

Topical treatment of infantile hemangiomas – where are we now?

Kristina SEMKOVA*, Sonya MARINA, Jana KAZANDJIEVA

Department of Dermatology and Venereology, Medical University – Sofia, Bulgaria

*Correspondence: Dr. Kristina Semkova, E-mail: kristina_semkova@yahoo.com

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Abstract

Infantile hemangiomas are the most common, benign vascular tumors of infancy. Their main feature is spontaneous involution over months to years after an initial phase of rapid proliferation. Small, superficial lesions usually resolve without sequel, but scarring and disfigurement are still possible, while the cosmetic outcome is unpredictable. Thus, infantile hemangiomas benefit from non-aggressive topical treatment, because it is safe and with an overall outcome comparable to spontaneous involution. The available topical agents reported in the literature to satisfy these requirements are topical beta-blockers, imiquimod and topical corticosteroids. However, none of these have been assessed in randomized controlled trials, and standardized treatment recommendations about precise dosing and patient selection are not available yet.

Key words

Hemangioma + diagnosis + therapy; Skin Neoplasms; Administration, Topical; Aminoquinolines; Neoplasm Regression, Spontaneous; Treatment Outcome

Infantile hemangiomas (IHs) are the most common, benign vascular tumors of infancy affecting up to 10% of all children. They are characterized by a natural course of three phases – fast initial proliferation, stabilization and prolonged spontaneous involution. According to the depth of involvement, IHs are classified into superficial, mixed and deep. Regarding their distribution, IHs are localized and segmental.

The current concept in the management of IHs is to prevent or improve scarring and disfigurement, as well as functional and life-threatening complications. Small lesions (< 5 cm) are usually managed with active non-intervention, i.e. active monitoring without active treatment. Nevertheless, even small superficial hemangiomas may leave residual lesions or be associated with complications, ulceration, crusting and bleeding. Besides from expected spontaneous involution, factors that lead to complications have not yet been identified, and the cosmetic outcome remains unpredictable. Additionally, IHs are often distressing

for both the parents and the growing child, especially when on the face and neck, and parents are anxious to achieve early improvement rather than wait and see.

Even though treatment is not warranted for small and superficial IHs, since the overall outcome may be compared with spontaneous involution in the long term, early non-aggressive therapeutic intervention with a safe and effective topical modality has several advantages over “active non-intervention”. Such advantages include prophylaxis for better cosmetic outcome, by preventing fibro-fatty tissue deposition and parents’ and patient’s psychological distress.

Several topical agents have been used in recent years to treat IHs with variable success. These include topical beta-blockers, imiquimod and topical corticosteroids. Unfortunately, data from large, prospective, randomized, controlled trials are not available for any of these agents, so recommendations about their use and monitoring are based on case reports/series and small studies. Currently, a protocol

for a standardized management of small, superficial IHs does not exist. Treatment associated morbidity prevents the use of systemic therapies, thus creating a niche for a therapeutic agent with a more favorable risks/benefits ratio is necessary. The ideal topical treatment for these cases should be both efficient and minimally irritant at the site of application. At the same time, it should provide very little absorption to prevent systemic effects.

Topical beta-blockers

Propranolol is a well-known non-selective β -adrenergic antagonist, which competitively inhibits the β_1 and β_2 -adrenoreceptors expressed on endothelial cells. It has been used to treat heart problems in children for over 40 years. Its anti-proliferative effect in IHs has been serendipitously found in 2008 by Léauté-Labrèze et al., during the treatment of secondary hypertrophic obstructive cardiomyopathy induced by systemic corticosteroid treatment administered for nasal capillary hemangioma (1). The first report of the index case was followed by numerous reports, case series and randomized clinical trials showing its remarkable efficacy and good safety. Propranolol has since become the first choice therapy for complicated and/or large IHs.

The knowledge about the action of beta-blockers in IHs is incomplete. Three pharmacodynamic mechanisms are believed to contribute to their effectiveness. These are early vasoconstriction, angiogenesis inhibition and apoptosis induction, clinically translated into change of surface color within the first 24-72h, growth arrest and regression, respectively (2).

