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去铁酮联合去铁胺治疗重型地中海贫血患儿的疗效及对血糖代谢和铁代谢的影响*

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摘要 目的: 探讨去铁酮联合去铁胺治疗重型地中海贫血患儿的疗效及对血糖代谢和铁代谢的影响。**方法:** 选取 2015 年 3 月~2017 年 12 月期间海南省妇女儿童医学中心儿科收治的 127 例重型地中海贫血患儿,根据数表法将患儿随机分为对照组($n=63$)和研究组($n=64$),其中对照组在基础治疗的基础上给予去铁胺治疗,研究组在对照组的基础上联合去铁酮治疗。比较两组患儿临床疗效、治疗前后的血糖代谢和铁代谢情况,记录两组患儿治疗期间不良反应发生情况。**结果:** 研究组患儿治疗后临床总有效率为 73.44%(47/64),高于对照组患儿的 55.56%(35/63)($P<0.05$)。两组患儿治疗后血糖代谢正常率均升高,且研究组高于对照组($P<0.05$)。两组患儿治疗后血清铁蛋白(SF)降低,尿铁排泄量(UIE)升高($P<0.05$);研究组治疗后 SF 低于对照组,UIE 高于对照组($P<0.05$)。两组不良反应发生率比较无统计学差异($P>0.05$)。**结论:** 去铁酮联合去铁胺治疗重型地中海贫血患儿,安全有效,可改善机体铁代谢,提高血糖代谢正常比例,具有一定的临床应用价值。

关键词: 去铁胺;去铁酮;重型地中海贫血;疗效;血糖代谢;铁代谢

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The Effects of Desferridone Combined with Desferrimine on Blood Sugar Metabolism and Iron Metabolism in Children with Severe Thalassemia*

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ABSTRACT Objective: To investigate the effects of desferriamine combined with desferridone on blood sugar metabolism and iron metabolism in children with severe thalassemia. **Methods:** 127 children with severe thalassemia who were admitted to pediatrics department of Women and Children's Medical Center of Hainan Province from March 2015 to December 2017 were selected, the children were divided into control group ($n=63$) and research group ($n=64$) according to random number table method. The control group was treated with desferriamine on the basis of basic treatment, and the research group was treated with desferridone on the basis of the control group. The clinical efficacy, and the blood sugar metabolism and iron metabolism of two groups before and after treatment were compared, and the adverse reactions of the two groups during treatment were recorded. **Results:** The total clinical effective rate of the research group was 73.44% (47/64), which was significantly higher than 55.56% (35/63) of the control group ($P<0.05$). The number of children with normal blood sugar metabolism increased after treatment in both groups, and the research group was higher than that in the control group ($P<0.05$). After treatment, serum ferritin (SF) decreased and urinary iron excretion (UIE) increased in both groups ($P<0.05$). SF in the research group was lower than that in the control group, and UIE was higher than that in the control group ($P<0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** Desferridone combined with desferriamine are safe and effective in the treatment of children with severe thalassemia, which can improve iron metabolism and increase the normal proportion of blood sugar metabolism. It has certain clinical application value.

Key words: Deferoxamine; Deferoxanone; Severe thalassemia; Efficacy; Blood sugar metabolism; Iron metabolism

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前言

地中海贫血是指由于染色体基因缺陷致使珠蛋白链合成障碍的溶血性贫血,是临床常见的遗传性血液系统性疾病^[1,2]。据以往文献报道,该类贫血疾病主要高发于热带地区,故而得名地中海贫血^[3]。轻型地中海贫血无明显症状,通常在调查家

族史时发现^[4];中型地中海贫血大多可存活至成年,早期表现为易疲倦、免疫力低下、发育缓慢等^[5];而重型地中海贫血出生数日即出现贫血、黄疸以及发育不良,严重者影响患儿视力和听力,且致残率、致死率较高^[6]。现临床针对此类疾病的主要治疗方式为输血,然而长期的输血可引起机体红细胞不断分解,铁质大量堆积,引发“铁过载”,损伤机体组织脏器功能^[7]。因此,

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临床输血的过程中多配合除铁剂治疗。去铁胺、去铁酮均是临床常见的除铁剂,去铁胺疗效确切,但其生物利用率较低,半衰期短,患儿需多次、长时间的注射,毒副作用较多^[9],去铁酮的临床使用经验较少,疗效尚存在争议^[9]。因此,本研究通过采用去铁酮联合去铁胺治疗重型地中海贫血患儿,并探讨其疗效,旨在为临床治疗重型地中海贫血提供参考。

