·临床研究·

尼可地尔与地尔硫卓治疗经皮冠状动脉介入治疗术后再发不稳定型心绞痛疗效分析

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【摘 要】 目的 研究尼可地尔和地尔硫卓对经皮冠状动脉介入(PCI)术后再发不稳定型心绞痛(UAP)患者的临床疗效。**方法** 入选2015年1月至2016年8月解放军第252医院PCI术后再发UAP患者72例，随机数字表法分为尼可地尔组和地尔硫卓组，每组36例。尼可地尔组患者男性24例，女性12例，年龄48～80(62.61±9.26)岁，常规治疗基础上加服尼可地尔片5 mg，口服，3次/d。地尔硫卓组患者男性21例，女性15例，年龄48～79(61.72±8.18)岁，常规治疗基础上加服地尔硫卓90 mg，口服，2次/d，比较两组患者服药60 d期间每周心绞痛发作次数及持续时间、硝酸甘油服用量、心电图改变及不良反应情况。**结果** 两组患者的年龄、性别、病程、吸烟史、SYNTAX评分、合并疾病差异无统计学意义($P>0.05$)。相比服药前，服药后两组患者每周心绞痛发作次数、持续时间、硝酸甘油服用量均有所减少，且尼可地尔组明显优于地尔硫卓组，差异有统计学意义($P<0.05$)。尼可地尔组患者服药有效率88.9%(32/36)，地尔硫卓组患者服药有效率75.0%(27/36)，两组有效率差异无统计学意义($\chi^2=2.347$，$P=0.126$)。相比尼可地尔，地尔硫卓易使患者出现头痛，差异有统计学意义($P<0.05$)。**结论** 尼可地尔与地尔硫卓均对PCI术后再发UAP有疗效，尼可地尔的临床疗效显著，可明显改善心绞痛症状，并且不良反应少。

【关键词】 尼可地尔；地尔硫卓；不稳定型心绞痛
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Clinical efficacy of nicorandil *versus* diltiazem for recurrent unstable angina pectoris after percutaneous coronary intervention

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【Abstract】 Objective To investigate the clinical efficacy of nicorandil and diltiazem in the recurrence of unstable angina pectoris (UAP) patients following postoperative percutaneous coronary intervention (PCI). **Methods** A total of 72 UAP patients who underwent PCI due to coronary heart disease in our hospital from January 2015 to August 2016 were enrolled in this study. They were randomly and equally divided into nicorandil (24 males and 12 females, at an age of 62.61±9.26 years, ranging from 48 to 80) and diltiazem groups (21 males and 15 females, at an age of 61.72±8.18 years, ranging from 48 to 79). The patients of the former group were given oral administration of 5 mg nicorandil, 3 times per day besides routine treatment, and those from the latter group received oral administration of 90 mg diltiazem, twice per day. During 60 days' treatments, the frequency and duration of angina, nitroglycerin dosage, electrocardiographic changes, and adverse reactions every week were observed and compared between the 2 groups. **Results** There were no significant differences in the age, gender, duration of disease, smoking history, comorbidity and score of Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) between the 2 groups ($P>0.05$). After 60 days' treatment, the frequency and duration of weekly angina attack and nitroglycerin dosage were reduced, and the nicorandil group had obviously better outcomes than the diltiazem group ($P<0.05$). The total effective rate was 88.9% (32/36) in the nicorandil group, and 75.0% (27/36) in the diltiazem group, with no statistical difference between them (Chi square = 2.347, $P=0.126$). Compared with the patients of nicorandil group, those of the diltiazem group were prone to headache ($P<0.05$). **Conclusion** Nicorandil and diltiazem have curative efficacy in postoperative recurrence of UAP after PCI. Nicorandil is more significant in the treatment, with obvious improvement of angina symptoms and less adverse reactions.

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冠状动脉粥样硬化性心脏病(coronary atherosclerotic heart disease, CAHD)的发病率近年逐渐增高。统计结果表明,中国每年死于CAHD人数≥100万,平均发病率6.42%,病死率15%[1]。随着经皮冠状动脉介入(percutaneous coronary intervention,PCI)治疗术的普及,患者的生存率及生存质量均得到提高,但仍有一部分患者由于供血不足或侧支循环闭塞而术后再发不稳定型心绞痛(unstable angina pectoris, UAP)。本研究通过对尼可地尔(nicorandil)和地尔硫卓(diltiazem)治疗PCI术后再发UAP患者的临床疗效进行对比,以探讨它们在临床中的实际意义。

