



## Topical timolol for superficial cutaneous infantile hemangiomas in very preterm infants

Lokalna primena timolola u lečenju površnih infantilnih hemangioma kod veoma rano prevremeno rođene dece

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### Abstract

**Introduction.** Infantile hemangiomas (IHs) occur 3 to 4 times more frequently in preterm infants than in those born at term. Yet, data about efficacy and safety of topical therapy for IHs in preterm infants, especially in those born with very low gestational age (less than 33 gestational weeks) is very scarce. **Case report.** We reported five very preterm girls treated with topical timolol maleate 0.5% gel for superficial cutaneous IHs. In four infants topical timolol was applied on a single IH each, and in one infant two IHs were treated. Out of six treated IHs, one was located on the face, four on the trunk and one on the leg. They were regularly monitored for IH involution and potential adverse effects of timolol for 6–13 months of local treatment. Good therapeutic effect was achieved in all the presented infants, with no adverse effects related to topical administration of timolol-maleate. **Conclusion.** Topical timolol is an effective and safe therapy for superficial cutaneous infantile hemangiomas in very preterm infants. The treatment should be discussed in detail with parents and individualized management plan should be tailored for each infant in order to maximize the chances of a successful outcome, while avoiding adverse effects.

### Key words:

hemangioma; skin neoplasms; timolol; administration, topical; child; infant, premature; treatment, outcome.

### Apstrakt

**Uvod.** Infantilni hemangiomi (IH) se javljaju 3 do 4 puta češće kod prevremeno rođene dece nego kod one rođene u terminu. Ipak, podaci o efikasnosti i sigurnosti lokalne terapije IH kod prevremeno rođene dece, naročito one sa veoma niskom gestacijom (manje od 33 nedelje gestacije) su veoma oskudni. **Prikaz bolesnika.** U radu je prikazano 5 devojčica rođenih sa veoma niskom gestacijom koje su lečene lokalnom primenom 0,5% gela timolol maleata zbog površnih kutanih IH. Kod četvoro dece, timololom je bio tretiran po jedan IH, a kod jednog deteta su tretirana dva IH. Od ukupno šest tretiranih IH, jedan je bio lociran na licu, četiri na trupu i jedan na nozi. Tokom trajanja terapije (od 6 do 13 meseci), redovno je praćeno napredovanje involucije IH i eventualna pojava neželjenih efekata. Dobar terapijski efekat je postignut kod sve dece, a neželjeni efekti, koji bi se mogli povezati sa lokalnom primenom timolola, nisu zapaženi. **Zaključak.** Lokalna primena timolola predstavlja efikasnu i bezbednu terapijsku opciju za lečenje površnih kutanih infantilnih hemangioma kod dece rođene sa veoma niskom gestacijom. O terapiji se mora detaljno prodiskutovati sa roditeljima i treba sačiniti individualizovani terapijski plan za svako dete, kako bi se povećale šanse za terapijski uspeh, a izbegli neželjeni efekti.

### Ključne reči:

hemangiom; koža, neoplazme; timolol; lokalna primena; deca; novorođenče, prevremeno; lečenje, ishod.

### Introduction

Infantile hemangiomas (IHs) occur more frequently in preterm infants than in those born at term. There is a growing body of evidence that IHs frequency increases with decreasing birth weight and gestation length<sup>1,2</sup>, making preterm in-

fants 3 to 4 times more likely to develop IH compared to term infant<sup>3</sup>. Yet, there are very few studies about the efficacy and safety of topical therapy for IHs in preterm infants, especially in those born with very low gestational age, i.e. those born before 33 gestational weeks. Topical therapy is even more important for treatment of IHs in this subpopula-

tion, since they are increasingly sensitive for potential adverse effects of systemic therapy.

### Case reports

We present therapy effects in 5 very preterm infants with one or more superficial cutaneous IHs, who were treated with topical timolol maleate.