1 资料与方法

1.1 临床资料

选取海南省妇女儿童医学中心儿科于2015年3月~2017年12月间收治的重型地中海贫血患儿127例,本研究经海南省妇女儿童医学中心伦理委员会批准。纳入标准:(1)参考《重型β地中海贫血的诊断和治疗指南》中的相关诊断标准^[10];(2)患儿均经基因检查和/或血红蛋白(Hemoglobin,HGB)分析确诊;(3)长期接受输血治疗;(4)患儿家属或监护人知情本研究并已签署同意书;(5)患儿临床资料完整。排除标准:(1)合并肝肾功能严重损伤者;(2)入组前服用影响血糖代谢、铁代谢者;(3)无法耐受治疗者;(4)合并急慢性感染、创伤及强烈应激反应者;(5)伴有精神障碍、智力异常者;(6)依从性差者。根据随机数字表法将患儿随机分为对照组(n=63)和研究组(n=64),其中对照组男29例,女34例,年龄2~12岁,平均(7.51±1.36)岁;病程1~6年,平均(3.27±0.63)年;体质指数8.4~16.5 kg/m²,平均(12.17±0.82)kg/m²;铁过载分期:II A期25例,IIIA期21例,IIIB期17例。研究组男31例,女33例,年龄2~13岁,平均(7.96±1.28)岁;病程1~7年,平均(3.36±0.75)年;体质指数8.1~17.2kg/m²,平均(12.26±0.93)kg/m²;铁过载分期:II A期26例,IIIA期23例,IIIB期15例。两组一般资料对比无统计学差异($P>0.05$),有可比性。

1.2 治疗方法

所有患儿均给予输注浓缩红细胞,间隔时间2~4周,剂量为每10 kg 体重质量0.5~1.0U,在此基础上,对照组给予注射用甲磺酸去铁胺(Wasserburger Arzneimittelwerk GmbH,注册证号:H20170147,规格:0.5 g)治疗,0.5 g 去铁胺溶于5 mL 注射用水,加入500 mL 生理盐水,静脉滴注,1次/d。研究组在对照

组的基础上口服去铁酮片(Apotex Inc.-Etobicoke Site,注册证号:H20140379,规格:0.5g),75 mg/(kg·d),3次/d。两组患儿均治疗12个月。治疗过程中,每3个月检查1次肝功能,每周检查1次血常规,当粒细胞低于 $1.5 \times 10^9/L$ 时,去铁酮停药,加用维生素B6、鲨肝醇口服提升粒细胞,服用3d后复查,当粒细胞增加至正常范围时,治疗加用去铁酮;当丙氨酸转氨酶 $>80U/L$ 时,治疗加用葡醛内酯护肝。

1.3 观察指标

1.3.1 标本采集和处理 于治疗前、治疗12个月后(治疗后)采集所有患儿清晨空腹静脉血5 mL,2800 r/min 离心12 min,离心半径8 cm,分离血清,置于-30℃冰箱中待测。收集患儿治疗前后24h 尿液样本。

1.3.2 实验室指标 采用美国Beckman公司生产的Access化学发光仪分析患儿尿铁排泄量(Urinary iron excretion,UIE)、血清铁蛋白(Serum ferritin,SF)水平;采用美国贝克曼库尔特公司生产的DXC800全自动生化分析仪检测空腹血糖(Fasting blood glucose,FBG),参考2007年美国糖尿病学会制订的标准^[11];正常值为 $FBG<5.6$ mmol/L,FBG在5.6~7.0 mmol/L范围内为FBG受损,FBG超过7.0 mmol/L为糖尿病,记录两组患儿治疗前后血糖代谢正常率。

1.3.3 临床疗效 对比两组患儿治疗后的临床疗效。SF较治疗前降低 >500 ng/mL且 ≤ 2000 ng/mL(显效);SF较治疗前降低100~500 ng/mL且 ≤ 2000 ng/mL(有效);SF持续升高且 >4000 ng/mL(无效)^[12]。

1.3.4 不良反应 记录治疗期间的不良反应,如腹痛、呕吐等。

1.4 统计学方法

采用SPSS20.0软件进行分析。以%表示计数资料,行 χ^2 检验。以($\bar{x} \pm s$)表示计量资料,行t检验,以 $\alpha=0.05$ 为检验水准。

2 结果

2.1 临床疗效比较

治疗后研究组临床总有效率为73.44%(47/64),高于对照组患儿的55.56%(35/63)($P<0.05$),详见表1。

表1 两组患儿临床疗效比较[n(%)]