Two topical beta-blockers are reported to be highly effective and safe in the treatment of IHs: timolol maleate and propranolol hydrochloride.

Timolol maleate

Timolol is a topical non-selective beta-adrenergic antagonist, licensed and used for the treatment of open-angle glaucoma and increased intraocular pressure for over 30 years. The drug is available as a 0.1% or 0.5% solution or gel formulation. Several case reports/series give evidence about its efficacy for small, superficial IHs (3-6).

The pharmacokinetics of topically applied timolol has not been thoroughly studied. Following

ophthalmic administration, up to 80% of the drug is systemically absorbed (7) with about 50% bioavailability in healthy volunteers (8). However, ophthalmic data should not be directly extrapolated for cutaneous application given the differences in structure, permeability and vascular supply between the skin and the ophthalmic tissues. Studies on the pharmacokinetics and beta-blocking effects of transdermal timolol patches (5% timolol, 0.2 mg/cm²) showed plasma concentration levels below the detection limit after application for 48 hours (9). The only side effect observed after patch application is skin irritation with 20% timolol. When used to treat IHs, 0.1% and 0.5% timolol maleate has so far not given any systemic adverse reactions (3-5). Nevertheless, the available safety data are still insufficient, and specialists involved in the treatment with timolol should be alert about the side effects of beta-blocker and monitor infants accordingly.

The first report on the topical treatment of IHs with timolol was published in 2010, when Guo and Ni observed complete regression of a superficial capillary peri-orbital hemangioma in a 4-month old baby treated with topical timolol solution 2 times daily for several months (10). They further reported 7 children with superficial peri-ocular IHs treated by the same protocol with reduction of the size and volume of lesions that varied from 55% to 95% (4). Regression of hemangiomas was associated with fast resolution of the visual impairment and function recovery.

Chakkittakandiyil et al. performed a retrospective, multicenter, cohort study, including 73 children with IHs. Sixty two were treated with 0.5% and the other 11 with 0.1% timolol gel solution twice daily without occlusion (6). The mean treatment duration was 3.4 ± 2.7 months with a mean visual analogue scale - VAS improvement at the last follow-up visit of $45 \pm 29.5\%$. Only one patient did not respond to the treatment, and only one experienced systemic side effects (sleep disturbance). The authors identified predictors of better response: superficial type of hemangioma, duration of treatment for more than 3 months and higher drug concentration.

The results from available studies and our experience from a prospective study (in press) show that topical timolol is highly effective and a relatively safe treatment option for superficial IHs. It can be recommended primarily for small, localized lesions on the face for achieving a predictable cosmetic

outcome. Timolol is also suitable for small, superficial hemangiomas on the trunk and extremities or for larger superficial lesions, when parents prefer treatment to active non-intervention.

For maximum effectiveness the treatment should continue for at least 4-6 months or until complete resolution, and should be started early - in the proliferative phase. The drug is also effective for involuting lesions in consistency with the reported effectiveness of oral propranolol (11). Therefore, topical timolol may also be used in patients who have not sought or have not benefited from early therapy. In contrast with recent literature reports (12), our experience and literature data show that IHs requiring systemic intervention are highly unlikely to benefit from topical treatment as both the amount of active substance applied and the rate of absorption are relatively low.

Propranolol

Topical formulations of 1% propranolol have also shown beneficial effects on small IHs without safety concerns (13). Kunzi-Rapp reported 45 children with 65 hemangiomas treated with 1% propranolol in a hydrophilic ointment. The drug was applied twice daily and treatment duration varied from 1 to 10.5 months. Seven infants included in the study were pre-term and low-weight. Regression or stabilization of growth was observed in 85% of hemangiomas with early intervention in the proliferative phase. No side effects, including changes in blood pressure or heart rate in pre-term infants, were noticed or reported by parents.

