International Journal of
Science Inventions Today
www.ijsit.com
ISSN 2319-5436
Review Article

NEW PROGRESS IN CLINICAL TREATMENT OF INFANTILE HEMANGIOMA

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ABSTRACT

Infantile hemangiomas (IH) are the most common benign tumor in infancy, with a prevalence of up to 10% in the first few years of life.Its pathogenesis is not completely clear. Although infantile hemangioma is characterized by spontaneous regression, complex hemangioma may lead to severe dysfunction and disfigure. Therefore, appropriate intervention therapy is needed in the early stage to facilitate the spontaneous regression process and control the growth of hemangioma and its invasion of surrounding tissues.With the continuous exploration and optimization of treatment regimens in recent years, topical tiemolol, oral propranolol, surgery or laser therapy have been applied in clinical practice and achieved good therapeutic effects. This article reviews the treatment progress of IH.

Keywords: Infantile hemangioma; Oral drugs; Laser treatment; Therapy.

INTRODUCTION

Infantile hemangiomas (IH) are the most common benign vascular tumors of infancy that are regulated by the renin-angiotensin system (RAS) and are of stem cell origin, involving abnormal proliferation and differentiation of hematopoietic endothelial cells with a neural crest phenotype and multidirectional differentiation ability. Most hemangiomas have a proliferative, regressive, and complete course, and the biological characteristics of each stage are different from those of vascular malformations.The biological characteristics of each stage are different from those of vascular malformations. Generally, the rapid proliferation phase occurs within 1 year of age, with the fastest growth occurring within the first 3 months of life, followed by a slow growth transition to the regression phase. It is more common in white, female, preterm and low birth weight infants, and multiple pregnancies, and amniocentesis,chorionic villus sampling, progesterone therapy, and preeclampsia are associated with an increased incidence of IH[1、2].Although most hemangiomas are sporadic, familial autosomal dominant inheritance has been reported.The goal of IH treatment is to move toward more convenient medication, better efficacy, and fewer side effects. Clinical treatment of infantile hemangiomas is mostly combined with topical topical medications or oral propranolol in the early stages and with surgery or laser treatment for residual skin changes after degeneration, even though most of the adverse effects of propranolol are mild, there are still potentially serious short- and long-term adverse effects, including rare hypoglycemia and unknown central nervous system effects and with possible long-term effects on the growth and development of the child. As treatment options have been explored and optimized in recent years, many treatment options have emerged and been applied in clinical practice, including clinical observation, topical drugs, oral drugs, injectable drugs, laser therapy, and surgical treatment. In this paper, we review the progress of treatment for IH.

DISCUSSION

1. Etiology and pathogenesis of hemangioma in infants and children

The etiology and pathogenesis of infantile hemangiomas have not been fully elucidated, and abnormal glucose metabolism, the placental theory, the role of endothelial progenitor cells (stem cells), and molecular pathways with hypoxia have been suggested as pathogenic factors[3]. Compared with human umbilical vein endothelial cells (HUVECs), hemangioma derived endothelial cells (HemECs) have higher glycolysis-related molecules at both mRNA and protein levels expression, with higher glucose consumption and ATP production in HemECs than in HUVECs,and lower lactate production than in HUVECs[4]. Infantile hemangiomas may also be due to the migration of circulating endothelial progenitor cells to sites favored by placenta-like tissue growth. Infantile hemangiomas may also originate from placental tissue embolism or somatic mutations that lead to differentiation of angioblasts into a placental microvascular phenotype. It has been found that the development of IH may be related to estrogen, and that estrogen and vascular endothelial growth factor act synergistically in the development of IH, promoting vascular endothelial cell proliferation and rapid angiogenesis[2]. Nicotine and

carbon monoxide have been found to induce vasoconstriction, leading to fetal hypoxia[2], and hypoxia plays an important role in tissue ischemia, causing circulating endothelial progenitor cells to neovascularize and endothelial cells to proliferate. Hypoxia will lead to overexpression of proteins involved in glycolysis (e.g. GLUT-1), vascular endothelial overproliferation (e.g. VECF), pH regulation (e.g. CA-X) and cell proliferation (e.g. p-Akt), thus promoting tumor cell growth, proliferation and metastasis. Expression of angiotensin-converting enzyme (ACE), angiotensin receptor 2 (AT2R) and renal pre-epitope receptor has been demonstrated in the hematopoietic endothelium of proliferating IH[5].