Table 1 Comparison of clinical efficacy between two groups [n(%)]

Groups	Effective	Good	Bad	Total effective rate
Control group(n=63)	10(15.88)	25(39.68)	28(44.44)	35(55.56)
Research group(n=64)	14(21.88)	33(51.56)	17(26.56)	47(73.44)
χ^2		2.437		
P		0.035		

2.2 两组患儿血糖代谢比较

治疗前两组患儿血糖代谢正常率比较无统计学差异($P>0.05$);两组患儿治疗后血糖代谢正常率均升高,且研究组高于对照组($P<0.05$),详见表2。

2.3 两组患儿铁代谢情况比较

两组患儿治疗前SF、UIE比较差异无统计学意义($P>$

0.05);两组患儿治疗后SF降低,UIE升高($P<0.05$);研究组治疗后SF低于对照组,UIE高于对照组($P<0.05$),详见表3。

2.4 不良反应比较

治疗期间两组不良反应发生率比较无统计学差异($P>0.05$),详见表4。

3 讨论

表 2 两组患儿血糖代谢比较[n(%)]

Table 2 Comparison of blood sugar metabolism between two groups[n(%)]

Groups	Normal rate of blood sugar metabolism	
	Before treatment	After treatment
Control group(n=63)	13(20.63)	26(41.27)*
Research group(n=64)	15(23.44)	42(65.63)*
χ^2	0.145	3.571
<i>P</i>	0.703	0.006

Note: Compared with before treatment, * $P<0.05$.表 3 两组患儿铁代谢情况比较($\bar{x}\pm s$)Table 3 Comparison of iron metabolism between two groups($\bar{x}\pm s$)

Groups	SF($\mu\text{g/L}$)		UIE($\mu\text{g/L}$)	
	Before treatment	After treatment	Before treatment	After treatment
Control group(n=63)	3057.35 $\pm$ 392.26	2239.15 $\pm$ 371.63*	0.58 $\pm$ 0.08	0.67 $\pm$ 0.11*
Research group(n=64)	3060.46 $\pm$ 428.41	1825.76 $\pm$ 296.34*	0.56 $\pm$ 0.11	0.75 $\pm$ 0.09*
<i>t</i>	0.043	6.936	1.170	4.489
<i>P</i>	0.966	0.000	0.244	0.000

Note: Compared with before treatment, * $P<0.05$.

表 4 两组不良反应比较[n(%)]

Table 4 Comparison of adverse reactions between two groups[n(%)]

Groups	Abdominal pain	Vomit	Granulocytopenia	Joint swelling	Total incidence rate
Control group(n=63)	3(4.76)	5(7.94)	6(9.52)	3(4.76)	17(26.98)
Research group(n=64)	4(6.25)	5(7.81)	8(12.50)	4(6.25)	21(32.81)
χ^2			0.514		
<i>P</i>			0.473		

重型地中海贫血是一种基因改变导致珠蛋白生成障碍性的血液系统性疾病,该病可导致患儿体格发育障碍,影响患儿听力及视力,此外,未经治疗的重型地中海贫血患儿的期望寿命为 5 岁,致残率、致死率极高,给患儿家属带来巨大的精神负担^[13]。由于其发病与遗传息息相关,因此,临床对其治疗尚缺乏有效的根治性方案。现阶段常采用移植干细胞、脾切除或栓塞、长期输血等方式治疗,由于患儿各器官系统尚未发育完全,而脾脏作为人体最大的免疫器官,若行脾切除或栓塞易使患儿免疫力低下引发感染,影响患儿生长发育及生活质量^[14,15];干细胞移植虽然被不少学者认为是重型地中海贫血的根治性方法,但该治疗方式费用昂贵,而供者来源需与人类白细胞抗原相合,寻找较为困难,且无法避免术后排斥反应,致使无法大规模开展治疗^[16-18]。因此,现临床多数重型地中海贫血患儿均选择长期输血治疗。由于重型地中海贫血患儿 HGB 被破坏,铁蛋白在肝、肾、心以及胰腺等器官中大量蓄积,体内铁负荷量又因长期输血增加,而机体铁代谢和血糖代谢密切相关,铁过载可引起机体血糖代谢紊乱^[19,20]。去铁酮、去铁胺作为临床最常用的除铁剂,去铁胺作为治疗重型地中海贫血患儿的一线治疗药物,疗效确切,但长期使用不良反应较多,而去铁酮的临床应用经