Similar to timolol, propranolol pharmacokinetics after topical cutaneous application has not been studied in details. *In vitro* studies of transdermal delivery systems for topical propranolol showed 10.4% to 36.6% skin accumulation of the drug (14). Absorption resulting in systemic bioavailability was 4.1% to 16.1%. Skin irritations have been reported with high concentrations and dosage, but in recent studies of percutaneous permeation of propranolol no signs of irritation were observed on both human and rat skin (15).

Imiquimod

Imiquimod is a topical immunomodulator that stimulates activation of immune response at the site of

application. It activates dendritic cells toll-like receptor (TLR) 7 and triggers production of proinflammatory cytokines - IFN- α , IFN- γ , TNF- α , IL-1, IL-5, IL-8, IL-10, IL-12, and the antiangiogenic factor such as tissue inhibitor of matrix metalloproteinases (16). Imiquimod has antiproliferative and antiangiogenic effects in a murine model of vascular tumor (17). Its primary function as an immune response trigger translates clinically into expected inflammation with erythema, edema and scales or crusts. Some children may not achieve satisfactory regression due to suppressed reactivity to TLR-antagonists in newborns, or due to the lack of effectively functioning TLR-7 in this age group (18).

Martinez et al. were the first to apply 5% imiquimod to treat IHs in 2002 (19). They reported regression in two children, aged 4 and 7 months, with mixed hemangiomas. The drug was applied 3 times a week for the first 4 weeks, followed by 5 times a week until achievement of desired results. This pioneering report was followed by several other case/series reports and trials (20-23).

Therapy with imiquimod 5% cream is effective only for superficial IHs or for the superficial part of mixed IHs, as observed in retrospective studies (20) and in an open prospective study designed to assess the efficacy and safety of this treatment modality (21).

To properly compare the efficacy versus spontaneous involution, Jiang et al. conducted a prospective self-controlled study of imiquimod 5% cream in uncomplicated, proliferative, superficial or mixed hemangiomas in 44 patients aged 1 to 12 months (24). Each treated lesion was divided into two sections: one half was treated with the active drug once every other night for 16 weeks, and the other half was left as an untreated self-control site. Marked improvement was observed in the treated half, compared to the non-treated one. Local skin reactions occurred in 61%. The most common were crusting (55%) and erythema or edema (16%). Scarring developed in 5% of all patients. The incidence of side effects was not statistically different between the sides with active treatment and control sides.

Currently, there are no established recommendations for dose and duration of treatment with imiquimod and the therapy should be individualized for each child's clinical response and rate of irritation. Most patients benefit from applying

imiquimod 3 times per week. In case of unsatisfactory response after 4 weeks, the frequency of application may be increased to 5-7 times a week (20-23). The average duration of treatment is 16 weeks, but this period may be prolonged or shortened if necessary. In case of serious skin irritation with crusting and/or erosion, drug application should be discontinued until fading of local symptoms to prevent or minimize the risk of scarring.

Imiquimod 5% cream has a good safety profile in children. Side effects are similar to those observed in adults and include local irritation at the site of application with erythema, crusts and development of contact dermatitis (21).

Pharmacokinetic studies in infants and children show that systemic absorption following local application is very low and, as a rule, systemic effects, including functional impairment of internal organs, are highly unlikely (21, 25). The most commonly reported systemic adverse reactions are flu-like symptoms, particularly fever (23).

Besides its proven efficacy and relative safety, imiquimod 5% cream is not widely used. Its main limitation is the risk of severe irritation resulting in scarring. Additionally, imiquimod should be used with caution for peri-orbital hemangiomas, since the expected but unpredictable extent of inflammation may lead to peri-orbital and intra-orbital edema and visual impairment (26).

Topical corticosteroids

Although systemic corticosteroids have been the mainstay of treatment for IHs for many years, the use of topical corticosteroids is not a common practice and only a limited number of case series in the literature support their efficacy (27-30). The main concern related to the use of topical steroids in children is atrophy and related skin side effects associated with prolonged application and suppression of the adrenal axis resulting from possible systemic absorption after extensive application. These effects, however, can be prevented by strict criteria for lesion size and controlled duration of treatment.

