doi: 10.13241/j.cnki.pmb.2019.20.028

普萘洛尔治疗增生期婴幼儿血管瘤的疗效观察及血清细胞因子检测的临床意义*

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摘要 目的:探讨普萘洛尔治疗增生期婴幼儿血管瘤的疗效及血清细胞因子检测的临床意义。**方法:**选取 2015 年 4 月 ~2018 年 5 月期间我院皮肤科诊治的 76 例增生期血管瘤患儿为治疗组,治疗组给予普萘洛尔治疗 8 周。同时选取同期来我院行健康体检的正常婴幼儿 50 例为对照组,检测并比较治疗组治疗期间以及对照组体检时血清血管内皮生长因子(VEGF)、基质金属蛋白酶 -9(MMP-9)、缺氧诱导因子 -1α(HIF-1α)以及表皮生长因子样结构域(EGFL7)水平,观察治疗组治疗后的疗效及不良反应发生情况，分析治疗 8 周后血清 VEGF、EGFL7、HIF-1α、MMP-9 下降水平与疗效等级的关系，分析治疗组血清 VEGF、EGFL7、HIF-1α、MMP-9 之间的相关性。**结果:**不同类型血管瘤患儿治疗 4 周后总有效率整体比较差异无统计学意义(*P>0.05*),治疗 8 周后混合型、深部型血管瘤患儿总有效率高于治疗 4 周后,且混合型、深部型血管瘤患儿总有效率高于浅表型血管瘤患儿(*P<0.05*)。治疗组治疗期间未出现严重不良反应现象。与对照组比较，治疗组不同时间点血清 VEGF、EGFL7、HIF-1α、MMP-9 水平均升高（*P<0.05*);随着时间的推移,治疗组血清 VEGF、EGFL7、HIF-1α、MMP-9 水平逐渐降低(*P<0.05*)。Spearman 等级相关法分析显示,治疗组治疗 8 周后血清 VEGF、EGFL7、HIF-1α、MMP-9 下降水平与疗效等级呈正相关(*P<0.05*)。Pearson 相关性分析显示,治疗组血清 VEGF、EGFL7、HIF-1α 以及 MMP-9 水平之间两两呈正相关(*P<0.05*)。**结论:**普萘洛尔治疗增生期婴幼儿血管瘤安全有效,其具体作用机制可能与下调血清 VEGF、EGFL7、HIF-1α、MMP-9 水平有关。

关键词:普萘洛尔;增生期血管瘤;疗效;细胞因子;临床意义

中图分类号:R729 **文献标识码:**A **文章编号:**1673-6273(2019)20-3925-04

Effect Observation of Propranolol on the Treatment of Infantile Hemangioma in Hyperplasia Stage and Clinical Significance of Serum Cytokines Detection*

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ABSTRACT Objective: To investigate the effect observation of propranolol on the treatment of infantile hemangioma in hyperplasia stage and clinical significance of serum cytokines detection. **Methods:** 76 children with proliferative hemangioma who were treated in dermatology department of our hospital from April 2015 to May 2018 were selected as treatment group. The treatment group was treated with propranolol for 8 weeks. At the same time, 50 normal infants who received health examination in our hospital during the same period were selected as the control group. Serum levels of vascular endothelial growth factor (VEGF), matrix metalloproteinase-9 (MMP-9), hypoxia inducible factor-1α (HIF-1α) and epidermal growth factor-like domain (EGFL7) were detected and compared in the treatment group duration of treatment and control group during physical examination. The curative effect and adverse reactions of the treatment group after treatment were observed. The relationship between decline levels of serum VEGF, EGFL7, HIF-1α and MMP-9 and curative effect grade at 8 weeks after treatment were analyzed. The correlation between serum levels of VEGF, EGFL7, HIF-1α and MMP-9 in treatment group were analyzed. **Results:** There was no significant difference in the total effective rate of children with different types of hemangioma at 4 weeks after treatment (*P>0.05*). The total effective rate of mixed type and deep type hemangioma at 8 weeks after treatment were higher than those at 4 weeks after treatment.The total effective rate of mixed type and deep type hemangioma was higher than that of superficial hemangioma (*P<0.05*). No serious adverse reactions occurred in the treatment group during the treatment period. Compared with the control group, the serum levels of VEGF, EGFL7, HIF-1α and MMP-9 were higher in the treatment group at different time points (*P<0.05*). With the passage of time, the serum levels of VEGF, EGFL7, HIF-1α and MMP-9 in the treatment group decreased gradually (*P<0.05*). Spearman grade correlation analysis showed that at 8 weeks after treatment, serum levels of VEGF, EGFL7, HIF-1α and MMP-9 in the treatment group were positively correlated with the curative effect grade(*P<0.05*). Pearson correlation analysis showed that there were positive correlation between serum levels of VEGF, EGFL7, HIF-1α and MMP-9 in the treatment group

