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初始小剂量甲硫咪唑对 Graves 病甲亢患者甲状腺功能和 Visfatin、TNF- α 、IL-6 水平的影响 *

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摘要 目的:分析初始小剂量甲硫咪唑治疗对 Graves 病甲状腺功能亢进症(甲亢)患者甲状腺功能和内脂素(Visfatin)、肿瘤坏死因子- α (Tumor necrosis factor- α , TNF- α)、白介素-6(Interleukin-6, IL-6)水平的影响。**方法:**选择我院 2017 年 1 月-2018 年 6 月诊治的 125 例 Graves 病甲亢患者,根据入院编号随机数字表法分为两组。对照组 63 例给予甲硫咪唑 15 mg/次,2 次/d;研究组 62 例给予甲硫咪唑 10 mg/次,2 次/d,两组均连续治疗 6 个月,对比两组治疗总有效率、治疗前后甲状腺功能和血清 Visfatin、TNF- α 、IL-6 水平的变化。**结果:**治疗后,研究组的治疗总有效率显著高于对照组(90.32% vs. 77.78%, $P < 0.05$);两组患者的甲状腺功能指标血清游离三碘甲状腺原氨酸(Free triiodothyronine, FT3)、血清游离甲状腺素(FT4)水平均显著降低、敏感促甲状腺激素(Sensitive thyroid stimulating hormone, sTSH)水平均显著升高,且研究组以上指标变化较对照组更显著($P < 0.05$);两组患者的血清 Visfatin、TNF- α 、IL-6 水平均较治疗前显著下降,且研究组以上指标均显著低于对照组($P < 0.05$)。**结论:**初始小剂量(10 mg/次)甲硫咪唑治疗 Graves 病甲亢的疗效显著优于甲硫咪唑 15 mg/次治疗,可能与其有效改善患者的甲状腺功能和血清 Visfatin、TNF- α 、IL-6 等炎症因子水平有关。

关键词:初始小剂量;甲硫咪唑;Graves 病甲亢;疗效;炎症因子

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Effect of Initial Low-dose Methimazole on the Thyroid Function and Serum Visfatin, TNF- α and IL-6 Levels in the Patients with Graves' Hyperthyroidism*

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ABSTRACT Objective: To analyze the clinical efficacy of initial low-dose methimazole in the treatment of patients with Graves' hyperthyroidism and its effect on the thyroid function and visfatin, TNF- α and IL-6 levels. **Methods:** 125 patients with Graves' hyperthyroidism who were diagnosed in our hospital from January 2017 to June 2018 were selected and divided into two groups according to the admission number. 63 cases in the control group were given methimazole 15 mg/time, twice a day. 62 cases in the study group were given methimazole 10 mg/time, twice a day, and both groups were treated continuously for 6 months. The total effective rate, changes of thyroid function and the levels of Visfatin, TNF- α , IL-6 of before and after treatment were compared between two groups. **Results:** After treatment, the total effective rate of study group was significantly higher than that of the control group (90.32% vs. 77.78%, $P < 0.05$). After treatment, the levels of thyroid function indexes of FT3 and FT4 in the two groups were significantly decreased, while the sTSH level was significantly increased, and the above indicators in the study group improved more significant than the control group ($P < 0.05$). After treatment, the levels of serum Visfatin, TNF- α , and IL-6 decreased in the two groups were significantly lower than those before treatment, and the above indexes of the study group were more significantly lower than the control group ($P < 0.05$). **Conclusions:** The initial low-dose (10 mg/time) methimazole was significantly better than methimazole 15 mg/treatment in the treatment of Graves' disease, which may be related to effectively improve the thyroid function of patients and the levels of inflammatory factors such as serum Visfatin, TNF- α , IL-6.

Key words: Initial low-dose; Methimazole; Graves' hyperthyroidism; Curative effect; Inflammatory factor

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前言

Graves 病甲状腺功能亢进症(甲亢)是一种临床上较为常见的、发病率高的代谢性疾病,具有器官特异性、自身免疫性等特点^[1,2],与遗传、环境、免疫系统异常等因素密切相关,多在机体受到感染、精神创伤等应急状态下诱发^[3,4],患者会表现出高代谢症状、甲状腺肿大、眼征、神经系统症状、心血管系统症状、血液和造血系统症状等^[5]。据资料显示,Graves 病约占所有甲状腺功能亢进症的 85%,发病率 1.5%左右,高发年龄段在 20-40 岁,在女性群体中的发病率显著高于男性,且存在一定的遗传倾向^[6,7]。

甲硫咪唑是一种咪唑类抗甲状腺药物,可通过抑制甲状腺内过氧化物酶的活性阻碍吸聚以甲状腺内碘化物的氧化及酪氨酸的偶联,进而阻碍 T4 和 T3 的合成,达到治疗甲亢的目的^[8-10],但临床上对于其使用剂量仍存在较大争议^[11-13]。本研究通过收集 2017 年 1 月-2018 年 6 月我院收治的 Graves 病甲亢患者 125 例作为研究对象,分析初始小剂量甲硫咪唑治疗 Graves 病甲状腺功能亢进症的疗效,以期临床用药提供参考,具体内容报道如下。