验较少,其疗效一直存在争议^[21,22]。

本研究结果显示,治疗后研究组临床总有效率较对照组升高,可见联合用药治疗重型地中海贫血患儿效果较好。去铁胺作为一种螯合剂,可与铁离子特异性结合,形成大分子铁胺复合物,并从尿及粪便中排出,有效防止铁超负荷,维护器官功能^[23,24]。去铁酮作为小分子螯合剂,口服易吸收,依从性好,通过与铁离子结合而将体内铁蛋白迅速清除,亦可促进与转铁蛋白结合的铁离子代谢,最终提高治疗效果^[25,26]。本次研究结果还显示,研究组治疗后 SF 低于对照组,UIE 高于对照组,提示去铁酮联合去铁胺治疗可有效调节机体铁代谢,去铁酮的半衰期较长,为 2~3h,且主要经由肾脏排泄,其可快速通过细胞膜并清除细胞内的铁,以 3:1 的比例结合铁离子,最终经由尿液排出。同时,两组患儿治疗后血糖代谢正常率均升高,且研究组高于对照组,可见去铁酮联合去铁胺治疗可有效调节患儿血糖代谢,分析其原因,骨成形蛋白是调控铁代谢的重要因子,同时也是调控机体胰岛素分泌的重要因子,当铁过载时,骨成形蛋白信号通路被激活,上调铁调素的表达,同时影响胰岛素分泌^[27,28]。而联合去铁酮的治疗可有效减少体内铁离子,同时去铁酮还具有减少脂肪重量、脂肪细胞体积、脂肪组织巨噬细胞浸

润以及负荷后血糖的作用^[29]。此外,两组患儿治疗期间不良反应发生率比较无差异,表明去铁酮联合去铁胺治疗重型地中海贫血患儿,安全性较好,不增加不良反应发生率。

综上所述,去铁酮联合去铁胺治疗重型地中海贫血患儿疗效显著,可有效改善机体血糖代谢和铁代谢,安全可靠,临床应用价值较高。

参考文献(References)

