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大剂量胰岛素联合西格列汀对老年 2 型糖尿病患者的疗效

熊慧丽¹ 王 毅² 赵晓宏¹ 周庆元¹ 柳 杨¹

(1 西安交通大学附属三二〇一医院内分泌科 陕西 汉中 723000;

2 西安交通大学第一附属医院内分泌科 陕西 西安 710061)

摘要 目的:研究大剂量胰岛素联合西格列汀对老年 2 型糖尿病患者的疗效。**方法:**选择 2012 年 1 月~2015 年 12 月在我院进行诊治的老年 2 型糖尿病患者 82 例,随机分为两组,观察组采用大剂量胰岛素联合西格列汀治疗,对照组采用大剂量胰岛素治疗,两组均治疗 3 个月。比较两组治疗前后的甘油三酯、总胆固醇、低密度脂蛋白和高密度脂蛋白水平,餐后 2 h 血糖、空腹血糖、糖化血红蛋白,胰岛素抵抗指数、胰岛素分泌指数、每日胰岛素总量和低血糖发生次数。**结果:**对照组治疗前后的血脂水平无明显差异($P>0.05$),观察组治疗后的甘油三酯、总胆固醇和低密度脂蛋白明显降低($P<0.05$),高密度脂蛋白明显升高($P<0.05$);治疗后,两组的餐后 2 h 血糖、空腹血糖、糖化血红蛋白均明显降低($P<0.05$),且观察组降低更为明显($P<0.05$);对照组治疗前后的胰岛素抵抗指数、胰岛素分泌指数和每日胰岛素总量均无明显差异($P>0.05$),观察组治疗后的胰岛素抵抗指数和每日胰岛素总量均明显降低($P<0.05$),胰岛素分泌指数明显升高($P<0.05$);两组治疗前后低血糖发生次数和身体质量指数均无明显差异($P>0.05$)。**结论:**大剂量胰岛素联合西格列汀能有效控制老年 2 型糖尿病患者的血糖水平,改善胰岛 β 细胞功能,减少胰岛素用量,是一种安全有效的治疗方法。

关键词:胰岛素;西格列汀;糖尿病;疗效

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Effects of High-dose Insulin Combined with Sitagliptin on Elderly Patients with Type 2 Diabetes Mellitus

XIONG Hui-li¹, WANG Yi², ZHAO Xiao-hong¹, ZHOU Qing-yuan¹, LIU Yang¹

(1Endocrinology Department, San Er Ling Yi Hospital, Hanzhong, Shaanxi, 723000, China;

2 Endocrinology Department, The First Affiliated Hospital of Xi'an Jiao Tong University, Xi'an, Shaanxi, 710061, China)

ABSTRACT Objective: To study the effects of high-dose insulin combined with sitagliptin on elderly patients with type 2 diabetes mellitus. **Methods:** 82 cases of elderly patients with type 2 diabetes mellitus who were treated in our hospital from January 2012 to December 2015 were selected and divided into two groups randomly, the patients in observation group were treated with high-dose insulin combined with sitagliptin, and the patients in control group were treated with high-dose insulin. The triglyceride, total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol levels, postprandial 2 h blood glucose, fasting glucose, glycosylated hemoglobin, insulin resistance, insulin secretion index, total daily insulin, and the frequency of hypoglycaemia of the two groups were compared. **Results:** The lipid level before and after treatment had no significant difference between the two groups ($P>0.05$), after treatment, the triglyceride, total cholesterol and low density lipoprotein of observation group was decreased significantly ($P<0.05$), the level of high-density lipoprotein cholesterol was increased significantly ($P<0.05$); the postprandial 2 h blood glucose, fasting glucose, glycosylated hemoglobin of two groups were significantly lower ($P<0.05$), and it was more significantly in observation group ($P<0.05$); the insulin resistance, insulin secretion index and total daily insulin had no significant difference between the two groups ($P>0.05$), the insulin resistance index and total daily insulin of observation group was decreased significantly ($P<0.05$), the insulin secretion index was increased significantly ($P<0.05$); the frequency of hypoglycaemia and body mass index had no significant difference between two groups before and after treatment ($P>0.05$). **Conclusions:** High-dose insulin combined with sitagliptin can effectively control the blood glucose level of elderly patients with type 2 diabetes mellitus, improve islet β -cell function, and reduce the dosage of insulin, which is safe and effective.