Corticosteroids inhibit the expression of vascular endothelial growth factor-A (VEGF-A), monocyte chemoattractant protein-1 (MCP-1), urokinase plasminogen activator receptor (uPAR),

and interleukin-6 (IL-6) by targeting the NF- κ B in hemangioma stem cells (HemSCs), but not in hemangioma endothelial cells (HemECs) in a murine model and *in vitro* (31,32). Downregulation of VEGF-A in these cells translates into vasculogenesis inhibition *in vivo*. This most probably accounts for the higher rates of effectiveness in the early proliferative phase when the ratio of immature stem cells to mature endothelial cells is higher.

Elsas and Lewis reported five children (27) and Cruz et al. reported three children (28) with vision-threatening peri-ocular capillary hemangiomas treated with topical clobetasol propionate cream. All patients experienced improvement with a reduction in the size of hemangioma and clearing of the visual axis, but the duration of treatment was not specified. The rate of improvement was slower compared to intralesional corticosteroids, but the overall effect was comparable. Local side effects were not observed in any of the 8 children, and the adrenal function was not impaired in patients reported by Cruz et al.

In a retrospective study, Garzon et al. (29) reviewed 34 infants aged 2.5 weeks to 8 months, 24 with superficial and 10 with mixed and deep hemangiomas. Patients were treated with topical clobetasol propionate, applied once or twice daily for a period of 2 to 21.5 weeks. Thirty-five percent had a good response, 38% had partial response, and 27% did not respond to the treatment. Cessation of growth occurred earlier than expected for spontaneous involution. No significant difference in the age among the 3 response groups or duration of treatment was observed. Due to the retrospective nature of the study, side effects were not evaluated.

A mid-potency topical corticosteroid was also assessed in one study as an alternative to intralesional application. Mometasone furoate, applied twice daily as a thin film, was used to treat 52 children with small (< 5 cm), superficial hemangiomas. Excellent response with cessation of growth, lightening of color and flattening of the surface was achieved in 50%, good response in 36.5% and poor in 13.4%. The overall response rate was 86.5%, comparable to the response rate of intralesional steroids. Complications observed were mild itching and irritation (19.2%) and hypopigmentation (7.6%).

Treatment of ulcerations

Becaplermin

Becaplermin is a platelet derived growth factor used in the treatment of diabetic ulcers. It was first used for pediatric patients in 2002, to treat an ulcerated hemangioma associated with PHACES (the association of large perineal haemangiomas – P, with the following congenital abnormalities: external genitalia malformations – E; lipomyelomeningocele – L; vesicorenal abnormalities – V; imperforate anus – I; and skin tags – S) syndrome leading to complete reepithelization (33). Metz et al. used 0.01% becaplermin gel in 8 children with perineal ulcerations and achieved 100% resolution during a period of 3 to 21 days (34). No adverse events were reported. Despite its high cost, the short course of treatment and the limited number of medical visits reduce the overall cost of treatment to make it the least expensive alternative compared with all other ulceration management modalities.

Nevertheless, becaplermin is currently recommended as a second line treatment for ulcerated IHs resistant to standard care. The main reason is a warning issued by FDA about increased mortality, but not morbidity, from malignancies in adult patients regular users of the drug. Even though such tendency has not been reported in infants, until further data are available, becaplermin is recommended only for ulcerated hemangiomas that fail to respond to first line management (35).

Conclusion

The majority of IHs are superficial, and the decision to treat or not should be individualized for each case. Although spontaneous involution with time is a rule, residual fibro-fatty depositions and scarring are not unusual and a potential for cosmetic disfigurement could be considered as a treatment rationale, given that there are therapeutic options that are comparable to active non-intervention, regarding efficacy and safety.

