatal intensive care unit or special care baby unit admission
* Age at which IH was first noted: at birth, <1 week, 2 weeks, 3 weeks, 4 weeks if age, 1-month, 2-month or >2months of age
* Weight at time of treatment

IH characteristics:

* Location – face, neck, axilla, perineum
* Size
* Thickness
* Colour
* Presence of ulceration or bleeding and size of ulceration

**Treatment**

0.5% (5mg/ml) Timolol gel-forming eye drops (Timoptol-XE) which is a fully subsidised by PHARMAC will be used for the study. Parents/caregivers will be shown how to apply one drop of this gel to the IH twice a day. Treatment will be increased to 1 drop three times day after 2 months if there is no improvement and there are no adverse effects. Treatment is continued until complete resolution of the lesion occurs, there is no change in lesion size, colour or consistency after 3 months of continued use, until the patient reaches 12 months of age, or if any criteria for removal from the study are met.

**Safety**

Parents/caregivers will also be given written information on how to apply topical timolol gel and the potential side effects of topical timolol and asked to contact the investigators or see a doctor if they notice any of these. Any child who experiences side effects that are considered to be a contraindication to the ongoing use of the topical timolol will be removed from the study.

## Criteria for Exit from the Study

These include:

* Side effects of the treatment that are considered to be contraindications to its ongoing use
* Proliferation or no change to the size of the lesion after total of 3 months of treatment
* Development or worsening of ulceration of the IH
* Decision by the parents/caregivers of the child to stop treatment

**Documentation of results by the clinicians**

Participants will be seen in the VAC at baseline, 1 month, 3 months, 6 months, 12 months or until the lesion has stabilised or resolved. At each clinic appointment any side effects of the treatment will be recorded, heart rate and blood pressure will be measured, and assessment of size, colour, thickness and consistency of the IH will be performed. Photographs of the IH(s) will be taken at baseline, 3 months, 6 months and 12 months.

**Assessment of Results**

Before and after treatment photographs will be evaluated by an independent panel using an analogue scale of 0 (no improvement and/or deterioration) to 10 (excellent improvement). Similarly, the parents/caregivers will be asked to evaluate the results of the treatment using this analogue scale.

Treatment failure will be defined as:

* A score of “0” on the analogue scale above
* Cessation of the growth of the lesion without regression in size, or improvement in consistency or colour
* Continued growth of the lesion
* Development of ulceration of the lesion or worsening of ulceration

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