All the presented patients were very preterm girls, hospitalized at the tertiary level institution within the university hospital after birth for prematurity and different early morbidities. None of the presented patients had severe neonatal asphyxia, there was no need for intubation at birth, no episodes of hypoglycaemia nor hemodynamic instability during the birth and primary hospitalization. In all the presented patients, brain and abdomen ultrasound examination did not reveal any additional hemangiomas on internal organs. As high-risk infants for different medical and developmental adverse outcomes, due to their very low gestation at birth, each of the presented patients had regular follow-up examinations after discharge; those examinations were the opportunity for check on IHs too, which were done by neonatologist and/or by dermatologist. The photographs were taken at different points in time, before as well as during the usage of topical timolol therapy. The effect of timolol therapy was assessed using Hemangioma Activity Score (HAS) <sup>4</sup> at the starting

point before initiating the therapy, as well as after 6–13 months of regular timolol application.

Timolol maleate was applied as a 0.5% gel, one drop twice a day rubbing directly on IH while avoiding surrounding skin. None of the adverse effects that could be related to timolol therapy were noticed in any of the presented patients. All the parents declared in later stage check-ups that they easily incorporated the local timolol therapy in the infant's routine daily care – therefore the daily use of timolol did not pose a burden to them.

The most important perinatal characteristics of the presented patients and their IHs are shown in Table 1.

Patient 1: At the age of five weeks (corrected age 37 weeks) we noted an oval superficial IH, 4 mm in diameter, touching the bottom edge of left mamilla. After four weeks, 3 more round IHs were also noted: one on the left forearm with diameter of 2 mm, and two punctiform IHs – one in the middle of the abdomen and the other in the right inguinal region; all three were at the level of the surrounding skin. At the age of 4 months (2 months corrected age) the near-mamilla IH was 16 × 10 mm, about 2 mm above the surrounding skin, with a granular surface; its HAS was 5. The forearm IH's longer diameter was 5 mm, and it was flat; the abdominal and inguinal IHs were about 2 mm, also flat (Figure 1a). Parents were acquainted with both management op-

Table 1

The most important perinatal characteristics of the presented very preterm infants and their superficial cutaneous infantile hemangiomas

Patient	Gender	Gestation (gestational weeks)	Birth weight (grams)	Early respiratory or cardiovascular morbidity	Number of IHs	Location of IHs	Number of IHs treated	Postnatal age at initiation of timolol (months)	Corrected age at initiation of timolol	Adverse effects of timolol
1	Girl	32 1/7	1450	Moderate RDS	4	Near the mamilla, forearm, abdomen, inguinal region	1	4	2 months	none
2	Girl	32	1370	Mild RDS	1	Abdomen	1	3	4 weeks	none
3	Girl	32 3/7	1620	Moderate RDS	1	Upper leg	1	3	4 weeks	none
4	Girl	29 4/7	1260	Moderate RDS	1	Abdomen	1	4.5	6 weeks	none
5	Girl	32 4/7	1960	PDA	2	Near the eye, abdomen	2	3	6 weeks	none

IHs – infantile hemangiomas; RDS – respiratory distress syndrome; PDA – patent ductus arteriosus.

