Topical Timolol Maleate 0.5% for Infantile Hemangioma: Its Effectiveness Compared to Ultrapotent Topical Corticosteroids – A Single-Center Experience of 278 Cases

Retno Danarti  Lukman Ariwibowo  Sunardi Radiono  Arief Budiyanto

Department of Dermatology and Venereology, Faculty of Medicine, Universitas Gadjah Mada/Dr. Sardjito Hospital, Yogyakarta, Indonesia

Lesion size was measured from scaled photodocumentation with the software program ImageJ®. Results: There were significant differences in IH size after treatment with timolol maleate 0.5% solution compared with ultrapotent corticosteroids (p < 0.001) and timolol maleate 0.5% gel compared with ultrapotent corticosteroids (p < 0.001). There was no significant difference in IH lesions after treatment with timolol maleate 0.5% solution versus gel (p = 0.744). Conclusion: Timolol maleate 0.5% solution and gel were significantly superior to topical ultrapotent corticosteroids in size reduction of superficial IH.

Introduction

Infantile hemangioma (IH) is the most prevalent benign vascular tumor in children [1, 2]. It is estimated to occur in about 4–10% of infants in the first year of life [2]. The disease is often present at birth, although it may not be noticed until a few weeks later when the lesion begins its proliferative phase. During the first 9 months of age, the lesion grows rapidly, then stabilizing. Involution is complete in most children by 4 years of age [3]. The majority of lesions are benign, regress spontaneously, and do
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not require treatment, but no reliable indicators predict the degree and rate of involution. As the lesions may be a significant source of parental distress, cosmetic disfigurement, and morbidity, appropriate management and optimizing patient outcomes are needed [4, 5].

Previous topical treatment for hemangiomas has included ultrapotent topical corticosteroids, which are most effective for superficial, small, and uncomplicated hemangiomas [6]. However, it has at least a 27% nonresponse rate and is associated with skin hypopigmentation and atrophy [6–8]. Another topical treatment was imiquimod 5% cream, which is effective and safe in the treatment of superficial and mixed hemangiomas [9–11]. However, it has crusting and scars as potential side effects [11, 12].

Topical β-blockers are a promising alternative in the treatment of IHs since they can improve the therapeutic efficacy and reduce systemic adverse effects of IH [13]. Likewise, systemic propranolol with a starting dose of 2 mg/kg/day has also been reported as safe and effective in the treatment of IH [14, 15].

Topical timolol has been reported to inhibit the growth and promote regression of superficial IHs [10, 16–33]. However, concerns have been raised regarding systemic absorption because it is 4–10 times as potent as propranolol [34], and there are reports of sleep disturbances [17]. This study is aimed to evaluate the effectiveness of ultrapotent topical corticosteroids, 0.5% timolol maleate solution and gel for superficial IH.

Patients and Methods

For further details, see the supplementary materials (for all online suppl. material, see www.karger.com/doi/10.1159/000448396) [6, 7] (fig. 1).

Results

The study included 278 children (203 female and 75 male infants, ratio 2.7:1) with superficial IH who had adequate follow-up. Characteristics of the sample of this

Fig. 1. Flowchart of the Research Methods.
study are shown in Table 1. There were no significant differences in sex, age of patients, age of IH lesions’ appearance, birth weight, gestational age, maternal age, and location of the lesion between the groups. Within 6 months following the initiation of treatment with ultrapotent topical corticosteroids, timolol 0.5% solution and gel, diminution of color of the hemangiomas were noted in all children (fig. 2–4). A significant decrease in size area (mm²) of the lesions after 6 months of treatment between the three groups had a significant statistical difference (Table 2). Analyses with the Kruskal-Wallis test and post hoc Mann-Whitney test showed that timolol maleate 0.5% solution was better in size reduction of IH lesions compared with ultrapotent corticosteroid (p < 0.001); timolol maleate 0.5% gel was better than ultrapotent corticosteroid (p < 0.001), and no significant differences were seen between timolol maleate 0.5% solution and timolol maleate 0.5% gel (p = 0.744). No children were excluded from our study, and no adverse effects were recorded during the treatment period.

