**Randomised controlled trial: Can topical timolol maleate prevent complications and reduce the need for further treatment for small superficial infantile haemangiomata in high risk areas?**

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**Abstract**

**Objective:** To define the role of topical timolol maleate (TTM) in the treatment of infantile haemangiomata (IH). We hypothesised that TTM is superior to watchful waiting for treatment of IH.

**Study design:** In this single-centre randomised controlled trial, we included all <1-year-old infants within a 13-month period presenting with small (<2cm) superficial IH located at high risk areas (i.e. tip of ears, tip of nose, eyelids, acral areas, facial areas, scalp, neck, buttocks, perineum and axilla). Patients either received 12 months of 0.5% timolol maleate solution (study group) or watchful waiting (control group). Both groups were monitored and treated similarly. The primary outcome was IH with development of complications that required additional interventions. The secondary outcomes included side effects of TTM and change in IH size.

**Result(s):** 42 children were eligible to the study. Patients who received TTM were noted to have significantly fewer complications than the control group (4.2% vs 29%, odds ratio 9.58 [95% CI 1.01 – 91.62], p=0.04). Mean IH volume percentage reduction was significantly more for the TTM group and no-TTM group at 3 months, 6 months and 12 months after study uptake.

**Conclusion(s):** TTM is an effective and safe treatment option to reduce complications, IH volume and the need for further intervention for infants with small superficial infantile haemangioma located at high risk areas.

**Introduction**

As the most common vascular tumour of infancy, infantile haemangiomata [“IH”] are major sources of concern and stress for parents around the world, affecting around 1-12.7% of all infants worldwide 2, 4, 5. They often proliferate rapidly in the first year of life and then spontaneously involute in young children 1. A small proportion of patients may develop ulceration and haemorrhage that can result in disfigurement, functional impairment, tissue necrosis and even life-threatening complications, with 10-38% warranting specialist assessment and further intervention 1, 5, 13. Ulcerations risks are reported to be at around 16%, with those located at areas of frequent mechanical trauma (that is, tip of ears, tip of nose, ends of phalanges, facial areas, buttocks, perineum and axilla) considered as higher risk 2, 12. Ulcerations cause further complications of pain, irritability, decreased appetite and sleep, secondary infection, haemorrhage, parental stress, scarring and disfigurement. Corticosteroids, propranolol and laser therapy are the current main therapeutic modalities for IH that require intervention 5, while watchful waiting with carer education and guidance is the mainstay of treatment for non-complicated IH 1, 5.

***Background***

More and more treatment options have been introduced for IH nowadays, and topical timolol maleate [“TTM”] eye drops - a non-selective beta blocker previously used for glaucoma patients - has been increasingly used across the world for eligible patients in view of its good safety profile and potential benefits 2, 3, 7, 17, 18.

Although the action of beta blockers on IH is not completely understood 3, proposed mechanisms include vasoconstriction, downregulation of vascular endothelial growth factor and basic fibroblast growth factor, and/or triggering of apoptosis 3, 4, 5. One drop of 0.5% timolol maleate is estimated to contain 0.25mg of the drug 3, 4. It is accepted that TTM does not penetrate deeply and does not show systemic effects unlike oral propranolol (with 13.7% of patients reporting systemic effects 16). Studies on systemic absorption have shown clinically insignificant timolol levels in the blood stream of patients who were given the medication topically 4, 10, 16.

Due to a lack of predictive indicators for degree of growth and involution, studies have used a wide range of values including size reduction, growth cessation, completeness of involution, visual analogue scales, haemangioma activity scores, among others. Moreover, the large variety of IH size, thickness, location, superficial versus deep components and stage of growth create further confusion for clinicians. There is currently no consensus on the optimal preparation, dose and duration for TTM use 4, 8, 10, 17, with the definite indications and benefits for TTM usage for IH still unknown and clinical significance still unclear 4, 8, 9, 17, 18. There is also a paucity of high-quality evidence on TTM, with only one single randomised controlled trial identified by guidelines, meta-analyses and systematic reviews 16, 17, 18.

Response rates of IH to TTM are quoted to range from 47% to 100% 16. While published studies have focused on the safety and optimal dosing regimen of TTM for IH, the vital question of the exact role of TTM in preventing complications and need for further intervention remains unanswered.