Key words: Insulin; Sitagliptin; Type 2 diabetes mellitus; Curative effect

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作者简介:熊慧丽(1979-),女,本科,主治医师,从事糖尿病、甲状腺疾病、痛风、骨质疏松、垂体、肾上腺疾病研究,电话:13892669622,
E-mail: xionghuili_197910@medicine360.net
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前言

近年糖尿病的发病率明显上升,临床主要采用胰岛素治疗,但部分患者会出现胰岛素抵抗现象,且老年患者的胰岛 β 细胞功能较差,病程较长,采用胰岛素的常规用药剂量往往不能有效控制血糖,而一味加大胰岛素剂量,会造成患者体质量的增加和胰岛素抵抗的进一步加剧,必须联合使用其他降糖药物^[1,2]。但传统的噻唑烷二酮类、磺脲类、糖苷酶抑制剂类药物等均存在一定程度的不良反应,老年患者难以耐受^[3]。西格列汀是一种新型的二肽基肽酶-4抑制剂,能有效控制2型糖尿病患者的血糖水平^[4]。临床上虽有对大剂量胰岛素联合西格列汀治疗老年2型糖尿病的报道,但都只研究其对血糖控制的效果,本研究不仅对联合用药对患者血糖的影响进行了探讨,还对血脂、胰岛 β 细胞功能、低血糖发生次数的影响进行了综合分析,以期为临床用药治疗提供参考。

1 资料和方法

1.1 一般资料

选择2012年1月~2015年12月我院诊治的老年2型糖尿病患者82例,均符合2型糖尿病的诊断标准^[5],排除恶性肿瘤,1型糖尿病,胰腺炎,妊娠、哺乳者,有严重肝、肾、心血管疾病,精神疾病者。随机分为两组,观察组41例,男23例,女18例;年龄65~76岁,平均 (71.23 ± 5.46) 岁;病程3~16年,平均

(12.36 ± 3.58) 年。对照组41例,男22例,女19例;年龄65~77岁,平均 (70.62 ± 6.35) 岁;病程3~17年,平均 (13.15 ± 4.12) 年。

1.2 治疗方法

对照组给予门冬胰岛素30注射液,每日给药剂量 >50 U,治疗过程中根据血糖检测结果随时调整胰岛素的用药剂量;观察组联合口服西格列汀100 mg,每日1次。在治疗期间密切监测血糖变化,两组均治疗3个月。

1.3 观察指标

比较两组治疗前后的血脂水平,餐后2 h血糖、空腹血糖、糖化血红蛋白,计算胰岛素抵抗指数(胰岛素抵抗指数=空腹胰岛素 $\times$ 空腹血糖 $\div 22.5$)、胰岛素分泌指数[胰岛素分泌指数= $20 \times$ 空腹胰岛素 $\div$ (空腹血糖 -3.5)]、每日胰岛素总量(每日测量胰岛素用量,然后取治疗3个月期间的平均值)和低血糖发生次数。

1.4 统计学分析

采用SPSS15.00软件,计量资料以 $\bar{x} \pm s$ 表示,组间对比用t检验,计数资料用 χ^2 检验, $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 两组血脂水平的比较

对照组治疗前后的血脂水平无明显差异($P > 0.05$),观察组治疗后的甘油三酯、总胆固醇及低密度脂蛋白明显降低($P < 0.05$),高密度脂蛋白明显升高($P < 0.05$),见表1。

表1 两组血脂水平比较($\bar{x} \pm s$, mmol/L)