* 基金项目:江苏省医学科研基金项目(H20130227);苏州市医疗卫生应用基础研究项目(sys2018076)

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(收稿日期:2019-01-04 接受日期:2019-01-29)

(*P<0.05*). **Conclusion:** Propranolol is safe and effective on the treatment of infantile hemangioma in hyperplasia stage. Its specific mechanism may be closely related to the down-regulation of serum levels of VEGF, EGFL7, HIF-1α and MMP-9.

Key words: Propranolol; Hemangioma in hyperplasia stage; Efficacy; Cytokines; Clinical significance

Chinese Library Classification(CLC): R729 Document code: A

Article ID: 1673-6273(2019)20-3925-04

前言

血管瘤是指血管内皮细胞异常增殖的肿瘤或者类肿瘤疾病，主要包括增生期血管瘤以及消退期血管瘤[1,2]，其中增生期血管瘤主要发生于婴幼儿期，往往在出生后 1 个月内出现，80%的增生在出生后 5 个月已完成，至 1 岁时进入消退期，半数在 5 岁内完全消退[3,4]。普萘洛尔是临床用于治疗增生期婴幼儿血管瘤的首选药物，可有效控制血管瘤增殖，并促进其消退，但有关其具体治疗机制目前尚不十分清楚[5,6]。血管内皮生长因子（Vascular endothelial growth factor，VEGF）与血管内皮细胞增殖密切相关，同时 VEGF 还可诱导内皮细胞分泌基质金属蛋白酶 -9（Matrix metalloproteinase-9，MMP-9）降解细胞外基质[7,8]。缺氧诱导因子 -1α（Hypoxia inducible factor-1α，HIF-1α）作为近年来备受关注的与血管生成有关的转录因子，同时还可诱导 VEGF 的转录[9]。表皮生长因子样结构域（Epidermal growth factor-like domain，EGFL7）可通过阻止平滑肌细胞的迁出，以保证肿瘤血管稳定性[10,11]。本研究探讨普萘洛尔治疗增生期婴幼儿血管瘤的疗效及血清 VEGF、MMP-9、HIF-1α、EGFL7 水平的变化，以期为临床治疗提供数据支持，现作如下报道。

1 资料与方法

1.1 一般资料

选取 2015 年 4 月 ~2018 年 5 月期间我院皮肤科诊治的 76 例增生期血管瘤患儿为治疗组，纳入标准：（1）均符合《口腔颌面部血管瘤和脉管畸形治疗指南》[12]中有关增生期血管瘤的相关诊断标准；（2）年龄≤ 12 个月；（3）入组前未接受过其他治疗者；（4）多发和（或）瘤体直径超过 2 cm；（5）监护人知情本次研究并已签署了同意书。排除标准：（1）对本次研究使用药物存在禁忌症者；（2）合并先天性心脏病者；（3）合并呼吸系统疾病者；（4）临床上考虑为脉管畸形患儿；（5）合并房室传导阻滞、窦性心动过缓者。治疗组中男 31 例，女 45 例，年龄 2~12 个月，平均（6.34± 1.25）个月；患病部位：颌面部 26 例，四肢 28 例，躯干 22 例；浅表型血管瘤 27 例，混合型血管瘤 32 例，深部型血管瘤 17 例。同时选取同期来我院行健康体检的正常婴幼儿 50 例为对照组，其中男 24 例，女 26 例，年龄 2~11 个月，平均（6.28± 1.37）个月。两组研究对象性别、年龄等一般资料比较无统计学差异（*P>0.05*），具有组间可比性，本次研究已获得我院伦理学委员会批准。