In this study, we aimed to evaluate the effectiveness of TTM in the prevention of complications and need for more aggressive interventions for IH located at high risk areas. We expected TTM to reduce complications and the subsequent need for further interventions for IH. 0.5% timolol maleate solution was chosen for our study based on its relative superior safety profile and availability at our unit 2, 4, 15, as well as its perceived superiority in efficacy as compared to more dilute formulations 3, 11. A treatment duration of at least 6 months was shown to be effective in prior studies 11, 15. We focused on small superficial IH of less than 20mm based on current evidence favouring a better outcome for these lesions with higher surface area to volume ratio, while study subjects of less than 1 year old were chosen due to data demonstrating more effective response in early proliferation stage IH 3, 8.

**Methods**

***Study design***

In 2016, a single-centre, prospective randomised study was initiated at United Christian Hospital in Hong Kong. Patients were enrolled over a 13-month period. Informed consents were obtained from all parents of the patients. The study was approved by the Hospital Authority Kowloon East Cluster Clinical Research Ethics Committee. All investigators were trained in study procedures and data collection by the principal investigator.

***Patients***

All patients who were referred to the Department of Paediatric and Adolescent Medicine outpatient clinic of United Christian Hospital for the management of IH from 12 October 2016 to November 2017 were recruited into the study. The inclusion criteria included Chinese patients, patients less than 1 year old at first consultation within the study period, superficial IH, IH less than 2cm in its longest diameter, and IH located in high risk areas (that is, tip of ears, tip of nose, eyelids, acral areas, facial areas, scalp, neck, buttocks, perineum and axilla).

The exclusion criteria included patients with pre-treated IH, IH with mixed or deep components, non-infantile haemangiomata such as non-involuting congenital haemangiomata (NICH), syndromal haemangiomata (e.g. PHACES syndrome), and IH that are already complicated or ulcerated at first consultation.

***Procedures***

Accepted patients were randomised by simple randomisation to either the TTM group or the no-TTM group. 0.5% timolol maleate ophthalmological solution was prescribed at 1 drop (0.25mg) per 10mm in length/width of lesion twice daily for 12 months. Patients were randomised and followed up at 1 month, 3 months, 6 months and 12 months after study uptake, with documentation of baseline patient demographics, details on TTM dosing, IH characteristics, IH complications and drug side effects. Blood pressure, respiratory rate and heart rate were performed for new cases but not routinely arranged unless ordered by the attending doctors. The lesion was then photographed by the trained investigators to document its colour, superficial and deep components and margin regularity. The width, length and depth of the IH were measured to the nearest mm and documented. Haemangioma size was measured in terms of IH volume by assuming the IH is a hemisphere.

*Intervention group (TTM group)*

TTM was initiated on parental consent to recruitment into the study. Local application of 0.5% timolol maleate solution at 1 drop (0.25mg) per 10mm in length or width of lesion for 6 months was prescribed for all patients in this group. Parents or carers were taught how to apply and gently rub the applied TTM onto the IH in a circular motion for 1 to 3 minutes. The lesion was not occluded. Follow up was arranged at 1 month, 3 months, 6 months and 12 months after initiation of the drug.

*Non-intervention group (No-TTM group)*

All treatment modalities and follow up intervals were identical to the intervention group albeit without the use of TTM.

***Outcome measures***

The primary outcome of the study was the number of IH with rapid increase in size, development of ulceration, or impairment of vital functions (e.g. breathing, vision). Any additional interventions including oral propranolol, laser therapy, corticosteroid injection or surgical excision were arranged should the aforementioned features be present.

Secondary outcomes included incidence of side effects of TTM, and the change in IH size. These were objectively measured and recorded by designated investigators on follow up clinics.

Study participants who failed to return for follow-up sessions were contacted by phone and enquired on any development of IH complications.

***Statistical analysis***

We hypothesised that TTM is superior to watchful waiting for treatment of IH. Assuming that the percentage of uncomplicated IH without need for further intervention would be 62% 13, whilst that after the use of TTM would be 99% 16, and the superiority margin 0.05, the required sample size with equal (1:1) allocation to achieve an 80% power (= 0.2) and α = 0.05 is 60 subjects (30 subjects in each group). Assuming a 5% dropout rate, we planned to recruit a total of 64 subjects into this study, with 32 subjects in the TTM group and 32 subjects in the no-TTM group. The primary and secondary analyses of all outcomes followed the intention-to-treat principle.

Patient characteristics were presented as frequencies and percentages for categorical data and means (SD) or medians (IQR) for continuous data.