1 对象与方法

1.1 研究对象

入选2015年1月至2016年8月解放军第252医院PCI术后再发UAP患者72例,随机数字表法分为尼可地尔组和地尔硫卓组。尼可地尔组36例,其中男性24例,女性12例,年龄48~80(62.61±9.26)岁。地尔硫卓组36例,其中男性21例,女性15例,年龄48~79(61.72±8.18)岁。纳入标准:(1)既往PCI治疗术后≥3个月,主要病变血管已开通;(2)具有典型UAP症状(心绞痛诊断符合中华医学会心血管病分会的诊断标准);(3)发作时心电图有ST-T改变;(4)本次入院后行冠状动脉造影术,非支架内血栓形成及支架内再狭窄,冠状动脉病变≥2支,SYNTAX(Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery)评分≥23分,无法行PCI治疗术且拒绝进一步行冠状动脉旁路移植术(coronary artery bypass grafting, CABG)患者。排除标准:(1)纽约心脏病协会(New York Heart Association,NYHA)心功能分级>Ⅲ级,射血分数(ejection fraction,EF)<30%;(2)二度房室阻滞及以上者、病态窦房结综合征;(3)肝肾功能不全、恶性肿瘤、甲状腺功能亢进、严重免疫及血液系统疾病者;(4)基础血压偏低(收缩压<90 mmHg);(5)对尼可地尔、地尔硫卓过敏或不耐受者;(6)急性心肌梗死患者[2,3]。本研究经医院伦理委员会同意,与患者或家属签署知情同意书。

1.2 方法

尼可地尔组予以常规治疗加尼可地尔,即常规降压(富马酸比索洛尔、盐酸咪达普利)、降脂(阿托伐他汀钙片)、扩张冠状动脉(单硝酸异山梨酯片)、抗血小板凝集(阿司匹林、氯吡格雷)治疗的基础上加服尼可地尔片(中外制药株式会社,批号H20110492)5 mg,口服,3次/d。地尔硫卓组在常规治疗的基础上加服地尔硫卓缓释胶囊(天津田边制药有限公司,批号H19990338)90 mg,口服,2次/d。若患者在治疗过程中有胸闷、胸痛发作,舌下含服硝酸甘油0.5 mg(1片),两组患者均服药60 d。

1.3 监测疗效指标

监测两组患者每周心绞痛发作次数及持续时间、硝酸甘油服用量及心电图改变情况。显效:静息心电图正常或大致正常。有效:静息心电图缺血性ST段压低未恢复正常,但回升>0.05 mV或T波由低平转为直立。无效:静息心电图较治疗前无明显变化。总有效率=(显效例数+有效例数)/总例数×100%。

1.4 统计学处理

应用SPSS19.0统计软件对数据进行分析。计量资料用均数±标准差($\bar{x}\pm s$)表示,两组比较采用t检验。计数资料用百分率表示,组间比较用χ^2检验。$P<0.05$为差异有统计学意义。

2 结 果

2.1 两组患者基线资料比较

两组患者的年龄、性别、病程、吸烟史、SYNTAX评分、合并疾病差异无统计学意义($P>0.05$;表1)。

2.2 两组患者疗效比较

两组患者服药前指标差异无统计学意义($P>0.05$)。相比服药前,服药后两组患者每周心绞痛发作次数、持续时间、硝酸甘油服用量均有所减少,且尼可地尔组明显优于地尔硫卓组,差异有统计学意义($P<0.05$;表2)。

2.2 两组患者心电图结果比较

根据心电图结果,尼可地尔组患者服药有效32例,无效4例,有效率88.9%(32/36)。地尔硫卓组患者服药有效27例,无效9例,有效率75.0%(27/36),两组有效率差异无统计学意义($\chi^2=2.347$, $P=0.126$)。

2.3 两组患者不良反应比较

随访期间,地尔硫卓组患者3例(8.3%)出现轻微头痛,17例(47.22%)心率较入组前有所下降,

表 1 两组患者基线资料比较

Table 1 Comparison of baseline data between two groups ($n = 36$)

Item	Nicorandil group	Diltiazem group	t/χ^2	P value
Age(years, $\bar{x} \pm s$)	62.61 ± 9.26	61.72 ± 8.18	0.432	0.667
Gender(male/female)	24/12	21/15	0.056	0.814
Duration of disease(years, $\bar{x} \pm s$)	10.81 ± 6.79	10.36 ± 7.92	0.256	0.799
SYNTAX score($\bar{x} \pm s$)	27.56 ± 3.26	26.86 ± 3.12	0.923	0.359
Smoking[n(%)]	21(58.33)	19(52.78)	0.056	0.813
Basic disease[n(%)]				
Hypertension	27(75.00)	24(66.67)	0.269	0.605
Diabetes mellitus	21(58.33)	18(50.00)	0.224	0.637
Dyslipidemia	26(72.22)	32(88.89)	2.217	0.135

SYNTAX: Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery

表 2 两组患者疗效比较

Table 2 Comparison of curative efficacy between two groups ($n = 36, \bar{x} \pm s$)

