COMPARATIVE STUDY BETWEEN SYSTEMIC AND TOPICAL PROPRANOLOL IN TREATMENT OF INFANTILE HEMANGIOMAS

By

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ABSTRACT

Background: Hemangioma is one of the most common benign infantile vascular tumors. Corticosteroids were used for a long time for treatment. However, it was associated with many complications. Thus, propranolol was introduced and become the first line of treatment. Initially, it was used orally, and then the topical use gained a wide acceptance. However, no study compared the effectiveness and safety profile of topical when compared to systemic propranolol therapy.

Objective: Comparison between systemic and topical propranolol in treatment of infantile hemangioma (IHs).

Patients and Methods: The study was carried out at Al-Azhar University Hospitals (Pediatric Surgery Unit) during the period from May 2015 to February 2016. Forty infants with hemangioma were included, and divided into two equal groups: The first group received systemic propranolol therapy; while the second group received topical propranolol therapy. Patients were evaluated before starting the treatment by full history taking and clinical examination. The treatment started in systemic group by 1mg/kg/day divided into three doses; then increased and maintained on 2mg/kg/day till the fifth month, then gradually withdrawn by the end of the sixth month. In topical group, 1mg/kg/day was prepared in an oily base received in daily two divided doses till the end of the sixth month. Outcome was compared between both groups.

Results: Topical propranolol therapy was effective as the systemic therapy with low side effects and even better effectiveness. However, the difference was statistically non-significant. In addition, both groups were comparable as regards patient demographics and hemangioma characteristics.

Conclusion: Topical propranolol was effective and safe as that or even better than systemic propranolol therapy. However, the small number of the studied subjects prevented the globalization of our results.

Keywords: Hemangioma, propranolol, infantile, systemic, topical.

INTRODUCTION

Potential risk factors for development of infantile hemangiomas included prematurity and low birth weight (<1500 grams) (Solman et al. 2014 and Fowell et al., 2016). Clinically, hemangiomas usually exhibit an initial phase of progressive growth followed by a plateau period followed by spontaneous regression, and 70% regress completely by the age of 7 years (Awadein and Fakhry, 2011). Regarding site of IHs, greater than 60% of IHs occur on the face, head and neck (Haggstrom et al., 2007).

Although benign, the involvement of the eyelids, nasal tip, lips and ears can also endanger respiration, feeding and
vision or cause irreversible disfigurement. Bleeding, ulceration and subsequent infection can arise in up to 20% of cases. Early recognition and treatment of critical IHs help in prevention or minimizing complications (Chamlin et al., 2007).

Before 2008, the usual treatment of IHs included systemic and intraregional injection of corticosteroids (Greene, 2008) and alpha-interferon (Fonseca Junior et al., 2008). These treatments were associated with significant side effects. The first report of successful use of propranolol (non-selective β-adrenergic receptor blocker) in treatment of IHs appeared in 2008 (Leaute-Labreze et al., 2008). Since that time, propranolol gained wide acceptance in treatment of IHs. Thus, it had become the first-line therapeutic agent in the management of IHs (Solman et al., 2014).

The mechanism of action of propranolol remains largely unknown. However, it appears to induce clinical improvement through inducing vaso-constriction, apoptosis and decreasing production of pro-angiogenic factors (Storch and Hoeger, 2010). Compared to previous treatment (systemic corticosteroids), propranolol had been shown to be associated with better and faster response with fewer adverse effects (Fuchsmann et al., 2011 and Balma-Mena et al., 2012).

Reviewing literature, no large clinical studies exist to support any highly effective topical therapy in the management of hemangiomas (Maguiness and Frieden, 2010). Topical remedy with corticosteroids and imiquimod has been reported. Topical robust corticosteroids can enhance skinny superficial heman- giomas however not their deep component. Unfavorable reactions encompass atrophy and hyper pigmentation (Emir et al., 2015).