Statistical analysis was performed using the Statistical Package SPSS 23 software. Categorical data was compared using the chi-square test or the Fisher Exact test (for cells less than 5), and odds ratio (OR) with 95% confidence interval (C.I.) was calculated. Continuous variables were compared using the independent t test or Mann-Whitney U test. For the secondary outcome, percentage changes over time at 3 months, 6 months and 12 months after study uptake were compared. Flat IH and subjects who defaulted the 12-month follow-up session were excluded from the secondary outcome analysis, while missing data were kept the same as the last measured size. IH were excluded from the secondary outcome analysis upon receiving additional treatment. A two-sided p-value of ≤ 0.05 was considered significant.

**Results**

**Figure 1: Trial profile**

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| **Table 1: Patient and IH demographics** |
|  | ***TTM group*** | ***No-TTM group*** | ***Mean difference (95% C.I.)*** | ***P value*** |
| **Number of patients** | 24 | 17 |  |  |
| **Gender*** Male
* Female
 | 9 (38%)15 (62%) | 5 (29%)12 (71%) |  | 0.60 |
| **Mean age** at study uptake (months) | 2.89 ± 1.91 | 2.67 ± 1.76 | 0.22 (-0.93 to +1.37) | 0.51 |
| **Site of IH*** Face
* Scalp
* Acral
* Neck
* Buttocks
 | 731211 | 102221 |  |  |
| **IH size** at study uptake (mm3)  | 153.2 ± 184.1 | 99.44 ± 120.0 | -53.77 (-155.2 – 42.76) | 0.29 |

Of the 43 children under 12 months old who were included in the study, 1 patient was ineligible due to beta blocker usage prior to study uptake. Of those eligible, parents of 1 patient declined consent to enter the study. 24 patients were randomised into the TTM group and 17 patients in the no-TTM group (Figure 1). The intragroup analysis for gender and age was similar among the two groups, but there were more acral lesions for the TTM group (Table 1).

The primary outcome comparing IH complications (Table 2a, 2b) showed significant results for the TTM group (1/24 [4.2%]) as opposed to the no-TTM group (5/17 [29%]; OR 9.58 [95% CI 1.01 – 91.62]; p=0.04\*], with complications including ulceration (5/41 [12%]) and 1 showing rapid progression of >150% per month increase in volume (1/41 [2.4%]). No patients suffered from impairment of vital functions due to IH complications. Propranolol and/or laser treatment were indicated and offered to the parents of all 6 patients. No patients required corticosteroid injection or surgical excision of IH. Analysis of mean IH volume percentage change for TTM group and no-TTM group from 0 to 3 months, 6 months and 12 months all showed significant results (Table 2c, p = 0.028, 0.035 and 0.015 respectively). No side effects were reported from any of the patients in the TTM group.

**Table 2: Outcomes**

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| **Table 2a: Primary outcome: number of complicated IH for TTM and no-TTM groups** |
|  | **TTM group** | **No-TTM group** | **OR** | **95% CI** | **P value** |
| **Complications** | 1 (4.2%) | 5 (29%) | 9.58 | 1.01-91.62 | 0.04 |

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| **Table 2b: List of complications and treatment offered for TTM and no-TTM groups** |
|  | **TTM group** | **No-TTM group** |
| **Complications*** Ulceration
* Rapid size increase *(Defined as IH with more than 150% per month increase in size)*
* Impaired function
 | 1 (4.2%)00 | 4 (23.5%)1 (5.9%)0 |
| **Treatment modality offered*** Systemic propranolol
* Laser treatment
* Corticosteroid injection
* Surgical excision
 | 01 (4.2%)00 | 4 (23.5%)3 (17.6%)00 |

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| **Table 2c: IH volume and percentage changes at 0, 3, 6 and 12 months for TTM and no-TTM groups** |
|  | **TTM group** | **No-TTM group** | **Mean difference (95% C.I.)** | **P value** |
| **Percentage change in haemangioma volume (in %)** |
| **3 months** | -1.71 ± 93.13 | 76.2 ± 107.9 | 77.91 (+9.098 - +146.7) | 0.028 |
| **6 months** | -17.01 ± 111.7 | 72.55 ± 131.1 | 89.56 (+6.529 - +172.6) | 0.035 |
| **12 months** | -65.36 ± 48.33 | 28.38 ± 116.4 | 93.75 (+21.32 - +166.2) | 0.015 |

**Discussion**

“To treat or not to treat?” - this has always been a question for clinicians in the management of patients presenting with IH located at high risk areas. While experts have agreed on the IH locations that pose higher complications risks, the lack of reliable signs to predict ulceration, disfigurement and other complications creates a treatment dilemma between watchful waiting (with anxiety and risks for complications) versus early treatment with systemic agents (with risks of discomfort and treatment side effects). The emergence of TTM offers hope to resolve this dilemma.