Table 1 Comparison of the lipid levels between two groups ($\bar{x} \pm s$, mmol/L)

Groups	n		Triglycerides	Total cholesterol	Low density lipoprotein	High density lipoprotein
Observation group	41	Before treatment	1.85 ± 0.31	4.88 ± 0.45	2.75 ± 0.41	1.08 ± 0.25
		After treatment	$1.16 \pm 0.23^{**}$	$3.42 \pm 0.46^{**}$	$1.42 \pm 0.28^{**}$	$1.35 \pm 0.26^{**}$
Control group	41	Before treatment	1.83 ± 0.26	4.83 ± 0.42	2.73 ± 0.32	1.07 ± 0.24
		After treatment	1.69 ± 0.25	4.61 ± 0.45	2.71 ± 0.35	1.10 ± 0.21

Note: Compared with control group, $*P < 0.05$; compared with before treatment, $^{**}P < 0.05$.

2.2 两组血糖水平的比较

治疗后,两组的餐后2 h血糖、空腹血糖、糖化血红蛋白均

明显降低($P < 0.05$),且观察组降低的更为明显($P < 0.05$),见表2。

表2 两组血糖水平比较($\bar{x} \pm s$)

Table 2 Comparison of the blood glucose levels between two groups ($\bar{x} \pm s$)

Groups	n		2hPG (mmol/L)	FBG (mmol/L)	Hb A1c (%)
Observation group	41	Before treatment	17.15 ± 2.13	10.26 ± 0.58	9.75 ± 0.62
		After treatment	$8.35 \pm 2.78^{**}$	$6.52 \pm 0.37^{**}$	$5.26 \pm 0.21^{**}$
Control group	41	Before treatment	17.26 ± 2.25	10.31 ± 0.79	9.53 ± 0.53
		After treatment	$13.26 \pm 2.31^{*}$	$8.53 \pm 0.32^{*}$	$7.15 \pm 0.35^{*}$

Note: Compared with control group, $*P < 0.05$; compared with before treatment, $^{**}P < 0.05$.

2.3 两组胰岛 β 细胞功能的比较

对照组治疗前后的胰岛素抵抗指数、胰岛素分泌指数和每日胰岛素总量均无明显差异($P > 0.05$),观察组的每日胰岛素总量和胰岛素抵抗指数均明显降低($P < 0.05$),胰岛素分泌指数明显升高($P < 0.05$),见表3。

2.4 两组低血糖发生次数和身体质量指数的比较

治疗期间2组患者均未见严重低血糖反应,观察组有轻微低血糖4人次,对照组有轻微低血糖5人次,与治疗前相比无明显差异($P > 0.05$),两组治疗前后身体质量指数相比无明显差异($P > 0.05$),见表4。

表 3 两组胰岛 β 细胞功能的比较($\bar{x} \pm s$)

Table 3 Comparison of the islet β-cell function between two groups ($\bar{x} \pm s$)

Groups	n		Insulin resistance index	Insulin secretion index	Total daily insulin(U)
Observation group	41	Before treatment	3.12± 0.58	4.85± 0.23	56.71± 6.23
		After treatment	1.58± 0.21* [#]	5.91± 0.32* [#]	41.23± 5.42* [#]
Control group	41	Before treatment	3.15± 0.46	4.82± 0.31	56.32± 6.12
		After treatment	2.93± 0.42	4.89± 0.33	55.21± 5.39

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

表 4 两组低血糖发生次数和身体质量指数的比较

Table 4 Comparison of the frequency of hypoglycaemia and body mass index between two groups

Groups	n		Frequency of hypoglycaemia	Body mass index($\bar{x} \pm s$)
Observation group	41	Before treatment	6	25.34± 2.53
		After treatment	4	25.51± 2.28
Control group	41	Before treatment	6	25.53± 2.42
		After treatment	5	25.76± 2.39