Table 1. Clinical characteristics and treatment

<table>
<thead>
<tr>
<th>Sex, n</th>
<th>Ultrapotent topical corticosteroid (n = 92)</th>
<th>0.5% timolol maleate solution (n = 93)</th>
<th>0.5% timolol maleate gel (n = 93)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>25 (27.17)</td>
<td>24 (25.81)</td>
<td>26 (27.96)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>67 (72.83)</td>
<td>69 (74.19)</td>
<td>67 (72.04)</td>
<td></td>
</tr>
<tr>
<td>Age at initial treatment, months</td>
<td></td>
<td></td>
<td></td>
<td>0.695</td>
</tr>
<tr>
<td>Median</td>
<td>5.5</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1 – 11</td>
<td>1 – 11</td>
<td>1 – 11</td>
<td></td>
</tr>
<tr>
<td>Age at IH lesion appearance, months</td>
<td></td>
<td></td>
<td></td>
<td>0.040</td>
</tr>
<tr>
<td>Median</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1 – 2</td>
<td>1 – 2</td>
<td>1 – 2</td>
<td></td>
</tr>
<tr>
<td>Mean birth weight ± SD, g</td>
<td>3,198±207.5</td>
<td>3,253±199.9</td>
<td>3,350±203.6</td>
<td>0.047</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td></td>
<td></td>
<td></td>
<td>0.888</td>
</tr>
<tr>
<td>Median</td>
<td>38</td>
<td>38</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>36 – 40</td>
<td>36 – 40</td>
<td>36 – 40</td>
<td></td>
</tr>
<tr>
<td>Mean age of the mother ± SD, years</td>
<td>28.3±3.8</td>
<td>28.6±3.0</td>
<td>28.8±3.4</td>
<td>0.151</td>
</tr>
<tr>
<td>IH location, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>82 (89.13)</td>
<td>84 (90.33)</td>
<td>83 (89.25)</td>
<td></td>
</tr>
<tr>
<td>Torso</td>
<td>6 (6.52)</td>
<td>6 (6.45)</td>
<td>6 (6.45)</td>
<td></td>
</tr>
<tr>
<td>Extremities</td>
<td>4 (4.35)</td>
<td>3 (3.23)</td>
<td>4 (4.30)</td>
<td></td>
</tr>
</tbody>
</table>

Figures in parentheses are percentages. Age at initial treatment/gestational age: analyses with the Kruskal-Wallis test. Age at lesion appearance: analyses with the Kruskal-Wallis test; post hoc analyses ultrapotent corticosteroid vs. timolol maleate 0.5% solution p = 0.386, ultrapotent corticosteroid vs. timolol maleate 0.5% gel p = 0.072, timolol maleate 0.5% solution vs. timolol maleate 0.5% gel p = 0.010. Birth weight: analyses with the Kruskal-Wallis test; post hoc analyses ultrapotent corticosteroid vs. timolol maleate 0.5% solution p = 0.303, ultrapotent corticosteroid vs. timolol maleate 0.5% gel p = 0.015, timolol maleate 0.5% solution vs. timolol maleate 0.5% gel p = 0.143.

Table 2. Comparison of the IH area (mm²) after treatment for 6 months

<table>
<thead>
<tr>
<th>n</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrapotent topical corticosteroid (group A)</td>
<td>28</td>
<td>-21.87 (-392.99 to 241.27)</td>
</tr>
<tr>
<td>0.5% timolol maleate solution (group B)</td>
<td>29</td>
<td>26.06 (-96.37 to 517.41)</td>
</tr>
<tr>
<td>0.5% timolol maleate gel (group C)</td>
<td>30</td>
<td>21.18 (0.18 to 727.57)</td>
</tr>
</tbody>
</table>

Analyses with the Kruskal-Wallis test. Post hoc Mann-Whitney test: ultrapotent corticosteroid vs. timolol maleate 0.5% solution p < 0.001; ultrapotent corticosteroid vs. timolol maleate 0.5% gel p < 0.001; timolol maleate 0.5% solution vs. timolol maleate 0.5% gel p = 0.744.
Until 6 months of topical treatment with ultrapotent topical steroids or timolol maleate 0.5% solution and gel, no patients were changed to systemic treatment.