1.2 方法

1.2.1 治疗方法 治疗组口服药物治疗前均行相关检查，包括血尿常规、心电图、肝肾功能、甲状腺功能、血压、血糖等。对于符合各项要求的患儿给予普萘洛尔（烟台鲁银药业有限公司，国药准字：H10970353，规格：10 mg）口服治疗，初始剂量为每天 0.5 mg/kg，分三次口服，随后在 1 周内逐渐加量至每天 1.5 mg~2 mg/kg，分三次口服，每次服药前 0.5h、服药后 0.5h 检查患儿心率、血压，当出现低于正常标准者或患儿出现较为严重的不良反应时，应立即停止服药。治疗组共治疗 8 周。

1.2.2 检测方法 治疗组于治疗前、治疗 4 周后、治疗 8 周后抽取外周血 2 mL，对照组于体检当日抽取外周血 2 mL，室温下静置 30 min，以 2000 r/min 离心 12 min，离心半径 6 cm，分离血清，置于 -20℃冰箱中保存待测。采用酶联免疫吸附试验检测所有研究对象 VEGF、MMP-9、HIF-1α 以及 EGFL7 水平，试剂盒购自深圳晶美生物科技有限公司。

1.3 疗效评价标准

疗效评价标准参照国际上常用的 4 级分类标准[13]：Ⅰ级（差）：瘤体缩小 <25%；Ⅱ级（中）：瘤体缩小 25%~50%；Ⅲ级（好）：瘤体缩小 51%~75%；Ⅳ级（优）：瘤体缩小 76%~100%，总有效率 = 优率 + 好率。

1.4 统计学方法

本研究数据均采用 SPSS25.0 软件进行统计学分析，计量资料用（$\bar{x}\pm s$）表示，比较应用 t 检验，计数资料以率或比表示，采用 x^2 检验，采用 Spearman 等级相关法分析治疗组血清 VEGF、EGFL7、HIF-1α、MMP-9 下降水平与疗效等级的关系，采用 Pearson 相关性分析治疗组血清 VEGF、EGFL7、HIF-1α、MMP-9 之间的相关性，*P<0.05* 表明差异具有统计学意义。

2 结果

2.1 治疗组不同类型血管瘤治疗后的疗效情况

不同类型血管瘤患儿治疗 4 周后总有效率整体比较差异无统计学意义（*P>0.05*），治疗 8 周后混合型、深部型血管瘤患儿总有效率高于治疗 4 周后，且混合型、深部型血管瘤患儿总有效率高于浅表型血管瘤患儿（*P<0.05*），详见表 1。

2.2 治疗组治疗期间不良反应发生情况

治疗组治疗期间有 4 例于初次服药后出现不同程度的心率减慢、血压下降现象，未予特殊处理，观察 12h 后逐渐恢复正常。2 例患儿转氨酶稍高，给予复方甘草酸苷片治疗，1 周后肝功能显示正常。3 例患儿出现腹泻，停药一周后，均缓解，继续口服药物治疗，无不适症状出现。

2.3 治疗组治疗期间以及对照组体检时血清 VEGF、EGFL7、HIF-1α、MMP-9 水平比较

与对照组比较，治疗组不同时间点血清 VEGF、EGFL7、HIF-1α、MMP-9 水平均升高（*P<0.05*）；随着时间的推移，治疗组血清 VEGF、EGFL7、HIF-1α、MMP-9 水平逐渐降低（*P<0.05*），详见表 2。