3 讨论

我国糖尿病患者的人数位居全球首位,老年糖尿病的发病人数逐年增加,老年患者一般病程较长,药物方案复杂,顺应性较差^[6]。临床常采用大剂量胰岛素进行治疗,但长期大剂量使用胰岛素会加重胰岛素抵抗,降低胰岛素受体数量,长期治疗效果并不理想,需要联合口服其他降糖药物,但这些药物往往存在不同程度的不良反应,如噻唑烷二酮类药物可能会增加体质量,以及心力衰竭的发生风险;磺脲类药物也会增加体质量,升高低血糖的发生率;二甲双胍可能会出现乳酸性酸中毒的危险;糖苷酶抑制剂类药物的降糖效果较弱,胃肠道不良反应较为明显^[7,9]。近年来,肠促胰素降糖药成为治疗 2 型糖尿病新的研究热点^[10]。西格列汀是基于肠促胰素机制的一种新型降糖药物,能高度选择性的抑制二肽基酶的水解活性,升高胰高血糖素样肽水平,从而抑制胰高血糖素的分泌并促进胰岛素的分泌,有效控制患者血糖水平^[11,12]。

大部分 2 型糖尿病患者均伴有不同程度的脂代谢异常,这会大大增加发生动脉粥样硬化等心血管事件的危险^[13]。严格控制血脂水平有利于预防并发症的发生和改善患者预后^[14]。结果显示,观察组的血脂水平明显改善(P<0.05),提示大剂量胰岛素联合西格列汀能有效调节血脂,从而降低心血管事件潜在的发生风险,其作用机制可能与西格列汀可以减少脂肪分解、改善糖脂代谢紊乱、增加胰岛素的敏感性有关;血清甘油三酯是评价胰岛素抵抗和胰岛素敏感性的最佳指标,在体内甘油三酯能分解成游离脂肪酸,引起继发性胰岛素抵抗,甘油三酯水平的降低也能间接说明大剂量胰岛素联合西格列汀能有效减轻胰岛素抵抗^[15,16]。治疗后,两组的餐后 2 h 血糖、空腹血糖、糖化血红蛋白均明显降低(P<0.05),且观察组降低的更为明显(P<0.05),提示大剂量胰岛素联合西格列汀对患者血糖水平的控制效果要明显由于单独使用大剂量胰岛素。

2 型糖尿病的发病原因主要为胰岛 β 细胞功能的减弱^[17]。本研究结果显示,对照组治疗前后的胰岛素抵抗指数、胰岛素分泌指数和每日胰岛素总量均无明显差异(P>0.05),观察组治

疗后上述指标均明显改善(P<0.05),提示大剂量胰岛素联合西格列汀能有效改善胰岛 β 细胞功能,与 Hong 等^[18]研究结果相一致。其原因可能为胰高血糖素样肽能结合胰岛 β 细胞的 G 蛋白耦联受体,升高胰岛 β 细胞内的环磷酸腺苷水平,促进胰岛素的出胞,从而升高自身胰岛素分泌水平,降低外源性胰岛素的使用剂量;胰高血糖素样肽还能激活磷酸酰肌醇-3 激酶信号通路,增加外周组织对胰岛素的敏感性,从而减少胰岛素的使用剂量^[19]。两组治疗前后低血糖发生次数和身体质量指数均无明显差异(P>0.05),Bo 等^[20]研究发现,胰岛素与二肽基肽酶 IV 抑制剂联合使用并不会使 2 型糖尿病患者发生低血糖的风险增加,与本研究结果一致。

综上所述,大剂量胰岛素联合西格列汀能有效控制老年 2 型糖尿病患者的血糖水平,改善胰岛 β 细胞功能,减少胰岛素用量,是一种安全有效的治疗方法。

参考文献(References)