**Discussion**

IHs typically grow in early infancy followed by spontaneous involution. The initial proliferative phase begins in the first 2 weeks of life, then followed by a plateau phase. The involution phase starts at after the first year and is continued until 4–6 years [35, 36]. In our study, the initial age for the first appearance of IHs was 4 weeks, compatible with previous studies [17, 36]. There were no significant statistical differences in birth weight between the three groups, and the subjects had no history of low birth weight, incompatible with the study of Ho et al. [37]. The ages of initial treatment in our study were between 5.5 and 6 months, i.e. in the proliferative phase. Treatment in the proliferative phase would give the most satisfactory results, while the lesion is growing, hence there is potential to halt development, reduce the size of the lesion, reduce its effect on surrounding structures, and finally improve the cosmesis of patients [5]. Xu et al. [38] found that the therapeutic response of children who started treatment with propranolol ointment between the ages of 0–3 versus 3–6 or 6–10 months had a statistically significant difference. Yu et al. [32] noted that patients treat-
ed with timolol before the age of 6 months had higher lesion regression rates than those treated between 6 and 12 months. Topical timolol 0.1% gel was more effective in the proliferation than the involution phase [26]. In all of our subjects, topical ultrapotent corticosteroids and topical timolol 0.5% were associated with growth arrest and a reduction in redness and thickness within the first 4 weeks of treatment. The limitation of our study was that we did not measure IHs without treatment (or placebo), hence we could not assess spontaneous regression.

The pathogenesis of IH is not completely understood and is likely multifactorial [39–43]. Increased risk factors for IH include Caucasian race, female gender, prematurity, low birth weight, and being the product of multiple gestations [44–46]. In our study, the female:male subject ratio was about 2.7:1, in accordance with previous studies [37, 47]. Two hundred and seventy-eight subjects only had a solitary lesion, similar to the study of Boye et al. [36]. IH lesions in our patients were predominantly located on the head and neck, similar to some studies [17, 48, 49].

From the literature search, no published report can be found, comparing treatment of IH with ultrapotent topical corticosteroids, timolol maleate 0.5% solution, and timolol maleate 0.5% gel. Chakkittakandiyil et al. [17] conducted a retrospective cohort study to compare 0.1 and 0.5% timolol maleate gel using a visual analog scale, based on photographic documentation of each patient’s lesion. A study from Ariwibowo and Danarti found that timolol maleate 0.5% solution was better than corticosteroids (mometasone furoate and triamcinolone cream) in reducing the size of superficial IH [50].

Ultrapotent topical corticosteroids have antiproliferative and vasoconstrictive effects which may play a role in treating superficial IH [51, 52]. The 2005 series of 35 patients of Garzon et al. [6] showed that 35% had a good response to clobetasol propionate 0.05% or betamethasone dipropionate 0.05%, but another 38% had only a partial response.

Regression of IHs treated using 0.5% timolol solution and gel in our studies occurred earlier than spontaneous regression which is generally not observed before the age of 9–12 months. However, this promising result needs to be confirmed in prospective randomized control trials on topical β-blocker administration for IHs which should address dose, duration, and mode of application. There was no adverse effect reported from our study. Adverse reactions due to topical corticosteroids for IH have been reported by Pandey et al. [8]. The topical use of β-blockers for IH was mostly safe; however, there were reports of sleep disturbance [17] and mild pruritus [20]. Our 6-year study of IH treatment in a tertiary referral hospital supports the safety and effectiveness of 0.5% timolol maleate solution and gel compared with topical ultrapotent corticosteroids.

Conclusions

The surface area reduction of superficial IHs treated with timolol maleate 0.5% solution and gel was greater than in those treated with topical ultrapotent corticosteroids. Neither group experienced any adverse effect.

Acknowledgments

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Statement of Ethics

The study had been approved by the Medical and Health Research Ethics Committee of the Medical Faculty, Universitas Gadjah Mada.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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