IHs are usually classified as superficial, deep or mixed, and further subdivided into localized and segmental types[6].The biological progression of IHs is complex and has a clinical profile of dynamic growth followed by self-resolution, with varying degrees of eventual regression due to the unpredictable nature of their development. Although infantile hemangiomas are benign and self-limiting diseases, up to 10% of patients with IH develop complications such as ulceration, bleeding, infection, airway obstruction and visual impairment that warrant consideration for intervention[7], therefore, early treatment is increasingly advocated clinically.

Current studies have confirmed that aggressive interventional treatment of IH in the proliferative phase can control the rapid growth of the tumor. Depending on the location, size, depth of invasion, and risk of the hemangioma, the treatment of IH varies, and it is difficult to treat IH with one treatment modality in clinical practice. Superficial hemangiomas often grow fastest between 5.5 and 7.5 weeks of age, and nearly 2/3 of children are born with pre-angiomatous lesions. Starting treatment before the end of the proliferative phase of the hemangioma (5 months of age in most patients) may prevent adverse outcomes. That is, treatment should be initiated early (preferably no later than 4 weeks of age) in infants with high-risk hemangiomas.

2. Treatment and methods of hemangioma

2.1 Clinical observations

Hemangioma is a benign tumor and most children can regress spontaneously, but in practice only a small percentage can regress spontaneously. The patient's family must be advised that even if the hemangioma completely regresses, it does not restore the skin to its normal appearance.

2.2 Topical topical medications

Topical drug therapy is mainly used to treat small or superficial infantile hemangiomas and is not suitable for the treatment of complex lesions. Topical glucocorticoids not only have a strong role in promoting capillary constriction, but also inhibit cell mitosis can effectively penetrate into the cutaneous stratum corneum which may be the main reason for their promotion of IH regression, but adverse effects of long-term topical corticosteroids include skin atrophy, decreased pigmentation and hypertrichosis. With the success of other topical treatments for IH, glucocorticoids have been phased out as topical agents for IH.

With topical β-blockers gradually being replaced by topical treatment in terms of color fading, onset of action time and safety significantly better than imiquimod[8]. β-blockers promote pericyte constriction, which in turn causes capillary constriction, which in turn causes hemodynamic changes within the hemangioma inhibiting endothelial cell apoptosis. Domestic studies have confirmed that topical timolol maleate eye drops

(6 times/day for 30 minutes) can achieve optimal efficacy without compromising efficacy and with minimal total dosing[9]. Some studies have shown that the efficacy of topical timolol for superficial hemangiomas is comparable to oral propranolol, superior to imiquimod, and that topical timolol has a lower incidence of adverse events compared to oral propranolol[10, 11]. Theoretically, topical β-blockers act only locally on the lesion and do not enter the systemic circulation and are more effective and safer than oral β-blockers for IH treatment (especially superficial infantile hemangiomas, IHs). Systemic adverse reactions are rare during clinical use, and local reactions such as skin redness, desquamation, and eczema are more common[12], but there are foreign reports of timolol eye drops causing allergic contact dermatitis (ACD) after use in infantile hemangiomas[8]. Topical timolol has no effect on the regression of regressing infantile hemangiomas[13].

2.3 Oral medication

Prior to the application of propranolol for IH, glucocorticoids were of value as first-line therapeutic agents for IH in refractory, complex IHS[14]. The possible mechanism is to inhibit vascular endothelial growth factor secretion through glucocorticoid receptor mediation, hinder vascular endothelial cell proliferation, and promote the regression of IH, but because abrupt discontinuation or rapid reduction of glucocorticoid dose may cause rebound, the therapeutic dose should be gradually reduced before discontinuation. Long-term administration of glucocorticoids can also bring about potential adverse drug reactions.