- [1] Thiagarajan A, Bagavandas M, Kosalram K. Assessing the role of family well-being on the quality of life of Indian children with thalassemia[J]. BMC Pediatr, 2019, 19(1): 100
- [2] Zahir H, Chakour M, Mouhib H, et al. Epidemiological, clinico-biological, therapeutic and evolutionary aspects of β -thalassemia in Morocco[J]. Ann Biol Clin (Paris), 2019, 77(2): 169-173
- [3] Demosthenous C, Vlachaki E, Apostolou C, et al. Beta-thalassemia: renal complications and mechanisms: a narrative review [J]. Hematology, 2019, 24(1): 426-438
- [4] Akinbami AO, Sobota AE, Luo HY, et al. A Mild Phenotype of Severe β^+ Thalassemia in a 16-Month-Old Boy[J]. J Pediatr Hematol Oncol, 2018, 40(3): e145-e147
- [5] Liu W, Liu J, Du H, et al. Non-invasive pre-implantation aneuploidy screening and diagnosis of beta thalassemia IVSII654 mutation using spent embryo culture medium[J]. Ann Med, 2017, 49(4): 319-328
- [6] Agarwal RK, Sedai A, Ankita K, et al. Information Technology-Assisted Treatment Planning and Performance Assessment for Severe Thalassemia Care in Low- and Middle-Income Countries: Observational Study[J]. JMIR Med Inform, 2019, 7(1): e9291
- [7] Mettananda S, Pathiraja H, Peiris R, et al. Blood transfusion therapy for β -thalassemia major and hemoglobin E β -thalassemia: Adequacy, trends, and determinants in Sri Lanka[J]. Pediatr Blood Cancer, 2019, 66(5): e27643
- [8] Arandi N, Haghpanah S, Safaei S, et al. Combination therapy - deferasirox and deferoxamine - in thalassemia major patients in emerging countries with limited resources[J]. Transfus Med, 2015, 25(1): 8-12
- [9] Saliba AN, Taher AT. Comment on "deferiprone versus deferoxamine in thalassemia intermedia: results from a 5-year long-term Italian multicenter randomized clinical trial"[J]. Am J Hematol, 2015, 90(9): E192-E193
- [10] 中华医学会儿科学分会血液学组. 重型 β 地中海贫血的诊断和治疗指南[J]. 中华儿科杂志, 2010, 48(3): 186-189
- [11] 钱荣立. 美国糖尿病学会 2007 版糖尿病诊疗标准 (二)[J]. 中国糖尿病杂志, 2007, 15(3): I-IV
- [12] 黄春生, 陈国华. 去铁胺治疗重型 β -地中海贫血患儿的疗效及不良反应分析[J]. 中国妇幼健康研究, 2016, 27(6): 726-728
- [13] 陈文强, 陈萍, 丘玉铃, 等. 广西地区 104 例泰国缺失型 α -地中海贫血 1 的研究[J]. 现代生物医学进展, 2015, 15(24): 4649-4652
- [14] Merchant RH, Shah AR, Ahmad J, et al. Post Splenectomy Outcome in β -Thalassemia[J]. Indian J Pediatr, 2015, 82(12): 1097-1100
- [15] Al-Salem AH. Splenectomy for Children With Thalassemia: Total or Partial Splenectomy, Open or Laparoscopic Splenectomy[J]. J Pediatr Hematol Oncol, 2016, 38(1): 1-4
- [16] Srivastava A, Shaji RV. Cure for thalassemia major - from allogeneic hematopoietic stem cell transplantation to gene therapy [J]. Haematologica, 2017, 102(2): 214-223
- [17] Strocchio L, Locatelli F. Hematopoietic Stem Cell Transplantation in Thalassemia[J]. Hematol Oncol Clin North Am, 2018, 32(2): 317-328
- [18] Patel S, Swaminathan VV, Mythili VS, et al. Quality Matters - Hematopoietic Stem Cell Transplantation versus Transfusion and Chelation in Thalassemia Major [J]. Indian Pediatr, 2018, 55(12): 1056-1058
- [19] Wahidiyat PA, Sekarsari D, Adnani NB, et al. Association of pancreatic MRI R2* with blood glucose and cardiac MRI R2* among thalassemiamajor patients in Indonesia [J]. Am J Hematol, 2017, 92(10): E620-E621
- [20] El-Samahy MH, Tantawy AA, Adly AA, et al. Evaluation of continuous glucose monitoring system for detection of alterations in glucose homeostasis in pediatric patients with β -thalassemia major[J]. Pediatr Diabetes, 2019, 20(1): 65-72
- [21] Badfar G, Mansouri A, Shohani M, et al. Hearing loss in Iranian thalassemia major patients treated with deferoxamine: A systematic review and meta-analysis [J]. Caspian J Intern Med, 2017, 8(4): 239-249
- [22] Kolnagou A, Kontoghiorghes CN, Kontoghiorghes GJ. Prevention of Iron Overload and Long Term Maintenance of Normal Iron Stores in Thalassemia Major Patients using Deferiprone or Deferiprone Deferoxamine Combination [J]. Drug Res (Stuttg), 2017, 67(7): 404-411
- [23] Al-Kuraishy HM, Al-Gareeb AI. Comparison of deferasirox and deferoxamine effects on iron overload and immunological changes in patients with blood transfusion-dependent β -thalassemia [J]. Asian J Transfus Sci, 2017, 11(1): 13-17
- [24] Hassan MA, Tolba OA. Iron chelation monotherapy in transfusion-dependent beta-thalassemia major patients: a comparative study of deferasirox and deferoxamine [J]. Electron Physician, 2016, 8(5): 2425-2431
- [25] 周传恩, 熊寿贵. 去铁胺联合去铁酮对重型地中海贫血患儿血糖代谢的影响[J]. 中国药业, 2018, 27(13): 46-49
- [26] 许金云, 杜立安, 马红艳, 等. 去铁酮致重型 β 地中海贫血患儿粒细胞缺乏 1 例并文献复习[J]. 中国小儿血液与肿瘤杂志, 2018, 23(4): 189-193
- [27] Voskaridou E, Ntanas-Stathopoulos I, Christoulas D, et al. Denosumab effects on serum levels of the bone morphogenetic proteins antagonist noggin in patients with transfusion-dependent thalassemia and osteoporosis[J]. Hematology, 2019, 24(1): 318-324
- [28] Morabito N, Catalano A, Gaudio A, et al. Effects of strontium ranelate on bone mass and bone turnover in women with thalassemia major-related osteoporosis [J]. J Bone Miner Metab, 2016, 34(5): 540-546
- [29] Ansari S, Azarkeivan A, Miri-Aliabad G, et al. Comparison of iron chelation effects of deferoxamine, deferasirox, and combination of deferoxamine and deferiprone on liver and cardiac T2* MRI in thalassemia major[J]. Caspian J Intern Med, 2017, 8(3): 159-164
- [30] 仇世伟. 去铁胺联合去铁酮治疗重型 β 地中海贫血铁过载疗效观察[J]. 安徽医学, 2016, 37(5): 595-597