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氯吡格雷强化治疗对老年急性心肌梗死患者炎性反应及氧化-抗氧化水平影响*

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摘要 目的:探讨氯吡格雷强化治疗对老年急性心肌梗死患者炎性反应及氧化-抗氧化水平的影响。**方法:**选择我院2012年1月至2016年12月收治的400例老年急性心肌梗死患者,根据随机数字表法分为观察组及对照组。对照组给予常规治疗,观察组给予氯吡格雷强化治疗,对比两组患者的疗效,治疗期间的不良心血管事件及不良反应的发生情况,治疗前后的血清白介素1(interleukin-1,IL-1)、白介素2(interleukin-2,IL-2)、白介素6(interleukin-6,IL-6)、白介素10(interleukin-10,IL-10)水平及超氧化物歧化酶(superoxide dismutase,SOD)、丙二醛(malondialdehyde,MDA)、过氧化酶(catalase,CAT)及谷胱甘肽氧化物酶(glutathione peroxidase,GSHPX protein)水平。**结果:**治疗后,观察组的总有效率为92.50%,明显高于对照组(72%,P<0.05);观察组的心血管不良事件发生率明显低于对照组(P<0.05);两组的不良反应发生率对比差异无统计学意义(P>0.05)。两组治疗后的血清IL-1、IL-2、IL-6、IL-10、MDA水平均较治疗前明显下降,且观察组以上指标水平均明显低于对照组(P<0.05),而两组治疗后的血清SOD、CAT、GSHPX水平均较治疗前明显上升,且观察组以上指标水平均明显高于对照组(P<0.05)。**结论:**与常规治疗相比,氯吡格雷强化治疗可显著提高老年急性心肌梗死患者的临床疗效,这可能与有效减轻患者的炎症反应,增强抗氧化作用有关。

关键词:氯吡格雷;强化治疗;老年急性心肌梗死;炎性反应;氧化-抗氧化水平

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Effect of Intensive Treatment combined with Clopidogrel on the Inflammatory Response and Oxidation-antioxidant Levels in Elderly Patients with Acute Myocardial Infarction*

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ABSTRACT Objective: To investigate the effect of clopidogrel intensive therapy on the inflammatory reaction and oxidation-antioxidant level in elderly patients with acute myocardial infarction. **Methods:** 400 cases of elderly patients with acute myocardial infarction from Jan. 2012 to Dec. 2016 in our hospital were selected and divided into the observation group and the control group according to random number table method, the control group was given conventional treatment, the observation group was given intensive treatment with clopidogrel, the therapeutic effects, incidence of adverse cardiovascular events and adverse reactions, serum levels of interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-10 (IL-10) and superoxide dismutase (SOD) malondialdehyde (MDA), catalase (CAT) and glutathione peroxidase (GSHPX protein) levels before and after treatment were compared between the two groups. **Results:** After treatment, the total effective rate of observation group was 92.50%, which was significantly higher than that of the control group (72%, P<0.05); the incidence of adverse cardiovascular events in the observation group was significantly lower than that of the control group (P<0.05); there was no significant difference in the incidence of adverse reactions between the two groups (P>0.05). After treatment, the levels of serum IL-1, IL-2, IL-6, IL-10 and MDA in both groups were significantly lower than those before treatment, and the above indexes in the observation group were significantly lower than those of the control group (P<0.05). the levels of serum SOD, CAT and GSHPX in observation group were significantly lower than those in control group (P<0.05). However, the levels of SOD, CAT and GSHPX in the two groups after treatment were significantly higher than those before treatment, and the above indexes in the observation group were significantly higher than those in the control group (P<0.05). **Conclusion:** Compared with conventional therapy, clopidogrel intensive therapy can significantly improve the clinical efficacy of elderly patients with acute myocardial infarction, which may be related to the effective reduction of inflammatory reaction and enhancement of antioxidation.