The exact mechanism of action of propranolol in IHs is not fully understood and there may be multiple mechanisms interacting with each other.Oral propranolol preparations consist of a racemic mixture of the active isomer of propranolol, S-propranolol, and the inactive unclosed isomer, R-propranolol, which is not dependent on adrenergic blockade[15, 16].The signal transduction pathway is one of the most important signaling pathways closely associated with hemangioma, and it has been reported in the literature that binding of vascular endothelial growth factor (VEGF) to its receptor VEGFR triggers intracellular PI3K/Akt, Ras/MAPK, NOS, PKC, FAK/ Paxillin and a series of signal transduction pathways are disrupted, leading to vascular endothelial cell proliferation, cytoskeletal rearrangement and vascular penetration[17], interfering with nitric oxide (NO) production to mediate vasoconstriction in hemangioma; inducing vascular endothelial cells by decreasing non-receptor tyrosine kinase Src leading to MAPK/ERK inhibition, increasing the expression of pro-apoptotic genes p53 and Bax apoptosis, reducing endothelial cell proliferation in hemangiomas; and reducing angiogenesis by decreasing regulatory stem cell self-renewal[18].

Oral propranolol has become the first-line treatment for infantile hemangiomas, but before its use, the child still needs to be examined for any contraindications, and the child's family should be informed of the adverse effects and the risk of recurrence and sign an informed consent form[19]. Many of the adverse effects associated with propranolol can be attributed to its non-selective action and its interaction with the receptor, resulting in side effects such as bronchial hyperactivity and hypoglycemia. Other adverse effects arise from its lipophilic nature, which allows propranolol to cross the blood-brain barrier to exert its central nervous system effects. It has been shown that hemangiomas recur earlier and more frequently in the face than in other sites after oral propranolol treatment[20]. Propranolol has no significant effect on neurodevelopment in children, while

differences in melatonin-pineal rhythms may make infants less susceptible to propranolol sleep disruption compared with adults, but close monitoring of the central nervous system, sleep-related events, and cognitive and developmental changes in children is still necessary[21, 22].Other studies have suggested that hemangioma necrosis with superimposed polymicrobial infection may be associated with rapid propranolol-induced regression[23]. Several studies have investigated the use of the selective receptor blocker atenolol to mitigate the adverse effects mediated by non-selective receptor blockers and, due to its hydrophilicity, theoretically reduce its ability to cross the blood-brain barrier and central nervous system effects. Interestingly, despite the hydrophilic nature of atenolol, some studies have reported transient sleep disturbances or agitation in infants with IH treated with atenolol[24]. Atenolol may not be inferior to propranolol in terms of adverse effects and relapse rates, and may have advantages[25].

2.3.1 Other potential drugs

The role of the renin-angiotensin system (RAS) in the proliferation of hemangioma endothelial cells has been demonstrated in recent years. Angiotensin-converting enzyme inhibitors have been used in the treatment of IHS. Pro-renin receptor (PRR), another component of the RAS, has the ability to bind precursors and active renin and is expressed in both endothelial and non-endothelial cell populations of IH. Renin has been shown to promote the proliferation of endothelial cell populations in which renin acts through the PRR via the wnt signaling pathway to promote IH cell proliferation[26, 27].Serum renin activity levels correlate negatively with age, reflecting the spontaneous regression of IH, and plasma renin activity is highest in the first year of life, five times the adult level at 5-9 years of age, and then gradually declines to normal adult levels reflecting the extent biological behavior of IH[1].

Itraconazole as early as 2007, several researchers found that itraconazole inhibited the growth of G1-phase endothelial cells and blocked VEGF/FGF-dependent angiogenesis. In addition, 14α-demethylase (14DM) is required for endothelial cell proliferation and is a target of itraconazole[28].

Rapamycin has been shown to be effective in the treatment of hemangiomas. Rapamycin significantly reduces the expression level of VEGF and decreases the proliferation of hemangioma endothelial cells (HemECs)[29]. In addition to its effect on endothelial cells, rapamycin inhibits the proliferation and self-renewal activity of HemSCs and in vivo angiogenesis[30]. Topical application of rapamycin combined with pulsed dye laser has been shown to be effective in the treatment of capillary malformations[31]. Sirolimus treatment has been shown to play a master switch role in the treatment of mammalian target of rapamycin (mTOR) in a variety of cellular processes such as angiogenesis and cell growth. After the failure of propranolol and prednisolone combination therapy, the successful application of sirolimus in combination with propranolol was successfully reported.The mTOR inhibitor sirolimus is a promising agent for the treatment of vascular malformations and vascular tumors[32]. Recent reports suggest that endothelial fatty acid binding protein 4 (FABP4) is required for angiogenesis. Although the potentially complex regulatory network of FABP4 expression requires more detailed studies to elucidate, FABP4 inhibitors may be potential therapeutic candidates for the treatment of infantile hemangiomas.