2.4 相关性分析

由表 2 可知，治疗 8 周后，血清 VEGF、EGFL7、HIF-1α、MMP-9 水平的下降水平分别为（143.06± 31.25）pg/mL、（12.85 ± 4.51）pg/mL、（19.78 ± 0.93）mg/L、（578.66 ± 47.53）

pg/mL，Spearman 等级相关法分析显示，治疗 8 周后疗效等级与血清 VEGF、EGFL7、HIF-1α、MMP-9 的下降水平呈正相关（*P<0.05*），见表 3。Pearson 相关性分析显示，治疗组血清 VEGF、EGFL7、HIF-1α 以及 MMP-9 水平之间两两呈正相关（*P<0.05*），见表 4。

3 讨论

血管瘤是婴幼儿期常见的良性肿瘤，虽绝大部分可自行消退，不必干预，但因其发展结果具有不可预测性，临床中仍有 20%的血管瘤无法自然消退，尤其针对唇黏膜、鼻尖处的血管瘤自行消退较难，且血管瘤在增长期生长迅速，轻者影响儿童容貌及心理健康，严重者可导致功能障碍进而危机儿童性命，故应及时给予干预治疗[14-16]。以往临床治疗增生期血管瘤的主要方法有长春新碱、激光手术以及糖皮质激素等，但上述疗法

表 1 治疗组不同类型血管瘤治疗后的疗效情况【例(%)】

Table 1 Curative effect of different types of hemangioma in treatment group[n(%)]

Typing	n	4 weeks after treatment					8 weeks after treatment				
		Excellent	Good	Middle	Bad	Total effective rate	Excellent	Good	Middle	Bad	Total effective rate
Superficial type	27	0(0.00)	3(11.11)	5(18.52)	19(70.37)	3(11.11)	0(0.00)	3(11.11)	20(74.07)	4(14.82)	3(11.11)
Mixed type	32	0(0.00)	8(25.00)	12(37.50)	12(37.50)	8(25.00)	2(6.25)	15(46.88)	12(37.50)	3(9.37)	17(53.13)[ab]
Deep type	17	0(0.00)	3(17.65)	8(47.06)	6(35.29)	3(17.65)	3(17.65)	11(64.70)	3(17.65)	0(0.00)	14(82.35)[ab]
x^2			1.892							22.993	
P			0.389							0.000	

Note: Compared with 4 weeks after treatment, [a]*P<0.05*; compared with superficial type, [b]*P<0.05*.

表 2 治疗组治疗期间以及对照组体检时血清 VEGF、EGFL7、HIF-1α、MMP-9 水平比较（$\bar{x}\pm s$）

Table 2 Comparison of serum levels of vascular endothelial growth factor, EGFL7, HIF-1αand MMP-9 in the treatment group duration of treatment and control group during physical examination（$\bar{x}\pm s$）

Groups	Time	VEGF(pg/mL)	EGFL7(pg/mL)	HIF-1α(mg/L)	MMP-9(pg/mL)
Control group(n=50)	-	89.24± 10.90	4.65± 1.71	10.58± 1. 31	684.64± 52.87
Treatment group (n=76)	Before treatment	269.33± 38.34[a]	20.24± 8.25[a]	35.32± 1.04[a]	1342.47± 60.91[a]
	4 weeks after treatment	210.22± 41.21[ab]	13.64± 5.32[ab]	27.32± 1.34[ab]	985.51± 72.98[ab]
	8 weeks after treatment	126.27± 37.12[abc]	7.35± 2.29[abc]	15.54± 1.07[abc]	763.81± 54.85[abc]

Note: compared with the control group, [a]*P<0.05*; compared with before treatment, [b]*P<0.05*; compared with 4 weeks after treatment, [c]*P<0.05*.