Compared to other available treatment modalities, considered in mild, uncomplicated IHs, topical beta-blockers have so far shown the same efficacy paired with a better safety profile. This highly favourable efficacy/safety ratio justifies their use as a

first-line treatment for this subset of IHs.

However, further studies are required to identify precise dosing regimens of all available therapies in order to minimize side effects and enhance the efficacy.

Abbreviations

His - Infantile hemangiomas
 VAS – visual analog scale
 TLR toll-like receptor
 IFN- α – Interferon gamma
 IFN- γ – Interferon gamma
 TNF- α – Tumor necrosis factor-alpha
 IL-1 – Interleukin – 1
 VEGF-A- vascular endothelial growth factor-A
 MCP-1 - Monocyte chemoattractant protein-1
 uPAR - Urokinase plasminogen activator receptor
 NF- κ B – Nuclear factor kB
 HemSCs - hemangioma stem cells
 HemECs - hemangioma endothelial cells
 PHACES - perineal haemangiomas (P) with the following congenital abnormalities: external genitalia malformations (E), lipomyelomeningocele (L), vesicorenal abnormalities (V), imperforate anus (I) and skin tags
 FDA - Food and Drug Administration

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Topikalni tretman infantilnih hemangioma – gde smo danas?

Sažetak

Uvod: Infantilni hemangiomi (IH) predstavljaju najčešće benigne vaskularne tumore u infantilnoj dobi; mogu biti prisutni kod 10% dece. Karakteriše ih prirodni tok koji protiče kroz tri faze: inicijalna s brзом proliferacijom; stabilizacija; prolongirana spontana involucija koja može trajati meseci i godinama. Male (< 5 cm), površinske lezije obično izčezavaju bez sekvela, ali ožiljavanje i kozmetički defekti mogu biti nepredvidivi.

Terapija: Savremeni koncept u lečenju IH se zasniva na prevenciji i ublažavanju ožiljavanja, kao i funkcionalnih pa i po život opasnih komplikacija.

Lokalna terapija: Trenutno ne postoji standardizovani protokol zbrinjavanja malih, površinskih IH. Morbiditet koji prati sistemsku terapiju, uslovljava da se lokalna terapija, kao lečenje prvog izbora u ovim slučajevima ogleda kroz efikasnost, minimalnu iritativnost na mestu aplikacije i nizak stepen apsorpcije a sve u cilju prevencije sistemskih efekata. Preparati za lokalnu primenu koji na osnovu literaturnih podataka ispunjavaju ove kriterijume su beta-blokatori, imikvimod i kortikosteroidi. Ipak, za sve tri grupe lekova, nedostaju rezultati randomiziranih kontrolisanih ispitivanja pa samim tim i standardizovane terapijske preporuke koje se odnose na izbor pacijenata i preciznost doziranja.

Beta-blokatori za lokalnu upotrebu: Pretpostavlja se da tri farmakodinamska mehanizma doprinose terapijskoj efikasnosti ovih preparata, rana vazokonstrikcija, inhibicija angiogeneze i indukcija apoptoze, što se klinički ogleda u promeni boje unutar prvih 24-72h, zaustavljanju daljeg porasta i sledstvenoj regresiji.

Lokalni pripravci dva beta-blokatora su u dosadašnjim ispitivanjima pokazala visok stepen efikasnosti i bezbednosti u lečenju IH: timolol maleat i propranolol hidrohlorid.

Timolol maleat: Ovo je lokalni neselektivni beta adrenergijski antagonist. Dostupan je u obliku rastvora/gela u koncentraciji od 0.1% i 0.5% i treba ga aplikovati 2 puta dnevno u toku nekoliko meseci. Podaci o bezbednosti lečenja s timolom su nedovoljni i lekari treba da budu na oprezu kada su neželjena dejstva beta-blokatora u pitanju. Mi smo na osnovu rezultata sopstvenih istraživanja utvrdili faktore

prediktore boljeg terapijskog odgovora: površinski tip hemangioma, trajanje lečenja duže od tri meseca, veća koncentracija leka. Timolol se preporučuje za lečenje prvenstveno malih, na licu lokalizovanih lezija, ali se može primeniti i kod onih lokalizovanih na leđima i ekstremitetima, kao i kod površinskih IH većih dimenzija, ukoliko roditelji to žele. Na osnovu svog iskustva, pojedini autori porede efikasnost u lečenju sa efikasnošću oralne primene propranolola.