Our traditional medicine has also accumulated rich experience and played an important role in the treatment of hemangioma, and Lycium barbarum polysaccharide (LBP) is a macromolecular substance with multiple biological activities extracted from the traditional Chinese herb Lycium barbarum. LBP induces apoptosis and inhibits proliferation of infantile hemangioma endothelial cells through downregulation of the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway[33]. Dihydrotanshinone I (DHTS) is a compound extracted from Salvia miltiorrhiza, DHTS can act by inhibiting the proliferation, inducing apoptosis and inhibiting the angiogenesis of hemangiomas, and has potential therapeutic effects on infantile hemangiomas, and preliminary in vitro and in vivo experiments have shown that DHTS is significantly more effective than propranolol[34].Curcumin reacted with endothelial cells in IH and observed altered pathways of cell proliferation and apoptotic signaling. The results showed that curcumin has an inhibitory effect anti-apoptotic proteins myeloid cells expressing leukemia-1, HIF-1α and VEGF, thus inducing apoptosis and inhibiting endothelial cell proliferation in IHs[28]. Here the author also hopes for further development of ancestral medicine in the treatment of hemangioma.

2.4 Inject drug

2.4.1 Local injection drugs

Local injection of this drug for IH has a precise range of action and is characterized by high local doses and few systemic side effects. Local injections of the drug are indicated for the treatment of early, limited, deep or thickened hemangiomas. One study comparing the efficacy of injectable bevacizumab and tretinoin in the treatment of hemangiomas found similar initial improvement in early proliferative IH after three injectable treatments, however, with continued injections, especially after six injectable tretinoin treatments the efficacy was significantly better than injectable bevacizumab[35]. However, local injections can also cause systemic side effects once excess glucocorticoids are absorbed into the bloodstream, and adrenal suppression has been reported with local trimethoprim injections[36].

Bleomycin is an antitumor drug that interferes with cell division and proliferation by blocking DNA replication. Pingyangmycin may promote apoptosis in proliferative hemangiomas, and the underlying mechanism may be related to blocking the cell cycle and activating apoptotic signaling pathways.Alternatively, with the advent of newer, safer, and more efficacious drugs, the value of pingyangmycin in IH treatment has gradually decreased, but studies have also confirmed that topical bleomycin injection may be an alternative to propranolol treatment for unresponsive or residual lesions[37]. The occurrence of adverse reactions is related to the concentration of the drug, control of the total dose, and the direction and level of injection.

Polycinnamol is a commonly used sclerosing agent, and local injection of polycinnamol blocks the blood supply to IHs, destroying the vascular endothelium and causing necrosis by vascular embolization. The use of layered injections not only promotes the regression of IH but also reduces the risk of ulceration, and polyunsaturated alcohol may cause scarring and ulceration during the treatment of IHs, so polyunsaturated alcohol is only recommended as an adjuvant treatment for hemangiomas[38]. Some studies have shown that a combination injection therapy consisting of lauryl alcohol and tretinoin not only reduces the dose of both drugs

but also reduces complications and takes advantage of their respective significant beneficial effects[39].

Local injections of urea have been used for many years in China for the treatment of IH[40], and the mechanism may be that the tissue at the site of the hemangioma exhibits acute sterile inflammation immediately after urea injection, by contracting the endothelial cells within the hemangioma and causing degeneration, necrosis and fibrosis within the lesion. Urea microsphere liposomes (ULIM) as a novel topical controlled release system to achieve slow release of urea has superior therapeutic efficacy to urea and propranolol and reduces the number of daily doses of urea[40].

2.4.2 Systemic injectable drugs

Systemic injections for the treatment of IH include vincristine and interferon. Vincristine has the effect of inhibiting mitosis and interfering with nucleic acid synthesis, and promoting apoptosis of vascular endothelial cells and tumor cells. Because of some serious side effects of systemic antitumor drugs, vincristine is currently used mainly in junctional or malignant hemangiomas.

