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二甲双胍联合维格列汀对初治 II 型糖尿病患者血糖的控制效果及安全性 *

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摘要 目的:研究二甲双胍联合维格列汀对初治 II 型糖尿病患者血糖的控制效果及安全性。**方法:**选择 2015 年 2 月至 2016 年 4 月在我院进行治疗的 2 型糖尿病患者 60 名,按照治疗方法分为观察组和对照组,对照组使用二甲双胍治疗,观察组在对照组基础上联合维格列汀治疗,观察和比较两组治疗后的临床疗效,治疗前后血清白介素-6、肿瘤坏死因子、C 反应蛋白、空腹血糖、糖化血红蛋白、餐后两小时血糖及血清淀粉酶及尿液淀粉酶水平的变化。**结果:**治疗后,观察组总有效率 90%,明显高于对照组有效率 66.7%,差异显著($P<0.05$)。观察组治疗后的血清白介素-6、肿瘤坏死因子、C 反应蛋白、空腹血糖、糖化血红蛋白、餐后两小时血糖水平均明显低于对照组 [(7.63±1.12)d vs (8.68±1.30)d, (7.23±0.95)d vs (7.89±1.20)d, (11.14±1.56)d vs (12.12±1.89)d], [(12.12±1.89)d vs (11.20±1.34)d, (6.89±0.96)d vs (8.23±1.10)d, (1.65±0.23)d vs (3.65±0.48)d] ($P<0.05$)。治疗后,观察组的 INS 水平较对照组显著降低($P<0.05$),且 GLP-1 水平较对照组明显升高显著差异($P<0.05$)。**结论:**二甲双胍联合维格列汀可有效控制初治 2 型糖尿病患者的血糖水平,并提高治疗安全性。

关键词:二甲双胍;维格列汀;2 型糖尿病;血糖控制;安全性

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Effects and Safety of Metformin Combined with Vildagliptin on the Glycemic Control for Patients with Newly Diagnosed Type 2 Diabetes Mellitus*

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ABSTRACT Objective: To study the effects and safety of metformin combined with vildagliptin on the glycemic control for patients with newly diagnosed type 2 diabetes mellitus. **Methods:** 60 patients with type 2 diabetes mellitus who were treated from February 2015 to April 2016 were selected and divided into the control group and the observation group according to different treatment methods. The control group was treated with routine treatment. The observation group was treated with vildagliptin based on the control group. The blood glucose, glycosylated hemoglobin, two-hour postprandial blood glucose and serum as well as urinal amylase were measured before and after treatment, and the clinical curative effect of the two groups and the levels of interleukin-6, tumor necrosis factor and C-reactive protein were compared. **Results:** After treatment, the total effective rate of observation group was 90%, which was significantly higher than that of the control group (66.7%, $P<0.05$). After treatment, the serum interleukin-6, tumor necrosis factor, C-reactive protein and fasting blood glucose, glycosylated hemoglobin and postprandial blood glucose levels were significantly lower than those of the control group [(7.63±1.12)d vs (8.68±1.30)d; (7.23±0.95)d vs (7.89±1.20)d; (11.14±1.56)d vs (12.12±1.89)d]; [(12.12±1.89)d vs (11.20±1.34)d; (6.89±0.96)d vs (8.23±1.10)d; (1.65±0.23)d vs (3.65±0.48)d] ($P<0.05$). After treatment, the INS level of observation group was significantly lower than that of the control group ($P<0.05$) and the GLP-1 level was significantly higher than that of the control group ($P<0.05$). **Conclusion:** Metformin combined with vildagliptin could effectively control the blood glucose of patients with newly diagnosed type 2 diabetes and enhance the safety.

Key words: Metformin; Vildagliptin; Type 2 diabetes mellitus; Blood sugar control; Safety

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前言

糖尿病是由生活方式等多种因素引发的慢性疾病,以 2 型糖尿病为主,主要集中在中老年人群体^[1,2]。我国 2 型糖尿病的

发病率高达 10%,目前临床治疗糖尿病的常用药物为口服降糖药二甲双胍,其可以降低血糖水平及炎症因子指标,但长期使用此药会导致患者血糖控制水平变差且不良反应率较高^[3,4]。维格列汀中含有 DPP-4 抑制剂,同样适用于治疗 2 型糖尿病,其