Group	Duration of angina pectoris(min)		Anginal attack (times/week)		Nitroglycerin consumption(tablet)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Nicorandil	14.24 ± 4.53	4.06 ± 1.66 *#	9.08 ± 2.70	1.94 ± 0.86 *#	7.58 ± 2.82	1.83 ± 0.81 *#
Diltiazem	13.85 ± 4.01	7.61 ± 2.61 *	8.89 ± 3.24	5.03 ± 1.50 *	7.69 ± 2.72	3.61 ± 1.25 *

Compared with before treatment, * $P < 0.05$; compared with diltiazem group, # $P < 0.05$

但未低于 60 次/min。尼可地尔组患者 1 例(2.8%)出现轻微头痛。相比尼可地尔,地尔硫卓易使患者出现头痛,差异有统计学意义($P < 0.05$)。

3 讨 论

CAHD 主要是由于冠状动脉粥样硬化引起血管腔狭窄或阻塞,从而造成心肌缺血、缺氧或坏死。扩张冠状动脉类药物可通过扩张冠状动脉、增加血供而缓解心绞痛症状,在药物治疗中占有重要地位[4]。硝酸酯类药物是目前应用最广泛的药物,但仍有缺陷存在[5,6]。如老年患者敏感性的差异较大,可诱发低血压,扩张全身小动脉,从而导致脑动脉扩张而引起头痛等不良反应,使得患者依从性下降;长期持续应用硝酸酯类药物,因其代谢有效产物一氧化氮逐渐减少也可导致耐药增加。

尼可地尔主要作用于平滑肌,因其化学成分具有硝酸基团,故具有类硝酸酯作用。可以扩张静脉及冠状动脉,从而降低心脏前、后负荷。另一方面,尼可地尔可以开放心肌细胞线粒体的 ATP 敏感性钾通道(ATP-sensitive potassium channel, KATP),使钾离子从细胞内流出,缩短动作电位,减少钙内流,从而降低细胞内钙离子水平[7]。并可间接阻断钙通道,减少钙离子内流,减轻钙超载,松弛血管平滑肌而使血管舒张,改善小冠状动脉内的血流灌注,减少心肌耗氧,解除冠状动脉痉挛[8,9]。此外,尼可地尔还可以通过对 C 反应蛋白(C-reactive protein, CRP)等炎症因子的抑制来调节血管内皮功能,进而改善微血管功能。从其药物机制而言,尼可地尔可多方面协同而改善心肌缺血,但对患者的血压、心率及传导系统无过多影响。尼可地尔可通过恢复线粒体功能,使心肌模拟缺血预适应;可保护缺血再灌注损伤心肌,避免心肌细胞凋亡,从而改善预后,减少心血管不良事件的发生[10]。荟萃分析结果表明,尼可地尔可减少心肌损伤,降低 PCI 对中国人口的不良反应发生率[11]。尼可地尔还可以改善心肌缺血后收缩功能的恢复,并以剂量依赖性方式显著降低心肌梗死面积[12]。

地尔硫卓为钙离子拮抗剂,能使钙离子内流受抑制,细胞内钙离子浓度降低,从而松弛血管平滑肌,缓解血管痉挛,降低血压以减轻心脏后负荷,减慢心率,降低负性肌力而减少心肌做功,使得心肌耗氧量降低,保护心肌细胞[13]。地尔硫卓可改善大鼠缺血再灌注损伤的心脏功能和心肌梗死面积,减少氧应激损伤,纠正能量代谢[14]。此外地尔硫卓还可以抑制炎症因子的分泌,减轻冠状动脉微血栓形成所带来的损伤,改善心脏功能[15]。

心绞痛或症状性心肌缺血反映冠状动脉受到损害,也可理解为心肌能量缺乏,即心肌需氧量与供应量之间矛盾的动态变化[16]。本研究表明,对于相对不适合通过手术重建血运的患者,尼可地尔与地尔硫卓均可调节心肌代谢效率,故服药后两组患者每周心绞痛发作次数、持续时间、硝酸甘油服用量较服

药前均有所减少。并且尼可地尔由于具有“类硝酸酯”效应,故疗效明显优于地尔硫卓,差异具有统计学意义($P<0.05$)。两组患者心电图改善的差异无统计学意义。地尔硫卓组患者3例(8.3%)出现轻微头痛,有17例(47.22%)患者心率较入组前有所下降,但未低于60次/min。尼可地尔组有1例出现(2.8%)轻微头痛,相比尼可地尔,地尔硫卓易使患者出现头痛,差异有统计学意义($P<0.05$)。本研究样本量不够大,可能存在统计学上的偏倚及误差。另外对于药物疗效的评价标准中主观因素较多,客观因素较少,后期研究需改进。

综上所述,尼可地尔与地尔硫卓均对PCI术后再发UAP患者有效,且尼可地尔的临床效果较显著,可明显改善心绞痛症状,并且不良反应少,值得在临床中推广应用。

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