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前言

冠状动脉粥样硬化性心脏病是由于冠状动脉粥样硬化引起的冠状动脉管腔阻塞或狭窄,导致患者缺氧、心肌缺血的症状,是老年患者常见的心血管疾病,也是引起老年患者致残、致死的重要原因之一[1-3]。急性心肌梗死是一种严重的冠心病,也是导致患者心源性猝死的重要诱因[4]。目前,我国急性心肌梗死的发病率逐年上升,尤其以老年患者多发[5]。有研究显示急性心肌梗死的发病原因与患者机体内自由基清除酶的活性降低有关,也与老年患者血管弹性、血管内皮功能障碍及血流阻力增加有关[6,7]。因此,临床常采用溶栓及调节血脂的方式治疗老年急性心肌梗死患者。

氯吡格雷是一种酚吡啶类衍生物,作为强效的血栓素合成酶抑制剂可发挥抗血小板聚集作用[8,9]。临床上,氯吡格雷常用于抗血栓、早期脑卒中、急性心肌梗死介入等治疗[10-12]。急性心肌梗死过程中,炎性细胞聚集参与了疾病进展的整个过程,包括斑块的启动、进展及破溃过程。因此,本研究主要探讨了氯吡格雷强化治疗对老年急性心肌梗死患者炎性反应及氧化 - 抗氧化水平的影响,以期为临床急性心肌梗死患者的治疗提供更多的参考依据。

1 资料与方法

1.1 一般资料

选择我院 2012 年 1 月至 2016 年 12 月收治的 400 例老年急性心肌梗死患者为研究对象,所有患者均符合中华医学会心血管分会制定的《急性 ST 段抬高型心肌梗死诊断和治疗指南》(2015 年)中急性心肌梗死的诊断标准,排除溶栓禁忌症者、有出血倾向者、严重肝肾功能不全者、严重代谢型疾病者、恶性肿瘤者、急腹症、急性肺动脉栓塞者、氯吡格雷过敏者、有急慢性炎症性疾病者、有肥厚型或扩张型心肌病者。其中,男 256 例,女 144 例,年龄范围为 65~79 岁,平均年龄为 71.8± 6.3 岁,急性心肌梗死部位位于前壁者 267 例,下壁者 112 例,其他 21 例。根据随机数字表法,将所有患者分为观察组及对照组,每组 200 例。两组患者的性别、年龄、发病部位对比差异均无统计学意义(P>0.05),均有可比性。本研究所有患者知情同意且经医院伦理委员会批准同意。

表 1 两组患者的一般资料对比

Table 1 Comparison of the general information between two groups of patients

Groups	n	Gender		Average age (years)	Site of disease		
		Male	Female		Antetheca	Paries inferior	Others
Observation group	200	129	71	71.91± 6.12	135	54	11
Control group	200	127	73	72.50± 6.43	132	58	10
x^2/t	-	0.043		-0.940		0.050	
P	-	0.835		0.348		0.823	

1.2 治疗方法

两组患者均行 PCI 治疗,之后给予低分子肝素,ACEI 类药物,β 受体阻滞剂等常规治疗。对照组患者给予标准治疗方法,包括拜阿司匹林(拜耳医药保健有限公司;国药准字 J20080078;规格:100 mg;生产批号:BJ38734,BJ39883,8J34998,BJ39576,BJ39485,BJ39762)100 mg/ 次,1 次 /d,氯吡格雷(赛诺菲(杭州)制药有限公司;国药准字 J20130083,规格:75 mg;生产批号:1A123,1A536,1A608,1A660,1A647,1A689)75 mg/d,1 次 /d,阿托伐他汀钙(辉瑞制药有限公司;国药准字:H20051408;规格:20 mg;生产批号:1137045,083811K,1137044,T93392,1237003,1237010)20 mg/d,1 次 /d;观察组给予氯吡格雷强化治疗,包括阿司匹林 100 mg/d,1 次 /d,氯吡格雷 150 mg/d,2 次 /d,阿托伐他汀 20 mg/d,1 次 /d。两组疗程均为 4 周。