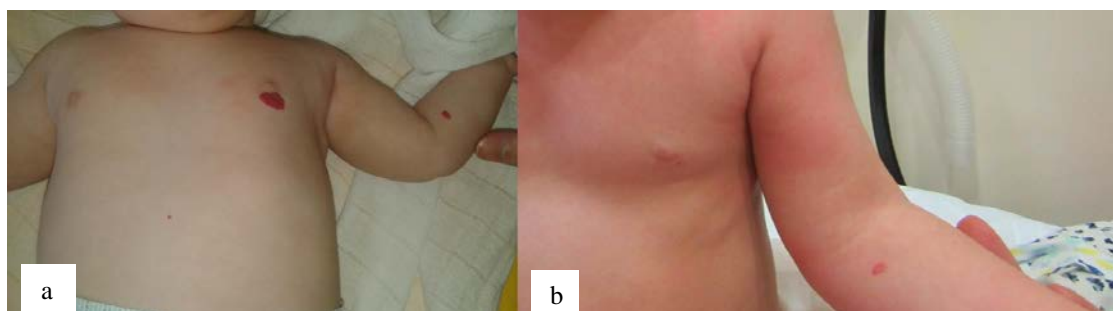


Fig. 1 – Superficial infantile hemangioma near the left mamilla and at the left forearm: a) at the age of 4 months (2 months corrected age), before topical timolol therapy was introduced; b) at the age of 15 months, after 11 months of timolol topical therapy on near-mamillar hemangioma, but without the treatment of left forearm hemangioma.

tions for near-mamilla IH: topical therapy with timolol maleate or oral with propranolol. They decided to use topical therapy. The other 3 IHs were small and flat, and there was no rationale for their treatment. The parents were advised to put baby oil on the left mamilla first, and then to rub timolol maleate on the IH avoiding mamillar ridge as much as possible. Two months later the treated IH was flattened almost to the level of the surrounding skin, and its surface was of greyish-red colour. Subsequent controls showed further gradual fading of the treated IH. At the age of 15 months, after 11 months of topical timolol usage, the near-mamilla IH was barely visible, with HAS 0. At the same time, the second largest IH at the left forearm was 7 mm in its longer diameter, light-red and still clearly visible (Figure 1b).

**Patient 2:** At the postnatal age of 3 weeks an IH was noticed on the left hemiabdomen. It had an irregular pentagon shape, size of  $17 \times 12$  mm, 1 mm above the surrounding skin, with a granular surface. At the age of 3.5 months (1.5 months corrected age), IH has increased in size to  $22 \times 18$  mm in diameter. It was 2 mm above the surrounding skin, with a red surface even more granulated than before (Figure 2a). Its assessed HAS was 5. Local therapy with 0.5% timolol maleate gel was introduced at this time. Subsequent fol-

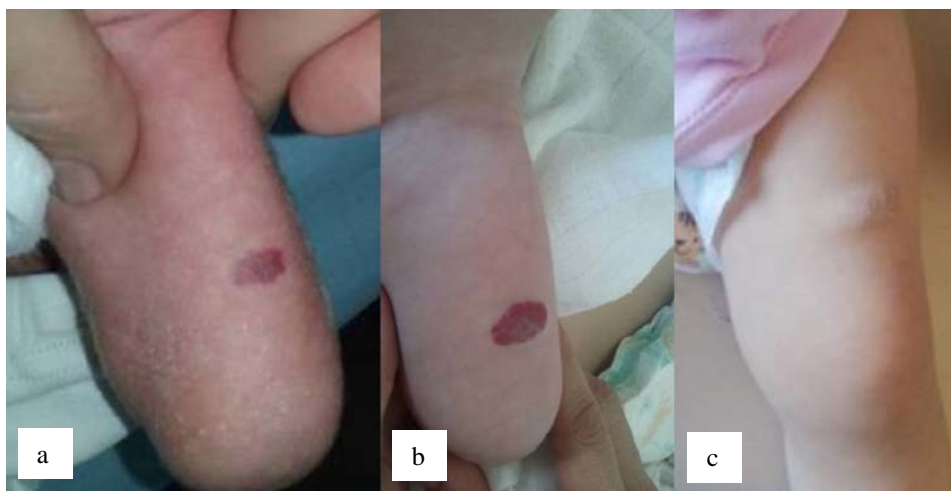
low-up showed that IH faded gradually starting from the middle (Figure 2b), with a more and more flattened surface. At the age of 16 months (12 months of timolol usage) the IH was completely flat and its whole surface was very pale (Figure 2c), similar in colour with the surrounding skin, and HAS score dropped to 0.