**PATIENTS AND METHODS**

The study was carried out at Al-Azhar University Hospitals (Pediatric Surgery Unit) during the period from May 2015 to February 2016. In the present work, we included infant and children aged from 1 to 10 months with IH needing treatment defined as functional impairment, aesthetic disfigurement, and if they were ulcerated. The study protocol was approved by local ethical committee of Al-Azhar Faculty of Medicine, and an informed consent was obtained from the legal guardian, after full explanation of the study. Patient confidentiality and right to withdraw at any time were ascertained.

Before initiation of therapy, a full history taking and clinical examination were performed, and all infants were checked for chest wheeze, any heart murmur, heart rate, blood pressure, and results for heart rate and blood pressure were compared to reference normal values for age and sex.

Significant deviation of heart rate (HR) or blood pressure (BP) from average values, presence of chest wheeze or heart murmur were considered as contraindications of initiation of therapy, and such infants were excluded from the study. In addition, a routine cardiologic consultation was done for every patient with exclusion of infants with significant cardiac morbidity. Other exclusion criteria included history of allergy or hypersensitivity to beta-blockers, second or third degree atrioventricular block,
heart failure, severe bradycardia, asthma or bronchial obstruction, and previous use of systemic corticosteroids or other beta-blocker.

In both groups, we started the treatment in a dose of 1mg/kg/day for two weeks, then elevated to 2mg/kg/day for the next two weeks, and maintained as such till the end of fifth month provided that there was no cause to stop treatment, or marked improvement was noted, then tapered gradually till the stoppage of the drug. Each week, there was a decrease of 0.5mg/kg/day, till the last week of 0.5mg/kg/day. Thus, all children were followed up for 6 months started at the time of initiation of therapy. Oral propranolol was administered at three divided doses daily, while topical drug was administered at two divided doses daily. All infants were monitored by heart rate and blood pressure measurements at baseline, 1, 2 and 3 hours after receiving the initial dose, and after dosage increments for the first 3 hours, and monthly till the end of the study. Any dropped infants were excluded and other equivalent numbers with same inclusion criteria were included.

**Clinical assessments:** The researchers judged the changes of hemangioma were compared through the photographs. A twenty cm visual analog scale with a range extending from -10 to 10 was used to represent the overall change to the hemangioma. Ten represented increase of the initial size of hemangioma to a double of its original size and extent at the start of treatment, 10 represented no change, and +10 stands for complete disappearance of the IHs (Ho et al., 2007). The response was classified as complete response (CR) when there was complete resolution, Partial response was defined as any size reduction, or change in color or consistency that did not meet the CR criteria. No response was defined as no change between photographs and/or growth during in treatment. Visual analogue scales of 8 to 10 were considered as complete response; grades 1-7 as partial response; 0 grade as no response and -10 to -1 as worsening (progression) of the condition. Adverse reactions were reported by the parent's or noted by the investigators.

**Statistical analysis of data:** The collected data were organized, coded and statistically analyzed by the means of statistical package for social science version 22 (IBM® SPSS® Inc, USA; 2013). Categorical data were presented as frequency and percent distribution; while numerical data were presented as mean and standard deviation. Statistically significant results were considered with a P value less than or equal to 0.05 (confidence level of 95%).

**RESULTS**

The present study included 40 infants presented with infantile hemangioma. They were divided into two equal groups according to the protocol of treatment; 20 for systemic oral propranolol and 20 for topical propranolol. The majority of infants were females (80.0% of systemic group and 70.0% of topical group), their ages ranged from 1 to 8 months; and there was no significant difference between systemic and topical groups (4.15±1.87 vs. 3.60±1.56 months respectively). The majority of lesions were in the upper limb (55.0% in systemic group and 45.0% in topical group), and there was no
significant difference between systemic and topical groups. The type of the lesion was superficial in 50% of studied infants, and 50% had a mixed lesion (superficial and deep). There was no significant difference between systemic and topical groups. Ulceration of the lesion was presented in 20% and 10% of the systemic and topical groups respectively. The initial size of the lesion ranged from 6 to 21 squared centimeters, and there was no significant difference between systemic and topical groups (13.80±4.53 vs. 15.70±4.52 respectively Table 1).