1.3 观察指标

(1)两组患者的临床疗效。治疗后,每日使用硝酸甘油剂量及心绞痛的复发次数降低超过 80%为显效,降低超过 50%为有效,降低低于 50%为无效;(2)心血管不良事件及不良反应发生情况;(3)治疗前后的血清炎性因子水平,包括白介素 1、白介素 2、白介素 6、白介素 10(IL-1、IL-2、IL-6 及 IL-10);(4)两组患者治疗前后血清中的氧化 - 抗氧化酶水平,包括超氧化物歧化酶(SOD)、过氧化酶(CAT)、谷胱甘肽氧化物酶(GSHPX 蛋白)、MDA(丙二醛),其中 IL-1 试剂盒购自 R&D 公司,IL-2 试剂盒购自武汉博士德生物工程有限公司,IL-6 试剂盒购自 Santa Cruz 公司,IL-10 试剂盒购自上海信帆生物科技有限公司,SOD、MDA、CAT 及 GSHPX 蛋白试剂盒购自南京建成生物工程研究所。

1.4 统计学方法

采用 SPSS19.0 软件进行数据分析,计数资料以 n 或百分比表示,组间比较采用卡方检验,计量资料以 $\bar{x}\pm s$ 表示,组间比较采用 t 检验,以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组治疗效果对比

治疗后,对照组总有效率为 72.00%(144/200),观察组总有效率为 92.50%(185/200),较对照组显著升高(P<0.05)。

表 2 两组治疗效果的对比

Table 2 Comparison of the therapeutic effects between the two groups

Groups	n	Markedly effective[n(%)]	Effective[n(%)]	Ineffective[n(%)]	Total effective rate
Observation group	200	114	71	15	185(92.50)
Control group	200	79	65	56	144(72.00)
x^2	-				28.781
P	-				<0.001

2.2 两组心血管不良事件及不良反应的发生情况比较

如表 3 所示,观察组的心血管不良事件发生率明显低于对照组(P<0.05);两组的不良反应发生率对比差异无统计学意义(P>0.05)。

表 3 两组心血管不良事件及不良反应的发生率比较[例(%)]

Table 3 Comparison of the incidence of adverse cardiovascular events and adverse reactions between the two groups [n(%)]

Groups	n	Cardiovascular adverse events					Adverse reaction					
		Death	Recurrent non fatal myocardial infarction	Stroke	Revascu-larization	Total incidence rate	Hemor-rhage	Gastroin-testinal reaction	granulo-cytopenia	granulo-cytopenia	Elevated liver enzymes	Total incidence
Observation group	200	2	4	4	4	14(7.00)	4	4	0	0	0	8(4.00)
Control group	200	4	4	9	9	26(13.00)	2	2	0	0	0	4(2.00)
x^2	-					4.0						1.375
P	-					0.046						0.241

2.3 两组治疗前后炎症因子水平的对比

治疗后，两组血清 IL-1、IL-2、IL-6、IL-10 水平均较治疗前明显下降(P<0.05),且观察组血清 IL-1、IL-2、IL-6、IL-10 水平明显低于对照组(P<0.05)。

表 4 两组治疗前后血清炎症因子水平对比($\bar{x}\pm s$,pg/mL)

Table 4 Comparison of the serum inflammatory factors levels between the two groups before and after treatment ($\bar{x}\pm s$, pg/mL)

Groups	n	IL-1		IL-2		IL-6		IL-10	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	200	0.89± 0.21	0.52± 0.10	0.85± 0.14	0.49± 0.11	0.78± 0.13	0.31± 0.08	0.89± 0.15	0.58± 0.10
Control group	200	0.85± 0.20	0.69± 0.12	0.86± 0.15	0.58± 0.11	0.76± 0.14	0.49± 0.10	0.88± 0.14	0.70± 0.21
t	-	1.951	-15.391	-0.681	-8.182	1.480	-19.878	0.689	-7.296
P	-	0.052	<0.001	0.491	<0.001	0.140	<0.001	0.491	<0.001

2.4 两组治疗前后血清 SOD、CAT、GSHPX 蛋白水平的对比

治疗后,两组血清 SOD、CAT、GSHPX 水平均较治疗前明显上升 (P<0.05)，而血清 MDA 水平较治疗前明显下降(P<0.05)，且观察组血清 SOD、CAT、GSHPX 水平显著高于对照组，而血清 MDA 水平显著低于对照组(P<0.05)。

表 5 两组治疗前后血清 SOD、CAT、GSHPX 蛋白水平对比(U/mL,$\bar{x}\pm s$)