Interferon has antiviral and antitumor effects, interferon inhibits cell proliferation and promotes apoptosis and angiogenesis inhibitor effects and has been used as an alternative when glucocorticoids are ineffective in aggressive hemangiomas, a meta-analysis of interferon treatment of hemangiomas, concluded that interferon is effective in the treatment of IH, but interferon adverse effects may be more severe[28]. Therefore, interferon is not recommended for use in infants under 1 year of age.

2.6 laser treatment

Lasers selectively act on chromophores in IHs that are dominated by oxygenated hemoglobin. However, different lasers have different ranges of application, and pulsed dye laser (PDL), Nd:YAG laser and fractional CO2 laser are commonly used for the treatment of IHS.

PDL has remarkable clinical efficacy due to selective photothermal cleavage and low incidence of adverse effects, although pulsed dye laser (wavelength 595 nm) is still used clinically and some reports suggest that its treatment is no better than untreated treatment, but pulsed laser still plays an important role in the treatment of residual lesions[41], and with the advantage of long-pulsed PDL in terms of transdermal depth, the success rate of treating IH is higher .

The Nd:YAG laser is an infrared laser with a wavelength of 1064 nm that is poorly absorbed by oxyhemoglobin. Nd:YAG laser therapy is divided into two categories, continuous Nd:YAG laser and pulsed Nd:YAG laser, according to the mode of energy output. Another study recommended caution in the use of Nd:YAG laser therapy on thick IH. The efficacy and safety of pulsed Nd:YAG laser treatment was superior to continuous Nd:YAG laser treatment, and the penetration depth was superior to that of PDL treatment[28].

The dual wavelength PDL/Nd:YAG laser has a more prominent position in the treatment of vascular diseases, which is achieved by successively emitting a 585 nm PDL and a 1064 nm Nd:YAG laser. First PDL converts hemoglobin into focal iron hemoglobin and leads to local microhematocrit, after which the Nd:YAG laser is emitted, and the dual-wavelength PDL/Nd:YAG laser is considerably more effective in treating vascular diseases than before because the energy absorbed by the Nd:YAG laser is three to five times higher than that of

normal blood by methemoglobin[42].

Fractional CO2 laser, which is a fractional laser, has a high transmission capacity and penetrates deep into the dermis. It has an exfoliating effect, promotes epidermal regeneration and achieves skin surface reconstruction with short recovery time[28]. It can be used to treat fibrofatty residuals and atrophic plaques after hemangioma regression.

Intense Pulsed Light (IPL) is a group of intense light with a non-coherent light source in the spectrum of 42 to 1400 nm. Its mechanism of action is similar to that of laser. It is mostly used for the treatment of superficial IH, which is easily affected by the depth, type, size and location of the tumor. The main limitations are shallow penetration depth, longer treatment time and higher cost.

Microneedle radiofrequency (MNRF) causes remodeling of dermal collagen deposition and collagen synthesis by emitting energy only through an insulated tip beneath the skin, with no damage to the skin surface. This minimally invasive treatment can prevent serious sequelae due to natural rejuvenation by precisely targeting the deeper components of IH and is limited to specific types of IH[43].

Laser is mainly used for the treatment of early, superficial hemangiomas, and is particularly suitable for hemangiomas that have undergone ulcerative changes and for residual capillary dilation after the hemangioma has subsided.

2.7 surgical treatment

Surgical excision may be an alternative treatment for some children with IH with residual fibrofat, persistent scarring after regression, or poor outcome after pharmacological treatment[44]. Propranolol is currently considered the first-line treatment for IHS, and surgery is not generally advocated clinically as the treatment of choice for IH, and is often considered as an option in cases that do not respond to pharmacologic therapy, or when effective control of the disease cannot be achieved when damage to vital organ function is involved[45].

Individual differences in the performance of IH are large, and the indications, advantages and disadvantages of various therapeutic approaches should be considered clinically according to the IH lesion, and comprehensive treatment should be given as early as possible and at the right time. With the great progress in the therapeutic research of infantile hemangiomas in recent years, the elucidation of the mechanisms of hemangioma onset and regression in infants and children remains an interesting challenge, and to address this challenge, an organized reconstruction of the sequential molecular perturbations in IH neovascularization is required, highlighting the increased knowledge of molecular pathways in IH pathogenesis to guide the development of effective and rationally designed therapeutic strategies and also lays the foundation for further research into anti-angiogenic drugs.

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