**Patient 3:** A superficial IH located on the front of the left upper leg has appeared during the third postnatal week. It was in the form of a horizontally elongated irregular rectangle, dark red in colour, almost flat,  $9 \times 4$  mm in diameter (Figure 3a). At the age of almost 3 months (4 weeks corrected age) IH has grown to  $18 \times 10$  mm in diameter (twice the size than on the onset) with a granular surface rising 2 mm above the surrounding skin (Figure 3b). Its HAS score was assessed at 3.5. At this point topical therapy with timolol maleate was advised. On subsequent follow-ups the colour of IH was more and more greyish-pale, evenly on the entire surface. At the age of 16 months, after 13 months of the regular usage of topical timolol, the entire surface of IH eventually became very pale, and only slightly elevated (Figure 3c), with HAS score of 0.

**Patient 4:** After discharge, at the postnatal age of 2.5 months (40 corrected weeks) parents noticed an oval flat IH



**Fig. 2 – Superficial infantile hemangioma on the left front trunk: a) at the age of 3.5 months (1.5-month corrected age), before initiating of topical timolol; b) at the age of 6 months, after 3 months of topical timolol; c) at the age of 15.5 postnatal months, after 12 months of usage of topical timolol therapy.**



**Fig. 3 – Superficial infantile hemangioma on the left upper leg: a) at the age of 3 postnatal weeks; b) at the age of 3 months, before the initiation of topical timolol; c) at the age of 16 postnatal months, after 13 months of topical timolol therapy.**

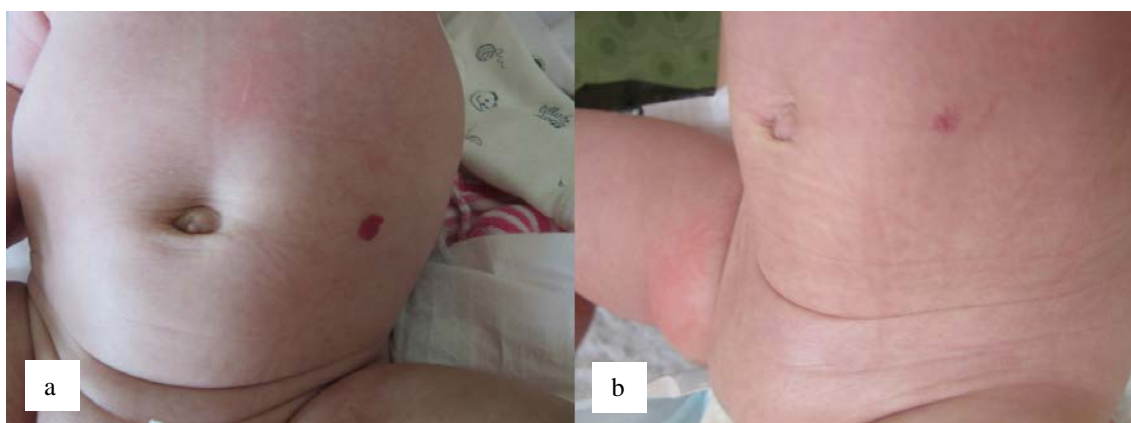
on the left hemiabdomen. At the postnatal age of 4.5 months (6 weeks corrected age) the widest diameter of IH was 11 mm and it was rising above the level of the surrounding skin by 1 mm, with HAS score 5 (Figure 4a). Infant's parents were concerned about possible side-effects of IH, even though it was not very big nor on the functional or cosmetologically sensitive location. Topical timolol was advised. After 6 months of topical timolol, IH was at the level of the surrounding skin, pale red and 6 mm in diameter (Figure 4b), with HAS score of 1.