- [1] Udell JA, Bhatt DL, Braunwald E, et al. Saxagliptin and Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus and Moderate or Severe Renal Impairment: Observations From the SAVOR-TIMI 53 Trial[J]. Diabetes Care, 2014, 38(4): 696-705
- [2] Hirshberg B, Parker A, Edelberg H, et al. Safety of saxagliptin: events of special interest in 9156 patients with type 2 diabetes mellitus[J]. Diabetes/metabolism Research & Reviews, 2014, 30(7): 556-569
- [3] Paneni F, Costantino S, Battista R, et al. Adverse epigenetic signatures by histone methyltransferase Set7 contribute to vascular dysfunction in patients with type 2 diabetes mellitus [J]. Circulation Cardiovascular Genetics, 2015, 8(1): 150-158
- [4] Plosker G L. Sitagliptin: A Review of Its Use in Patients with Type 2 Diabetes Mellitus[J]. Drugs, 2014, 74(2): 223-242
- [5] Grimaldi A, Heurtier A. Diagnostic criteria for type 2 diabetes [J]. La Revue Du Praticien, 1999, 49(1): 16-21
- [6] Amer M S, Ali-Labib R, Farid T M, et al. Link between vitamin B12, type 2 diabetes mellitus, and bone mineral density in elderly patients [J]. Journal of Clinical Gerontology & Geriatrics, 2015, 6(4): 120-124

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- seen by prehospital care:gender differences [J]. Rev Bras Epidemiol, 2014, 17(1): 3-16
- [8] Shrivastava P, Goel A. Pre-hospital care in burn injury [J]. Indian J Plast Surg, 2010, 43(Suppl): S15-22
- [9] 杨艳新,买买提·牙森,刘金宝,等. 新疆卫生资源配置人口公平性研究[J]. 新疆医科大学学报, 2010, 33(12): 1398-1400
Yang Yan-xin, Maimaiti·Yasen, Liu Jin-bao, et al. Study on equitable allocation of health resources in Xinjiang [J]. Journal of Xinjiang Medical University, 2010, 33(12): 1398-1400
- [10] 刘江. 1143 例老年患者的院前急救分析 [J]. 中国医学工程, 2013, 21(04): 94-95
Liu Jiang. Analysis of pre hospital first aid in 1143 elderly patients[J]. China Medical Engineering, 2013, 21(04): 94-95
- [11] 王亚丽. 分析 120 急救中心院前急救患者的疾病谱 [J]. 中国继续医学教育, 2016, 8(23): 16-17, 18
Wang Ya-li. Analysis of the Spectrum of Disease in Patients With Pre-hospital Emergency Care in the 120 Emergency Center[J]. China Continuing Medical Education, 2016, 8(23): 16-17, 18
- [12] Mort AJ, Rushworth GF. Exploration of key stakeholders' preferences for pre-hospital physiologic monitoring by emergency rescue services [J]. J Clin Monit Comput, 2013, 27(6): 599-607
- [13] McIver L, Kim R, Woodward A, et al. Health Impacts of?Climate Change in Pacific Island Countries: A Regional Assessment of Vulnerabilities and Adaptation Priorities[J]. Environ Health Perspect, 2016, 124(11): 1707-1714
- [14] Nangia R, Singh H, Kaur K. Prevalence of cardiovascular disease (CVD)risk factors [J]. Med J Armed Forces India, 2016, 72 (4): 315-319
- [15] Hegde SK, Vijayakrishnan G, Sasankh AK, et al. Lifestyle-associated risk for cardiovascular diseases among doctors and nurses working in a medical college hospital in Tamil Nadu,India[J]. J Family Med Prim Care, 2016, 5(2): 281-285
- [16] 李延文,谈建国,蒋锦琪,等. 气象因素对心力衰竭的影响[J]. 现代生物医学进展, 2015, 15(7): 1275-1280
Li Yan-wen, Tan Jian-guo, Jiang Jin-qi, et al. The Influence of Meteorological Factors on Heart Failure [J]. Progress in Modern Biomedicine, 2015, 15(7): 1275-1280
- [17] Turan S, Bastepe M. GNAS Spectrum of Disorders [J]. Curr Osteoporos Rep, 2015, 13(3): 146-158
- [18] Pallavisarji U, Gururaj G, Girish RN. Practice and perception of first aid among lay first responders in a southern district of India [J]. Arch Trauma Res, 2013, 1(4): 155-160
- [19] Chen S, Sun H, Lei Y, et al. Validation of the Los Angeles pre-hospital stroke screen (LAPSS) in a Chinese urban emergency medical service population[J]. PLoS One, 2013, 8(8): e70742
- [20] Pepper GA. A new era in geriatric nursing education [J]. J Prof Nurs, 2014, 30(6): 443-444