1 资料与方法

1.1 一般资料

收集 2017 年 1 月-2018 年 6 月来我院诊治的 Graves 病甲亢患者 125 例,纳入标准:符合《中国甲状腺疾病诊治指南》中 Graves 病甲亢的诊断标准;对本研究用药物不过敏者;能全程配合治疗且接受随访者。排除标准:患有甲状腺炎、桥本甲状腺炎等病史者;存在晒剂、免疫制剂、激素等药物史者;肝肾功能不全者;依从性较差者;药物过敏史者。根据入院编号随机数字表法将患者分为两组,对照组 63 例,男/女比例为 29/34,年龄 21-76 岁,平均年龄为(40.3±4.5)岁,病程范围在 6 个月-11 年,平均病程为(5.3±1.7)年;研究组 62 例,男/女比例为 27/35,年龄范围在 20-78 岁,平均年龄为(39.6±4.8)岁,病程 8

个月-10 年,平均病程为(5.5±1.5)年。两组患者的基础资料比较无统计学差异($P>0.05$),具有可比性。本研究已获得我院医学伦理委员会的批准,且患者均自愿签署《知情同意书》。

1.2 治疗方法

对照组:给予甲硫咪唑(德国默克公司,注册证号 H20100528)15 mg/次,2 次/d,餐前服用。研究组:给予甲硫咪唑 10 mg/次,餐前服用,2 次/d。待患者临床症状减轻,甲状腺功能 FT3、FT4 水平恢复正常,可酌情将服用剂量降低为 5 mg/次,1 次/d。所有患者均治疗 6 个月。

1.3 观察指标

(1)治疗后随访 3 个月,对比治疗总有效率^[14,15]。疗效评价标准:临床症状消失,甲状腺肿大减轻 $>1^{\circ}$ 即为临床控制;临床症状基本消失,甲状腺肿大减轻 $\leq 1^{\circ}$ 内即为显效;临床症状得到缓解,甲状腺功能出现好转,即为有效;未达到上述指标者为无效,其中,总有效率=[(临床控制+显效+有效)/总例数]×100%。(2)治疗前后取两组的空腹静脉血 10 mL,离心得血清,一部分采用罗氏 E170 化学发光仪检测其血清游离三碘甲状腺原氨酸(FT3)、血清游离甲状腺素(FT4)、敏感促甲状腺激素(sTSH)等水平变化^[16]。另一部分采用酶联免疫吸附法检测其内脂素(Visfatin)、肿瘤坏死因子- α (TNF- α)、白介素-6(IL-6)等水平,试剂盒均购买于上海酶联免疫有限公司^[17]。

1.4 统计学分析

采用 SPSS20.0 统计学软件对本研究所得数据进行处理,计数资料以例数、百分比表示,对比经卡方分析;计量资料以均数±标准差表示,对比经 t 检验; $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组的治疗总有效率对比

治疗后,研究组的治疗总有效率为 90.32%(56/62),显著高于对照组[77.78%(49/62)],差异具有统计学意义($P<0.05$),见表 1。

表 1 两组的治疗总有效率对比(例,%)

Table 1 Comparison of the total effective rate of treatment between the two groups (n,%)

Groups	n	Clinical control	Significant effect	Effective	Invalid	Total efficiency
Research group	62	23(37.10)	20(32.26)	13(20.97)	6(9.68)	56(90.32)*
Control group	63	18(28.57)	16(25.40)	15(23.81)	14(22.22)	49(77.78)

Note: compared with the control group, * $P<0.05$.

2.2 两组治疗前后的甲状腺功能对比

治疗前,两组的甲状腺功能指标 FT3、FT4、sTSH 等对比无统计学差异($P>0.05$);治疗后,两组的甲状腺功能指标 FT3、

FT4 水平均较治疗前显著降低,而 sTSH 水平均较治疗前显著升高,且研究组以上指标改善显著优于对照组($P<0.05$)。见表 2。

表 2 两组治疗前后的甲状腺功能对比($\bar{x}\pm s$)

Table 2 Comparison of the thyroid function before and after treatment between the two groups ($\bar{x}\pm s$)

Groups		FT3(μ U/L)	FT4(μ U/L)	sTSH(U/L)
Research group(n=62)	Before treatment	12.45±3.81	46.35±5.98	0.13±0.03
	After treatment	5.39±1.36**	14.16±2.63**	1.33±0.26**
Control group(n=63)	Before treatment	12.40±3.96	46.09±5.57	0.13±0.04
	After treatment	7.03±1.92*	25.26±4.01*	0.70±0.18*

2.3 两组治疗前后的血清炎症因子水平对比

治疗前, 两组的血清 Visfatin、TNF- α 、IL-6 水平对比无显著性差异($P>0.05$); 治疗后, 两组的血清 Visfatin、TNF- α 、IL-6

水平均较治疗前显著下降, 且研究组以上指标显著低于对照组($P<0.05$)。见表 3。

表 3 两组治疗前后的血清 Visfatin、TNF- α 、IL-6 水平对比($\bar{x} \pm s$)