**Patient 5.** Within the 4th postnatal week (36 corrected weeks) an irregularly shaped IH appeared at the right hemiabdomen, and one week later another oval IH appeared near the outer corner of the right eye. At the age of 3 months (6 corrected weeks) the IH near the eye was oval,  $9 \times 6$  mm in diameter, dark-red, and about 1 mm above the surrounding skin in its central part (HAS score 5). IH on the abdomen was in the shape of an irregular pentagon,  $20 \times 18$  mm in diameter, elevated more than 1 mm above the skin, with a red, granulated surface (Figure 5a); HAS score was also 5. Infant's parents were concerned about IHs, especially the one near the eye, about their enlargement and the potential adverse medical and aesthetic effects. Since echocardiography showed that ductus arteriosus was still patent, we decided to

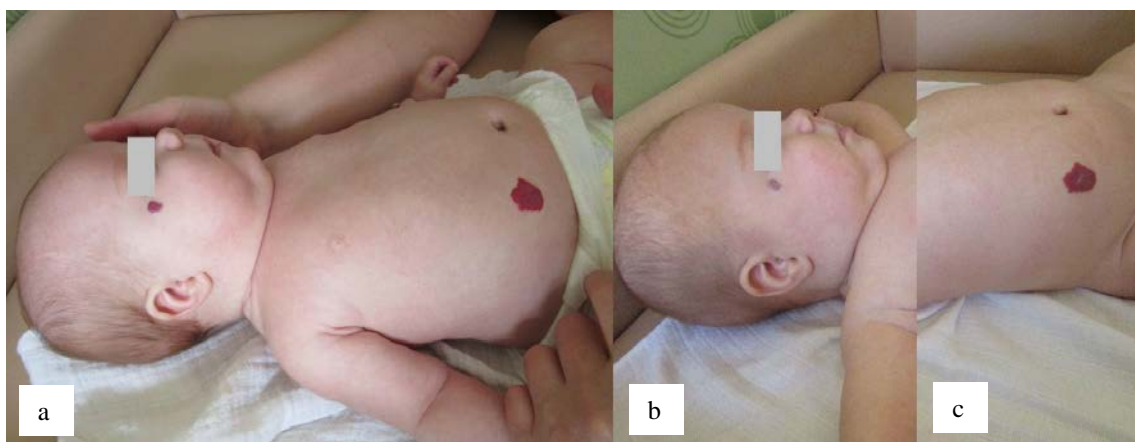
start topical timolol therapy, with additional advice of eye protection when applying timolol on the facial IH. At the age of 6.5 months (4.5 months corrected age) we observed significant improvement of IHs, especially the one located near the eye. At that time echocardiographic exam revealed the spontaneous closure of ductus arteriosus. The possibility of changing the IH therapy from topical to oral propranolol was discussed with the parents. They, however, were satisfied with the progress accomplished with topical therapy and decided to continue with timolol. At the age of 9 months (7 corrected months), after 6 months of timolol therapy, the IH near the eye was reduced ( $6 \times 4$  mm), flat and had a pale bluish surface with HAS score 1 (Figure 5b). The involution of IH on the abdomen was slower; it was also reduced in size ( $20 \times 17$  mm), with further enlargement of the pale central part. Its surface almost became flat (Figure 5c), and HAS score decreased to 2.

### Discussion

There are some important differences in the occurrence of IHs between preterm and term infants. The incidence of IHs increases with the decreasing gestation and birth weight<sup>2</sup>. Furthermore, the number of IHs per child also in-



**Fig. 4 – Superficial hemangioma of the left hemiabdomen: a) at the age of 4.5 months (6 corrected weeks), before timolol therapy; b) at the age of 9.5 months, after 6 months of topical timolol therapy.**



**Fig. 5 – Superficial infantile hemangioma: a) near the right eye and on the right hemiabdomen at the age of 3 months, before the initiation of topical timolol; b) after 6 months of topical timolol therapy near the right eye; c) after 6 months of topical timolol therapy on the right hemiabdomen.**

creases with decreasing gestation, with 2 to 5 IHs found in 40% of preterm vs 24.5% of term infants, and more than 5 IHs in 7.5% preterm vs 3% of term infants. These data indicate that preterm infants are especially prone to solitary and multiple IHs.