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能有效抑制血糖、血脂水平及控制肥胖等且不良反应率较低,其临床疗效及安全性较高^[5,6]。目前,临床上将二甲双胍与维格列汀联合治疗 II 型糖尿病患者相关案例较少,其联用效果相对空白,为观察其联合用药效果,本次研究探讨了二甲双胍联合维格列汀对初治 II 型糖尿病患者血糖控制效果及安全性。报道如下:

1 材料与方法

1.1 一般资料

选择 2015 年 2 月至 2016 年 4 月在我院进行治疗的 2 型糖尿病患者 60 名。纳入标准:(1)符合 2000 年 WHO 糖尿病诊断标准^[7],近 3 个月内血压控制平稳;(2)确诊为 2 型糖尿病患者;(3)病程 10 年以上,排除标准(1)排除其他肾脏疾病;(2)排除对研究药物严重过敏反应者;(3)排除妊娠或哺乳期妇女。分为两组观察组及对照组进行观察,观察组 30 例患者,年龄在 34-46 岁,平均年龄(30.23± 4.60)岁,病程(13.63± 3.60)年;对照组 30 例患者,年龄在 37-51 岁,平均年龄(38.42± 6.92)岁,病程(12.61± 2.52)年;两组患者的年龄、性别及病程等一般资料无显著性差异($P>0.05$)。

1.2 方法

所有患者均采用 2 型糖尿病的饮食及运动治疗,对照组患者口服二甲双胍降糖药(北京太洋药业有限公司生产,0.5 g× 48 片,H20153371),0.5 g 三次/d;观察组在对照组的治療基础上联合维格列汀(瑞士诺华有限公司生产,50 mg× 14 片,H20160358)口服 50 mg 两次/d,持续 24 周治疗。

1.3 观察指标

① 治疗前后于清晨抽取静脉空腹血,患者至少空腹 8 h 采集静脉血,观察血糖、肿瘤坏死因子(TNF- α)、白介素-6(IL-6)、C 反应蛋白(CRP)的变化情况,方法:血糖采用免疫酶法检测;TNF- α 采用肿瘤坏死因子测定试剂盒、IL-6 采用白介素测定试剂盒、CRP 采用散射比浊法。② 血、尿淀粉酶水平:治疗前后采集两组患者的空腹静脉血及晨尿,检测血、尿淀粉酶水平观察两组入院治疗前后血清淀粉酶及尿液淀粉酶水平变化。③ 不良反应观察:记录治疗 24 周内的所有不良反应症状。④ 观察治疗前后胰岛素指标 INS、GLP-1 水平变化。

判定标准^[8]:① 显效:在治疗后血糖水平及炎症因子指标恢复正常水平;② 有效:治疗后患者的血糖水平及炎症因子指标明显降低;③ 无效:治疗后血糖水平及炎症因子指标无明显变化。

1.4 统计学分析

选择 SPSS 18.0 进行数据统计,本研究计量资料数据用均数± 标准差($\bar{x} \pm s$)来表示,比较使用 t 检验,计数资料的比较[n(%)]表示,比较则使用 χ^2 检验,当 $P<0.05$ 时表示其差异具有统计学意义。

2 结果

2.1 两组患者治疗前后血糖水平比较

治疗前,两组的 FPG、HbA1c、2hPG 比较差异无统计学意义($P>0.05$);治疗后,观察组的 FPG、HbA1c、2hPG 的水平均明显低于对照组,差异具有统计学意义($P<0.05$),详见表 1。

表 1 两组治疗前后血糖水平的比较($\bar{x} \pm s$)

Table 1 Comparison of the blood glucose level between two groups before and after the treatment ($\bar{x} \pm s$)

Groups	n	FPG(mmol/L)		HbA1c(%)		2hPG(mmol/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	30	9.65± 1.56	7.63± 1.12 ^b	8.46± 1.21	7.23± 0.95 ^b	17.21± 2.53	11.14± 1.56 ^b
Control group	30	9.42± 1.22	8.68± 1.30 ^a	9.13± 1.35	7.89± 1.2 ^a	16.02± 2.02	12.12± 1.89 ^a

Note: Compared with the same group before treatment ^a $P<0.05$; different groups after treatment ^b $P<0.05$.