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- [7] Jahan S. Pre-pregnancy Body Mass Index and the Risk of Adverse Pregnancy Outcome in Two Thousand Type 2 Diabetes Mellitus Bangladeshi Women[J]. 2014, 3(3): 491-501
- [8] Rosilio C, Ben-Sahra I, Bost F, et al. Metformin: A metabolic disruptor and anti-diabetic drug to target human leukemia [J]. Cancer Letters, 2014, 346(2): 188-196
- [9] Niu B, Frias A, Nguyen B, et al. 278: The association between race/ethnicity and adverse perinatal outcomes among women with diabetes mellitus type 2 (T2DM)[J]. American Journal of Obstetrics & Gynecology, 2014, 210(1): S147
- [10] Hibuse T, Maeda N, Kishida K, et al. A pilot three-month sitagliptin treatment increases serum adiponectin level in Japanese patients with type 2 diabetes mellitus- a randomized controlled trial START-J study[J]. Cardiovascular Diabetology, 2014, 13(8): 167-172
- [11] Mori H, Okada Y, Arao T, et al. Sitagliptin improves albuminuria in patients with type 2 diabetes mellitus [J]. Journal of Diabetes Investigation, 2014, 5(3): 313-319
- [12] Ommen E S, Lei X, O'Neill E A, et al. Comparison of Treatment with Sitagliptin or Sulfonylurea in Patients with Type 2 Diabetes Mellitus and Mild Renal Impairment: A Post Hoc Analysis of Clinical Trials [J]. 2015, 6(1): 29-40
- [13] Sprandel M C O, Hueb W A, Segre A, et al. Alterations in lipid transfers to HDL associated with the presence of coronary artery disease in patients with type 2 diabetes mellitus [J]. Science Education, 2015, 14(1): 1-9
- [14] Rosenson R S, Rigby S P, Jones M R, et al. Effect of colessevelamHClmonotherapy on lipid particles in type 2 diabetes mellitus[J]. Cardiovascular Drugs & Therapy, 2014, 28(3): 229-236
- [15] Qian L,Chitnis A, Hammer M, et al. Real-World Clinical and Economic Outcomes of LiraglutideVersusSitagliptin in Patients with Type 2 Diabetes Mellitus in the United States [J]. Diabetes Therapy, 2014, 5(2): 579-590
- [16] Kim H M, Lim J S, Lee B W, et al. Optimal candidates for the switch from glimepiride to sitagliptin to reduce hypoglycemia in patients with type 2 diabetes mellitus[J]. Endocrinology & Metabolism, 2015, 30(1): 84-91
- [17] Hivert M F, Vassy J L, Meigs J B. Susceptibility to type 2 diabetes mellitus--from genes to prevention[J]. Nature Reviews Endocrinology, 2014, 10(4): 198-205
- [18] Hong E S, Khang A R, Yoon J W, et al. Comparison between sitagliptin as add-on therapy to insulin and insulin dose-increase therapy in uncontrolled Korean type 2 diabetes: CSI study [J]. Diabetes Obesity & Metabolism, 2012, 14(9): 795-802
- [19] Lee M, Rhee M K. Sitagliptin for Type 2 diabetes: a 2015 update[J]. Expert Review of Cardiovascular Therapy, 2015, 13(6): 597-610
- [20] Bo A. Insulin plus incretin:A glucose-lowering strategy for type 2-diabetes[J]. World Journal of Diabetes, 2014, 5(1): 40-51