The introduction of beta-blockers in the therapy of IH – oral propranolol in 2008<sup>5</sup>, and topical timolol in 2010<sup>6</sup>, and, to a much lesser extent, some other oral or topical agents from the same pharmacological group (atenolol, nadolol, carteolol) revolutionized the treatment of the most common tumour in infancy. The management of IH in the era before beta-blockers consisted of different modalities (systemic or intralesional corticosteroids, interferon-alfa, vincristin, cryotherapy, laser, surgery), with an uncertain and often non-satisfactory outcome, and with numerous, sometimes very serious adverse effects. Beta-blockers, oral as well as topical, turned out to be an effective and safe treatment for IH, as a number of studies demonstrated<sup>7–15</sup>. Their high level of efficacy and safety broadened the list of IHs indicated for the treatment, including those on the face, scalp, neck, hands, feet and intertriginous and perineal regions<sup>16,17</sup>.

Most of superficial cutaneous IHs are benign and harmless. However, significant proportion of them can be complicated by a central ulceration, bleeding and pain during their proliferative phase, as well as life-long functional and aesthetic consequences<sup>17</sup>. Naturally, critical IHs i.e. those which are life-threatening (in the airways), function-threatening (on the eyelids), ulcerated or with a high-risk thereof, or with a risk for acute or chronic disfigurement must be treated. But this list is not exhausted, since there is a growing body of evidence of a high proportion of residual deformity found in 69–88% of IHs, even with those that do not possess apparently aggressive properties<sup>18,19</sup>. According to some authors, every IH over 8 mm in diameter can be predisposed to express residual effects after involution, hence it should be among those being considered for treatment<sup>13</sup>. Aesthetics is among rational reasons for IH treatment, because of the potential for mental pressure on the parents as well as an unpredictable psychological burden in the child<sup>15</sup>. This reason is especially pronounced in girls with IH. All our patients were girls, which might be the reason for the increased parents' concern for medical but also aesthetic long-term effects of the IHs on their infants. The reasons for the introduction of IH therapy were, besides aesthetics, the potential for disfigurement. In patient 1, the girl with IH near her left mamilla, there was a fear of significant residuals on the breast; even breast hypoplasia has been described in the literature<sup>20</sup>, although with mixed IH. In patient 3 IH showed rather fast growth, and in patient 5 IH was on the face, near the eye.

Today beta-blockers are considered the first-line therapy for different types of IH, either in systemic or topical form. Systemic therapy, most frequently with oral propranolol, turned out to achieve faster and more complete involution of IH compared to topical beta-blockers<sup>21</sup>. But the associated adverse effects are more frequent with systemic beta-blockers compared to topical application. Adverse effects of oral propranolol in paediatric population are hypotension,

bradycardia, pulmonary symptoms (bronchial obstruction, apneic episodes), hypoglycaemia, sleep disturbances, somnolence, cool or mottled extremities, and gastrointestinal symptoms (gastroesophageal reflux, diarrhoea)<sup>17</sup>. These side-effects are rare, but potentially dangerous, as some reports showed<sup>22–24</sup>. For these reasons in many hospitals, ours included, introduction of oral propranolol is performed in the hospital settings, with cardiological, respiratory and metabolic testing and monitoring. Besides, propranolol as a lipophilic molecule crosses the blood–brain barrier and may cause several effects in the central nervous system (CNS). In a small study, propranolol has been found to impair short- and long-term memory, psychomotor function, sleep quality, and affect mood<sup>25</sup>. On the other hand, some other authors did not confirm such an effect of propranolol<sup>26</sup>. Nevertheless, this possibility should not be neglected in very preterm infants, in whom psychomotor development is already affected by low gestation at birth. Special medical issues concerning therapy for superficial IH in very preterm infants are their comorbidities, as well as a greater potential for the manifestation of adverse reactions on any therapy. Although oral propranolol is, by today's knowledge, the first line therapy for IH, its application in preterm infants raises numerous questions about proper indication, timing of initiations and surveillance of potential adverse effects of this therapy mode.