2.2 两组治疗前后血清 IL-6、TNF- α 、CRP 水平的比较

两组在治疗前血清 IL-6、TNF- α 、CRP 的水平比较差异无

统计学意义($P>0.05$);治疗后,观察组血清 IL-6、TNF α 、CRP 的水平明显低于对照组($P<0.05$),差异具有统计学意义,详见表 2。

表 2 两组治疗前后血清 IL-6、TNF- α 、CRP 水平的比较($\bar{x} \pm s$)

Table 2 Comparison of the serum IL-6, TNF- α , CRP levels between two groups before and after the treatment($\bar{x} \pm s$)

Groups	n	IL-6(ng/L)		TNF- α (ng/L)		CRP	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	30	12.98± 1.89 ^c	7.89± 1.22 ^b	9.01± 1.32 ^c	6.89± 0.96 ^b	4.65± 0.82 ^c	1.65± 0.23 ^b
Control group	30	13.02± 1.66	11.20± 1.34	10.65± 1.45	8.23± 1.10	4.95± 0.86	3.65± 0.48

Note: Compared with the same group before treatment ^a $P>0.05$; different groups after treatment ^b $P<0.05$.

2.3 两组治疗前和治疗后血尿淀粉酶水平的比较

治疗前,两组的血清淀粉酶及尿液淀粉酶水平比较差异无统计学意义($P>0.05$);治疗后,观察组的血清淀粉酶及尿液淀粉酶水平明显低于对照组,差异均具有统计学意义($P<0.05$),详见表 3。

2.4 两组治疗后不良反应发生情况的比较

治疗后,观察组患者不良率为 16%,明显低于对照组(43.33%, $P>0.05$),差异无统计学意义,详见表 4。

2.5 两组患者治疗后疗效比较

治疗后,观察组的总有效率明显高于对照组,显著性差异($P<0.05$),详见表 5。

表 3 两组治疗前后尿淀粉酶水平的比较($\bar{x} \pm s$, IU/L)

Table 3 Comparison of the urine and serum amylase levels between two groups before and after the treatment($\bar{x} \pm s$, IU/L)

Groups	n	Serum amylase		Urine amylase	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	30	59.68 $\pm$ 8.56 ^c	54.77 $\pm$ 5.75 ^b	280.11 $\pm$ 35.32 ^c	263.68 $\pm$ 29.58 ^b
Control group	30	55.62 $\pm$ 6.88	58.91 $\pm$ 8.85	293.33 $\pm$ 42.82	291.32 $\pm$ 39.66

Note: Compared with the same group before treatment ^cP>0.05; different groups after treatment ^bP<0.05.

表 4 两组患者治疗后不良反应发生情况的比较[例(%)]

Table 4 Comparison of the incidence of adverse events between two groups after the treatment [n(%)]

Groups	n	Digestive tract reaction	Skin allergies	Hypoglycemia	Adverse reaction rate
Observation group	30	3(10.00) ^b	1(3.33) ^b	1(3.33) ^b	5(16.00%) ^b
Control group	30	8(26.67)	2(6.67)	3(3.33) ^a	13(43.33%)

Note: Comparison of adverse reactions in different groups ^bP<0.05.

表 5 两组患者治疗后疗效对比分析[例(%)]

Table 5 Comparison of the efficacy between two groups after the treatment [n (%)]

Groups	n	Markedly	Effective	Invalid	Total effective rate
Observation group	30	20(66.67) ^b	7(23.23) ^b	3(10.00) ^b	27(90%) ^b
Control group	30	8(26.67)	12(40.00)	10(33.33)	20(66.67%)

Note: Comparison of different groups of treatment analysis ^bP<0.05.

2.6 两组患者治疗前后 INS、GLP-1 水平的比较

治疗前, 两组患者 INS、GLP-1 水平比较差异无统计学意义(P>0.05); 治疗后, 观察组的胰岛素抗体(INS)水平较对照组

显著降低(P<0.05), 且胰高血糖素样肽(GLP-1)水平较对照组明显升高, 差异具有统计学意义(P<0.05), 详见表 6。

表 6 两组患者治疗前后 INS、GLP-1 水平比较

Table 6 Comparison of the INS and GLP-1 levels before and after treatment between two groups

Groups	Time	INS(mmol/L)	GLP-1(mmol/L)
Observation group (n=30)	Before treatment	59.53 $\pm$ 7.62 ^c	66.98 $\pm$ 9.01 ^c
	After treatment	45.16 $\pm$ 5.89 ^b	84.59 $\pm$ 12.28 ^b
Control group (n=30)	Before treatment	58.26 $\pm$ 7.01	67.03 $\pm$ 9.35
	After treatment	52.39 $\pm$ 6.63	74.34 $\pm$ 11.88

Note: Compared with the same group before treatment ^cP>0.05; different groups after treatment ^bP<0.05.