To the best of our knowledge, this is the first randomised controlled trial in showing reduction in complications in small superficial high risk IH, as well as the first Chinese randomised controlled trial on timolol for the treatment of IH. The first reported use of TTM for IH was in 2010 by Guo and Ni 7, though the medication has been used for ophthalmology as an eye drop for over 30 years even in the paediatric population 2. Since then TTM has gained a lot of popularity as a safe alternative to conservative treatment and has been used with mixed results for deep, large or even ulcerated haemangiomata in certain studies 4.

In particular, a randomised placebo controlled trial of 41 patients by Chan et al 3 has shown a significant reduction in size, colour and proportional growth in the TTM group compared with the placebo group for lesions of <100mm3 volume, albeit slower than oral propranolol. It concluded that 2 drops per day application of 0.5% timolol maleate gel is a safe and effective treatment for IH that do not require systemic treatment, and that further studies may be needed to investigate “factors such as site-dependent efficacy […], duration of treatment and age-group-specific data”.

A review by Khan et al. 17 - the first meta-analysis and systematic review focusing on TTM for IH treatment - analysed 31 studies of 691 patients in total who used TTM for IH, concluding that the various response rates using clinical scores and photograph comparisons showed significant improvement with a 91% resolution rate for a mean treatment duration of 4.11 months in pooled meta-analysis, with the quality of evidence being low to moderate. The study suggested adequately powered randomised controlled trials and less biased studies using clearer diagnostic criteria and validated outcome measures.

Although earlier studies have suggested that TTM will improve IH progression, the results of our single-centre randomised controlled trial help to shed light on the vital question of which IH should be treated with TTM. We have demonstrated that for patients of less than 12 months old with superficial small IH of less than 20mm in longest diameter located over high risk areas, the use of TTM successfully reduced complications and the need for further interventions.

The early regression of IH demonstrated by our treatment group illustrates the effectiveness of TTM. Regression at this early age is not typical of that of the natural course of IH 8. The early regression and the reduction in the need for further systemic interventions demonstrated by our study, highly supports the use of TTM for patients less than 1 year old with superficial IH located at high risk areas.

Our study also supports the safety of TTM, with no reported side effects in a period of 12 months from all subjects. Most other studies have also demonstrated minimal adverse effects 2, 3, 7, 8, 10, 15, 16, 17. Larger studies have pointed out that potential side effects include local irritation, rebound growth and sleep disturbance, while evidence for the safety of TTM for ulcerated, mucosal and large IH are lacking 8, 9, 11, 17. It must however be stressed that TTM usage must be supported with diligent follow-up and carer education. “However, any potential long term side effects of timolol is not investigated in this study”.

While a recent retrospective multi-centered study by Puttgen et al. 8 suggested TTM could prevent potential permanent disfigurement and is indicated for superficial IH without aggressive growth or threat of functional impairment, our study suggests that early TTM treatment has the additional benefit of reducing the need for further intervention on these IH, thereby sparing young patients from the risk of systemic beta blockers and more invasive procedures. However, as the above study focused on low risk patients only, the clinical significance of the study in treatment for IH that have minimal risks of complications from watchful waiting is debatable.

The strengths of the study include the prospective design, randomisation, photo documentation of IH, objective outcome measurements, presence of an observation group, and significant power from the results. However, despite the sample size being sufficient for a statistically significant primary outcome, it may not be adequate for detection of rare but significant adverse effects. Although the outcomes are significant, objectively defined and professionally assessed whenever possible, blinding would further reduce selection bias. A longer follow-up period beyond 1 year old may also be of benefit to monitor the IH until regression sets in, as well as to assess for any rebound IH growth upon cessation of TTM 15. Preliminary phone contact of patients 2 years after our study has shown no rebound growth of IH.

This study demonstrates that 0.5% topical timolol maleate solution is an effective and safe treatment option for patients of less than 1 year old presenting with small superficial infantile haemangioma of less than 2cm in largest diameter located at high risk areas to reduce complications, IH volume, and the need for further intervention. These findings should help paediatricians, dermatologists and family doctors by shedding light on the treatment dilemma for the management of IH, specifically on the use of TTM for this group of patients.

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