Numerous studies confirmed that topical timolol was proven to be an agent with good therapeutic efficacy for the management of superficial and mixed IHs<sup>11–14</sup>. Among them is the study conducted by Yu et al.<sup>15</sup>. Out of 101 treated infants, in 12 of them the complete involution of IH was achieved in 4 months of topical timolol usage. The same study also showed significantly better effects in the subgroup of infants in which topical timolol was initiated at the age of 1–6 months, compared to those in which the same therapy was initiated at the age of 7–12 months. It is well known that the management of IHs should be initiated in the early proliferative phase – during first 2–3 months of life, for the maximum effect<sup>27</sup>.

Bearing all of the above in mind, topical timolol seems to be a good alternative to systemically applied therapy in preterm infants, including those with very low gestation. It achieves quicker and more complete involution of IH than naturally, but with low potential for adverse events in especially vulnerable patients. Topical timolol therapy may have some adverse effects, although they occur very rarely: bradycardia, hypotension, apnea, sleep disturbances and hypothermia<sup>28,29</sup>. In most studies dealing with the efficacy and safety of topical timolol for IHs these effects have not been recorded at all<sup>13,28</sup>. In the study conducted on 103 infants treated with topical timolol for IHs, 22 infants were considered at high-risk for adverse effects for any reason: low age at the initiation of therapy (less than 4 weeks corrected age); those receiving more than two drops per day; application to a site with potential for high systemic absorption (mucosal, ulcerated IH, under occlusion). This high-risk group included 6 preterm infants born with 33–36 and one with 26 gestational weeks. Adverse effects were observed in two infants: brady-

cardia and hypothermia in 33-weeker, and bradycardia and apnea in 26-weeker<sup>29</sup>. The introduction of timolol in these infants started at the corrected age of 37 and 34 gestational weeks, respectively. In all our cases, infants were at the corrected age of 4 weeks or older at the initiation of timolol therapy. Also, in all our patients timolol was applied on the skin, not on mucosal surfaces, nor on ulcerated IH or in the diaper area. All the presented infants received just 2 drops of timolol per day, except patient 5, in which topical timolol was applied on 2 IHs simultaneously, that is – she received 4 drops of topical timolol per day. But even in this girl there were no adverse effects of therapy, even though she still had PDA at the time of topical therapy initiation. We think that not initiating topical timolol before 4 corrected weeks in preterm infants is the most important factor contributing to the avoidance of adverse therapy effects.

Discussing the management of IH with parents is very important. The therapeutic effects are most favourable in the early proliferative phase of the IH during the first 2–3 months of age, at the time when long-term residuals are still neither visible nor predictable. A detailed explanation and cooperation with parents is crucial in order to achieve good

therapy compliance as well as to monitor possible side effects. On the other hand, parents of very preterm infants have already undergone an emotionally difficult period after the childbirth and have a high degree of concern for the health of their infant. They are less willing to use the therapy requiring hospitalization, as is the case with oral propranolol.

All the girls presented here had relatively small and uncomplicated IHs, which is a limiting factor in evaluating the efficacy and safety of local timolol therapy. Further studies that would include large and/or complicated IHs in preterm infants would be needed to better evaluate the effect of timolol in this vulnerable group of patients.

### Conclusion

Topical timolol is an effective and safe therapy for superficial cutaneous IHs, in our case – a group of very preterm infants. Treatment modalities for IHs should be discussed in detail with parents. An individualized management plan should be tailored for each child, in order to maximize the chances of successful treatment, and avoid adverse effects.

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