3 讨论

近年来, 随着人们生活水平发生重大改变, 糖尿病患者数量逐年上升, 主要表现为 2 型糖尿病^[9]。2 型糖尿病是一种严重的慢性非传染性疾病多在 30~40 岁之后发病, 因患者体内糖代谢紊乱, 导致脂肪及蛋白质等指标也变化异常, 促使血糖及血脂水平急剧升高, 令胰岛素反应降低且受到抑制导致恶性循环^[10]。研究结果表明, 2 型糖尿病患者 HbA1c 增加 2%, 就约有 15% 的患者死于心血管类疾病, 我国约有 2/3 的糖尿病患者的病情得不到有效地治疗^[11]。二甲双胍口服降糖药对抑制糖尿病患者的血糖、血脂水平、胰岛素及炎症因子指标具有一定作用, 但若单用二甲双胍降糖口服药治疗无法达到良好的效果且用其治疗后 43.33% 的患者出现不良反应。目前, 临床上对于治疗 2 型糖尿病无更加有效的治疗手段, 据相关文献报道, 联合使用降糖药物可提升该病治疗效果^[12,13]。经研究发现, 新药维格列汀对抑制血糖水平具有双向调节作用且不良反应发生率, 但联合二甲双胍治疗 2 型糖尿病其疗效并不明确, 本研究为观察

联合用药的临床治疗效果及对血糖、血脂水平、胰岛素及炎症因子指标的影响^[14]。

二甲双胍是治疗 2 型糖尿病的临床常用药物能降低患者的血糖指标, 其能一定程度抑制血糖、血脂水平但效果并不显著。作为新型药物的维格列汀是一种内含二肽基肽酶(DPP-4)的抑制剂, 其 DPP-4 复合物可抑制该酶的活性达到控制血糖血压等目的^[15]。而本次研究观察二甲双胍及维格列汀联合用药之后, 患者的病情得到了有效的控制, 治疗后患者的空腹血糖、糖化血红蛋白、餐后两小时血糖均明显降低。对比使用单药二甲双胍治疗 2 型糖尿病的患者, 联合用药可进一步控制血糖、血脂指标, 是目前治疗 2 型糖尿病的主要方法^[16,17]。

据国外相关文献报道, 2 型糖尿病与炎症因子 IL-6、TNF- α 、CRP 密切相关^[18]。IL-6 是种多功能细胞因子可对人体的造血系统及神经系统等作用显著; TNF- α 是人体内重要的介质, 具备多种化学功能并能形成免疫调节保护机体; CRP 是一种急性敏感性反应蛋白是人体内常见的炎症指标^[19]。本次研究中, 所有 2 型糖尿病患者在不同方式治疗后其 IL-6、

TNF- α 、CRP 水平均明显减低,但联合用药治疗效果更显著,IL-6、TNF- α 、CRP 水平均明显降低表示维格列汀中 DPP-4 成分能有效改善人体内的炎症因子水平。胰高血糖素样肽 GLP-1 是由肠道内分泌细胞合成分泌的肠促胰岛素,可显著改善患者的血糖水平^[20]。2 型糖尿病的一个重要发病原因就是机体胰岛功能逐步衰退造成,当患者体内的血糖指标急剧升高将作用于胰岛细胞膜受体促进胰岛素分泌。治疗前所有患者的 INS 水平明显偏高、GLP-1 水平偏低,治疗后,患者 INS 水平下降且 GLP-1 水平明显升高,联合用药患者较单用二甲双胍药物治疗的患者改善更明显。据相关文献表示,其差异造成的原因可能是维格列汀中 DPP-4 可阻断 GLP-1 降解并提高 GLP-1 的浓度及生物活性^[21]。本次 2 型糖尿病研究患者在经过不同方式的治疗后也有不同程度的改善,使用二甲双胍治疗后多数患者出现胃肠不适、皮肤过敏及低血糖等不良反应,而使用联合用药治疗的患者预后良好,不良反应发生率较低,表明联合用药可改善预后,减少不良反应。通过本此研究结果表示,经联合治疗的 2 型糖尿病患者其血糖、血脂水平、炎症因子指标、血尿酸酶水平及不良反应发生率均有明显减低。

综上所述,维格列汀联用二甲双胍降糖药能有效降低 2 型糖尿病患者血糖水平且安全性较高,治疗后不良反应发生率较低且能避免引起肥胖。联合应用降糖药物具有较高临床价值应广泛应用。

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