As regards outcome, the VAS ranged from -5 to 10. It was smaller in systemic group when compared to topical group (5.20±3.63 vs 6.45±3.36 respectively). However, the difference was statistically non-significant. These results were reflected on the overall response, either complete or partial, in 15.0%, 70.0% in systemic group; compared to 50.0%, 40.0% in topical group. No response was reported in 10.0% and 5.0% in systemic and topical groups respectively. The lesion continued to grow in one patient (5%) in each group. Side effects were reported in 20% (4 infants) in systemic group, and 2 patients (10.0%) in the topical group. These were in the form of hypotension, difficult breathing, bradycardia, skin irritation and diarrhea in 5% for each side effect compared to diarrhea and skin irritation in 5% for each side effect. No significant difference was found between systemic and topical groups (Table 2).

Table (1): Patient demographics and lesion characteristics.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Systemic group</th>
<th>Topical group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (month) (mean±SD)</td>
<td>4.15±1.87; 1-8</td>
<td>3.60±1.56; 2-7</td>
<td>0.32</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 4(20.0%)</td>
<td>6(30.0%)</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td>Female 16(80.0%)</td>
<td>14(70.0%)</td>
<td></td>
</tr>
<tr>
<td>Site</td>
<td>Face 3(15.0%)</td>
<td>4(20.0%)</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>Upper limb 11(55.0%)</td>
<td>9(45.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trunk 4(20.0%)</td>
<td>3(15.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lower limb 2(10.0%)</td>
<td>4(20.0%)</td>
<td></td>
</tr>
<tr>
<td>Type</td>
<td>Superficial 9(45.0%)</td>
<td>11(55.0%)</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td>Mixed 11(55.0%)</td>
<td>9(45.0%)</td>
<td></td>
</tr>
<tr>
<td>Ulceration</td>
<td>4(20.0%)</td>
<td>2(10.0%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Initial size (cm²)</td>
<td>13.80±4.53; 6-20</td>
<td>15.70±4.52; 7-21</td>
<td>0.19</td>
</tr>
</tbody>
</table>
Table (2): Outcome in studied infants.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups</th>
<th>Systemic group</th>
<th>Topical group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS (Mean ±SD)</td>
<td></td>
<td>5.20±3.63; -5: 9</td>
<td>6.45±3.36; -4: 10</td>
<td>0.27</td>
</tr>
<tr>
<td>Response</td>
<td>CR</td>
<td>3(15.0%)</td>
<td>10(50.0%)</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>PR</td>
<td>14(70.0%)</td>
<td>8(40.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>2(10.0%)</td>
<td>1(5.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Worse</td>
<td>1(5.0%)</td>
<td>1(5.0%)</td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td>None</td>
<td>15(75%)</td>
<td>18(90.0%)</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>Bradycardia</td>
<td>1(5.0%)</td>
<td>0(0.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
<td>1(5.0%)</td>
<td>0(0.0%)</td>
<td></td>
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<tr>
<td></td>
<td>Difficult breathing</td>
<td>1(5.0%)</td>
<td>0(0.0%)</td>
<td></td>
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<tr>
<td></td>
<td>Skin irritation</td>
<td>1(5.0%)</td>
<td>1(5.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>1(5.0%)</td>
<td>1(5.0%)</td>
<td></td>
</tr>
</tbody>
</table>

Figure (1): Infantile hemangioma before treatment.

Figure (2): Infantile hemangioma after topical treatment of the previous child.

Figure (3): Infantile hemangioma before treatment.