Table 5 Comparison of the serum SOD, CAT and GSHPX levels between the two groups before and after treatment (U/mL,$\bar{x}\pm s$)

Groups	n	SOD		CAT		GSHPX		MDA	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	200	7.9± 2.0	26.8± 7.6	8.7± 2.1	32.7± 7.8	41.0± 10.7	91.8± 23.5	58.9± 12.4	18.9± 3.5
Control group	200	7.8± 1.7	15.1± 3.4	8.9± 1.8	17.8± 5.1	40.8± 11.4	67.9± 13.5	57.6± 13.1	31.9± 8.9
t	-	0.539	19.873	-1.023	22.61	0.181	12.471	1.019	-19.224
P	-	0.590	<0.001	0.307	<0.001	0.856	<0.001	0.309	<0.001

3 讨论

随着我国人口老龄化的加剧,老年急性心肌梗死的发病率逐年上升,发病原因主要是冠状动脉痉挛、心肌耗氧量剧烈增加、暴饮暴食、过劳或激动、便秘或大量饮酒等[13-15],临床症状多为剧烈持久的胸骨后疼痛,伴有心电图变化及心肌酶活性增高,且多会引发心律失常,危及患者生命[16-18]。临床上,他汀类药物、阿司匹林、血管紧张素转化酶抑制剂、β 受体阻滞剂、氯吡格雷等均可改善急性心肌梗死患者的预后[19-21]。氯吡格雷是 ADP 受体阻滞剂,可结合血小板膜表面的 ADP 受体,使得 GPIIb/IIIa 受体不能结合纤维蛋白,对血小板聚集造成抑制,可用于急性心肌梗死的治疗,而氯吡格雷强化治疗急性心肌梗死较常规治疗具有更强的抗血小板抑制作用,疗效显著[22,23],但其作用机制尚不完全明确。本研究主要分析了氯吡格雷强化治疗对急性心肌梗死患者的疗效及作用机制,以期为临床急性心肌梗死的治疗提供更多的参考依据。

本研究结果显示氯吡格雷强化治疗老年急性心肌梗死的疗效较常规治疗高,且不良心血管事件发生率较低,可能与强化治疗增加了氯吡格雷剂量有关。氯吡格雷的主要不良反应主要为出血及胃肠道不适[24]。本研究中,观察组的出血及胃肠道不适发生率高于对照组,但组间对比差异无统计学意义,表明氯吡格雷强化治疗老年急性心肌梗死较为安全。

炎性反应可发生于机体的各个器官及组织中,是细胞内最常见的病理学及生理学过程,也是心血管疾病的主要发生原因。有研究显示[25-27]炎性因子水平与心肌梗死的发生密切相关,可反映疾病的严重程度[28]。其中,白细胞介素与机体免疫细胞活化、增殖、免疫调节及成熟等密切相关。因此,本研究选择血清 IL-1、IL-2、IL-6、IL-10 水平作为观察指标。氧化酶可反映细胞内的过氧化状态,其表达水平的升高或降低与心脑血管疾病的发生发展相关,也与急性心肌梗死的发生密切相关。有研究表明氧化酶是药物干预心血管疾病的一个重要靶点[29]。本研究选择 SOD、CAT、GSHPX、MDA 作为观察指标,结果显示氯吡格雷强化治疗较常规治疗可显著降低患者机体内的血清 IL-1、IL-2、IL-6、IL-10 水平,改善患者的血清 SOD、CAT、GSHPX、MDA 水平,可能是由于氯吡格雷可阻滞 ADP 受体,抑制血小板活化脱颗粒,从而减少血小板 - 白细胞聚集物的形成,抑制血小板第 IV 因子释放,从而阻止巨噬细胞诱导、迁移、增殖,也可抑制 5- 羟色胺、血栓素 A2 及组织胺的释放,氯吡格雷强化治疗进一步降低了患者机体的炎性反应,改善了患者的氧化 - 抗氧化酶水平[30]。

综上所述,与常规治疗相比,氯吡格雷强化治疗可显著提高老年急性心肌梗死患者的临床疗效,这可能与有效减轻患者的炎症反应,增强抗氧化作用有关。

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