表 3 治疗组血清 VEGF、EGFL7、HIF-1α、MMP-9 水平与疗效等级的相关性分析

Table 3 Analysis of the correlation between serum levels of vascular endothelial growth factor, EGFL7, HIF-1α, MMP-9 and curative effect grade in treatment group

Indexes	8 weeks after treatment	
	r	*P*
VEGF	0.513	0.000
EGFL7	0.495	0.002
HIF-1α	0.503	0.001
MMP-9	0.715	0.000

表 4 治疗组血清 VEGF、EGFL7、HIF-1α 及 MMP-9 的相关性分析

Table 4 The correlation analysis of serum levels of VEGF, EGFL7, HIF-1α and MMP-9 in treatment group

Variable	VEGF		EGFL7		HIF-1α	
-	r	*P*	r	*P*	r	*P*
EGFL7	0.335	0.000	-	-	-	-
HIF-1α	0.461	0.000	0.321	0.000	-	-
MMP-9	0.397	0.002	0.392	0.000	0.451	0.002

均会产生一定的不良反应[17,18]。普萘洛尔是典型的非选择性肾上腺β受体阻断剂，其在心脑血管疾病的疗效已得到证实，其潜在的不良反应有低血压、心动过缓、支气管痉挛、暂时性转氨酶升高等[19,20]。普萘洛尔于2008年首次应用于血管瘤治疗，取得了较好的疗效，随着近年来研究的深入，普萘洛尔在治疗增生期血管瘤方面以其疗效显著、不良反应轻微等优势已被国内外所普遍认可，有望成为治疗血管瘤的一线药物[21,23]，但有关其作用于增生期血管瘤的具体作用机制的相关报道并不多见。

本次研究结果显示，普萘洛尔治疗增生期婴幼儿血管瘤疗效显著，且治疗时间越长，其治疗效果越好，且混合型、深部型血管瘤患儿治疗效果更佳，同时治疗过程中未出现较严重的不良反应现象。普萘洛尔治疗增生期婴幼儿血管瘤的分子生物学机制主要分为以下三种：血管收缩、血管生成抑制以及诱导细胞凋亡，其中血管生成抑制主要体现为对促血管生成因子的调控，现已有较多研究证实VEGF信号转导通路在血管瘤的发生发展中起重要作用，而VEGF不仅可促进血管内皮细胞增殖，同时也可促进内皮细胞表达MMP-9，MMP-9可从胞内分泌到胞外，进而降解细胞外机制，参与着血管生成[24-26]。EGFL7基因是一个在血管内皮特异性表达的基因，主要存在于细胞的内质网和高尔基体，在生理性以及病理性血管的管腔形成、功能完善等方面发挥重要作用。HIF-1α作为与血管生成有关的转录因子，可促使血管内皮细胞产生VEGF及间质细胞衍生因子，通过整合进血管壁或提供生长因子两种方式来促使新生血管形成[27]。本研究中，治疗组血清VEGF、EGFL7、HIF-1α、MMP-9水平均高于正常婴幼儿，且经治疗后，其水平呈现不断下降趋势，提示普萘洛尔治疗增生期婴幼儿血管瘤的具体作用机制可能与血清VEGF、EGFL7、HIF-1α、MMP-9水平下调有关，普萘洛尔作用于肾上腺β受体，通过抑制肾上腺β受体的激活，进而影响了细胞外相关信号/有丝分裂原激活蛋白激酶通路的激活，而EGFL7是血管管腔形成所必需的，高水平的EGFL7表达与血管增生和重塑有关，EGFL7表达降低，其对VEGF的调控能力减弱，进而下调VEGF、HIF-1α水平，抑制MMP-9表达[28-30]。本次研究发现治疗组血清VEGF、EGFL7、HIF-1α、MMP-9下降水平与疗效等级呈正相关，再一次证实了普萘洛尔通过下调上述相关因子，从而抑制血管瘤生长，促使瘤体消退。同时Pearson相关性分析显示，治疗组血清VEGF、EGFL7、HIF-1α以及MMP-9水平之间两两呈正相关，表明上述相关细胞因子在血管生成方面起到互相调控作用，普萘洛尔可能通过调控上述相关细胞因子进而达到消退瘤体，以达到抑制病情生长的目的。

综上所述，普萘洛尔治疗增生期婴幼儿血管瘤疗效确切，无严重不良反应发生，普萘洛尔发挥药效的具体作用机制可能与血清VEGF、EGFL7、HIF-1α、MMP-9水平下调有关，进而抑制血管瘤生长，促使瘤体消退，且血清VEGF、EGFL7、HIF-1α、MMP-9下降水平与疗效等级存在联系。

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