Figure (4): Infantile hemangioma after systemic treatment of the previous child.
DISCUSSION

Infantile hemangiomas (IHs) are the most common type of benign vascular tumor (Awadein and Fakhry, 2011). It usually runs a self-limiting course. However, some may result in residual telangiectasias or redundant skin. Thus, early intervention is indicated for IHs (Buckmiller et al., 2009). Systemic corticosteroids were used to be the first-line remedy for IHs. However, long term use tends to result in severe side effects, like high blood pressure, adrenal cortical insufficiency, and delayed growth (Maturo and Hartnick, 2010). Other
treatment remedies include laser ablation, interferon-alpha, vincristine and surgical excision. However, there are reserved as second- or third-line of treatment for IHs because of their inconsistent efficacy, side effects and potential for toxicity (Nguyen and Fay, 2009).

Leaute-Lamberer et al. (2008) successfully treated IHs with oral propranolol, and found tumor color regression in all instances soon after the treatment. Big medical studies have confirmed the efficacy and safety of propranolol. However, Leaute-Labreze et al. (2015) reported that diarrhea, sleep-disorder, bronchitis and cold hands and feet were side effects of systemic treatment. The use of topical beta-blockers for treatment of IHs become more common due to its readily availability for sensitive areas such as the eye, ease of use and favorable efficacy and safety (Coppens et al., 2009). However, the comparison between systemic and topical propranolol therapy were not yet investigated.

In general, the presently available evidence suggested that propranolol was extra successful within the treatment of IHs than other modalities, with a great efficacy in every type and locations of IH (Price et al., 2011, Drolet et al., 2013, Hermans et al., 2013 and Sagi et al., 2014). These studies reported a response rate of over 90%. Our results were in accordance with many studies and meta-analyses, and showed that propranolol was effective in 87.5% of patients.

The clinical and demographic characteristics of our patients were consistent with the ones described formerly inside the literature, with a predominance of females, with ages ranged from 1-11 months (Haggstrom et al., 2007).

Interestingly, results of the present study revealed that topical propranolol treatment of IHs was as effective as systemic propranolol therapy or even more efficacious, and had a better safety profile although the differences were statistically non-significant. The effective treatment of topical propranolol in the present study confirmed previous study done by Kunzi-Rapp (2012) who reported that, even in low-weight preterm infants, topical propranolol was effective and devoid of local or systemic side effects. Topical propranolol was also effective for IH beyond the proliferative phase, as is the case for oral propranolol treatment. They added, if propranolol is applied topically onto the skin at the hemangioma two times a day, it accumulates near the vessel walls without metabolic changes. Thus, topical applications seem to be advantageous.

Our outcomes revealed that the beta-blocker acts transdermally in the hemangioma. Topical propranolol was comparable to those reported by Wang et al. (2012) who reported that propranolol gel is effective and safe in treating IHs, especially for superficial hemangiomas in different sites.

In addition, Chen et al. (2015) reported that, for the first time to their knowledge, the apparent efficacy of topical nano-propranolol hydro gel in treatment of superficial IHs, and it was efficacious and tolerable. Meanwhile, no extreme damaging outcomes were located in their patients. Our study was superior than this work in inclusion of all
superficial and deep IHs with comparable success rate between both studies. Furthermore, topical β-blockers are used for the management of IHs, although there are no commercially available forms of topical propranolol (Xu et al., 2012).

Mouhari-Toure et al. (2013) reported fast regression of childish hemangioma with 2% propranolol ointment in female patients. Additionally, an in vivo study demonstrated that topical delivery of propranolol can offer higher drug concentrations in local tissues than oral and intravenous administration (Hao et al., 2011). This may be due to the fact that the drug in the tissues was slowly cleared, and significant amounts of the drug were still present at 24 h after topical application (Torres-Pradilla and Mand Baselga, 2014).

In conclusion, results of the present study confirmed previous results of the efficacy and safety of propranolol local treatment for infantile hemangioma. Over the previous studies, the present one was superior in comparison results of such local treatment in comparison to systemic treatment by the same drug. However, the small number of the studied subjects prevented the globalization of our results. Thus, it is recommended to examine the situation on a large scale of patients. However, the shift from oral (systemic) propranolol to topical (local) form is recommended, due to its convenience and effectiveness with higher safety profile.