Propranolol: Hidrofilna mast sa 1% propranololom aplikovana dva puta dnevno u trajanju od 1 do 10.5 meseci pokazala se efikasnom za lečenje malih IH. Na osnovu ispitivanja *in vitro* posle lokalne primene, akumulacija propranolola u koži dostiže 10.4% do 36.6%. Posle apsorpcije, sistemska bioraspoloživost je 4.1% do 16.1%. Do iritacije je dolazilo samo u slučajevima gde je primenjena visoka koncentracija leka.

Imikvimod: Imikvimod je imunomodulator a koristi se za lokalno lečenje, pri čemu je njegov antiproliferativni i antiangiogeni efekat na vaskularne tumore ispitivan i dokazan kod eksperimentalnih životinja. Pokazao se efikasan bezbedan u obliku 5% krema za lečenje površinskih IH i za lečenje površinskih delova mešanih IH. U odsustvu zvaničnih preporuka, a u cilju postizanja maksimalne terapijske efikasnosti ali i izbegavanja iritacije, dozu leka i dužinu lečenja treba prilagoditi svakom pojedinom pacijentu. I pored dokazane efikasnosti i relativne bezbednosti, imikvimod se nekoristi rutinski, uglavnom zbog povišenog rizika od pojave iritacije i ožiljavanja. Ukoliko se primeni za lečenje periorbitalnih IH, potreban je veliki oprez, s obzirom na nepredvidivu mogućnost pojave inflamacije, peri- i intra-orbitalnog edema, sa oštećenjem vida.

Kortikosteroidi: I pored toga što se lečenje IH godinama zasnivalo na sistemske primeni kortikosteroida, lokalna primena kortikosteroida ne predstavlja svakodnevnu praksu. Najveći oprez kod lokalne primene kortikosteroida kod dece usmeren je na prevenciju razvoja neželjenih efekata koji se javljaju nakon njihove dugotrajne i ekstenzivne aplikacije, kada usled atrofije kože može doći do njihove sistemske resorpcije te i supresije adrenalne povratne sprege.

Prevenција ovih neželjenih efekata sastoji se u poštovanju kriterijuma prilikom određivanja veličine površine na koju će se aplikovati kortikosteroidi i vremenskog trajanja njihove primene. Komparativne studije, koje su imale za cilj poređenje terapijskog efekta lokalne aplikacije i intralezionog ubrizgavanja kortikosteroida, nisu utvrdile značajnost razlika u stepenu postignutog poboljšanja nego u brzini njegovog nastanka.

Lečenje ulceracija: Bekaplermin predstavlja faktor rasta izolovan iz trombocita. Bekaplermin 0,01% gel preporučuje se samo za lečenje ulcerisanih hemangioma koji nisu reagovali povoljno na primenu

prve terapijske linije.

Zaključak: Najveći broj infantilnih hemangioma pripada grupi površinskih hemangioma. Odluku o započinjanju lečenja treba uvek doneti individualno za svakog pacijenta. Iako do spontane regresije dolazi vremenom, gotovo po pravilu, nije neuobičajen razvoj lokalnog fibrolipomatoznog zadebljanja i ožiljnog tkiva na mestu postojeće lezije. Ukoliko govorimo o odnosu između poželjnog terapijskog benefita i bezbednosti njegovog postizanja, onda lokalna primena beta blokatora predstavlja prvu terapijsku liniju u lečenju infantilnih hemangioma.

Ključne reči

Hemangiom + dijagnoza + terapija; Neoplazme kože; Topikalna primena lekova; Aminokvinolini; Spontana regresija neoplazmi; Ishod lečenja