Table 3 Comparison of the serum Visfatin, TNF- α and IL-6 levels between the two groups before and after treatment($\bar{x} \pm s$)

Groups		Visfatin(ng/mL)	TNF- α (ng/mL)	IL-6(pg/mL)
Research group(n=62)	Before treatment	144.18 $\pm$ 37.32	13.15 $\pm$ 3.58	509.16 $\pm$ 59.63
	After treatment	45.06 $\pm$ 8.36* [#]	9.62 $\pm$ 2.06* [#]	442.65 $\pm$ 55.27* [#]
Control group(n=63)	Before treatment	143.63 $\pm$ 36.95	11.02 $\pm$ 2.94	510.35 $\pm$ 65.98
	After treatment	72.61 $\pm$ 15.31*	9.58 $\pm$ 2.11*	482.41 $\pm$ 57.05*

Note: * $P<0.05$ compared with before treatment; [#] $P<0.05$ compared with the control group.

3 讨论

Graves 病又称为毒性弥漫性甲状腺肿, 是一种伴随甲状腺激素分泌增加的自身免疫系统疾病, 导致自身抗体增加, 机体出现高代谢症候群, 包括高代谢症候群、弥漫性甲状腺肿、眼症、皮损和甲状腺肢端病^[18], 可能和遗传、创伤, 自身免疫性有关, 目前病因不是很明确。典型病例的诊断一般并不困难。轻症患者, 或年老和儿童病例的临床表现少而不典型, 诊断常须借助实验室检查。由于 Graves 病的病因尚未明确, 所以治疗 Graves 病的基础并不是根据病因而确定。目前, 临床上控制甲亢症群的基本方法为放射性核素碘治疗、抗甲状腺药物治疗、手术治疗、介入栓塞治疗^[19,20], 抗甲状腺药物疗法使用方便、容易被病人接受, 治疗后不会引起不可逆的损伤, 应用范围广。

甲硫咪唑商品俗称为他巴唑、甲硫咪唑、甲硫噻唑, 甲硫咪唑片其实是属于抗甲状腺药物, 适用于各种类型的甲状腺功能亢进症。目前, 甲硫咪唑是治疗 Graves 病甲状腺功能亢进症的首选药物, 但对于其最佳初始剂量临床上尚无定论, 国内也相对缺乏此类系统性的研究^[21]。本研究结果显示研究组的治疗总有效率显著高于对照组, 表明初始小剂量甲硫咪唑治疗 Graves 病甲亢的效果显著, 提示甲硫咪唑作为临床上常用的抗甲状腺药物, 治疗作用主要取决于在甲状腺内的药物浓度, 初始小剂量服用甲硫咪唑可使机体甲状腺体内的有效药物浓度较为稳定, 同时小剂量对机体的不良反应少, 而且患者对药物的依赖性小, 从而提高了治疗的总有效率。

甲状腺激素作为参与人体脂类代谢的重要内分泌激素, 是调节机体发生氧化分解反应的重要物质^[22-24]。FT3、FT4 由于含量不受甲状腺结合蛋白浓度和结合力度的影响, 被广泛应用于甲亢、甲减的临床诊断、病情评估、疗效检测等过程中。sTSH 是一种由脑垂体分泌的激素, 可促进机体内甲状腺的合成, 分泌甲状腺激素^[25-27]。本研究结果显示两组患者治疗后的甲状腺功能指标 FT3、FT4 水平均显著降低, sTSH 水平均显著升高, 且研究组以上指标变化地更显著, 表明初始小剂量甲硫咪唑可有效改善患者的甲状腺功能, 提示甲状腺摄取甲硫咪唑存在着饱和和状态, 而且有效时间能维持 24 h 以上, 初始小剂量甲硫咪唑, 可以使血液中与甲状腺的甲硫咪唑维持一致, 从而有助于调节下丘脑 - 垂体 - 甲状腺轴的稳定, 进一步改善甲状腺功能, 降低 FT3、FT4 水平, 升高 sTSH 水平^[28]。Visfatin 是一种脂肪细

胞因子, 不仅具有类胰岛素活性, 还可促进脂肪的合成, 同时, 脂肪细胞也可分泌 TNF- α , 已有大量研究表明显示, TNF- α 参与了胰岛素抵抗的形成, 并在其发病机制中具有重要作用^[29]; IL-6 是一种重要的引起胰岛素抵抗的炎症因子, 不仅本身参与炎症反应, 还是重要的能量平衡中调节因子^[30]。本研究结果显示, 治疗后, 两组患者的血清 Visfatin、TNF- α 、IL-6 水平均比治疗前显著下降, 且研究组降低地更显著, 表明初始小剂量甲硫咪唑可有效改善 Graves 病甲亢患者的炎症因子水平, 提示促炎细胞因子与 Graves 病甲亢密切相关。

综上所述, 初始小剂量(10 mg/次)甲硫咪唑治疗 Graves 病甲亢的疗效显著优于甲硫咪唑 15 mg/次治疗, 可能与其有效改善患者的甲状腺功能和血清 Visfatin、TNF- α 、IL-6 等炎症因子水平有关。

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