REFERENCES


دراسة مقارنة بين تناول البروبرانولول بالطريقة الجهازية وإستخدامه بطريقة موضعية في علاج الوحمات الدموية لدى الأطفال

إبراهيم محمود الصياد - محمد محمد شاهين - سيد أحمد الهادي عبد المنعم - أحمد طلعت مهروس
أحمد الشامي - سمير جودة - زكريا مهران

قسم جراحة الأطفال، وقسم الأمراض الجلدية (4)، كلية طب الأزهر

خلفية البحث: تمثل الوحمات الدموية أكثر أورام الجهاز العصبي لدى الأطفال، وقد استخدم الكورتيزون في علاج الوحمات الدموية لمدة طويلة. ونظراً لزيادة الأعراض الجانبية لتلك المواد، فقد أسفر البحث العلمي عن نجاح البروبرانول في علاج ورم مع النقص من معظم الأعراض الجانبية للكورتيزون، واستخدام البروبرانول عن طريق الفم ما أدى إلى ظهور بعض الأعراض الجانبية غير مرغوب فيها مثل بطء ضربات القلب وانخفاض ضغط الدم، بالإضافة إلى عدم تجربة المرضى والاستمرار في العلاج بهذه الطريقة. لذلك بدأ استخدام البروبرانول بطريقة موضعية. وقد أظهرت الدراسات السابقة نجاح تلك الطريقة في علاج الوحمات الدموية بالاختصار من مضاعفات استخدام البروبرانولول عن طريق الفم.

المستند من البحث: لم تجد دراسات سابقة قررت بين كلا الطريقتين (التعاطي بالفم وبالطريقة الموضعية) من ناحية النجاح في علاج المرض، وأمان استخدام المركب، ولذلك فقد صممت الدراسة الحالية لبحث تلك النقطة.

المرضى وطرق البحث: اشتملت الدراسة على 40 فتيل يعانون من الوحمات الدموية، تم تقسيمهم إلى مجموعتين متساويتين عدد طبقًا لطريقة تناول البروبرانولول: الأولي بالفم، والثانية بالطريقة الموضعية. وتم أخذ التاريخ المرضي لكل الحالات، كما تم فحص الجميع إكلينيكياً، وتم البدء بالعلاج بجرعة بلغت 1 مجم/كمجم/يوم مقدمة على 2 مرات يومياً بالنسبة للمجموعة الأولى، وتم زيادة الجرعة إلى 2 مجم/كمجم/يومية مقدمة أيضاً على 3 جرعات، وتم تتبع الجرعة حتى الشهر الخامس، ثم بدأ سحب الدواء تدريجياً لنتيجة شهر السادس. بينما في المجموعة الموضعية تم استعمال جرعة ثابتة مقدارها 1 مجم/كمجم/يوميا مقدمة على مرتين يوميا، مادياً في قاعدة موضعية بطرقة موضوعية طوال فترة الدراسة (6 أشهر). وفي النهاية تم المقارنة بين كلتا المجموعتين بالنسبة ل الحمل، ومعدل حدوث المضاعفات.

النتائج: أسفرت نتائج الدراسة عن نجاعة العلاج الموضعى بالبروبرانولول بطريقة تتمثل بـ وتريد على العلاج عن طريق الفم، كما وجد إنخفاضًا في معدل حدوث الأعراض الجانبية لدى المجموعة الثانية. ولكن الفرق بين كلا المجموعتين لم تكن كبيرة لكونها دالة إحصائية.

الاستنتاج: أثبتت نتائج تلك الدراسة كفاءة العلاج الموضعى مقابلة بالعلاج عن طريق الفم، ولكن نظراً لقلة عدد الحالات في الدراسة فلا يمكننا تعليم تلك النتائج قبل إجراء مزيد من الدراسة على عدد أكبر من الحالات المشابهة.