

伊布利特联合阿托伐他汀对冠状动脉搭桥围术期房颤的预防效果

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摘要: 目的 探讨伊布利特联合阿托伐他汀对冠状动脉搭桥围术期房颤的预防作用。方法 回顾性分析2020年1月—2020年12月在安徽省立医院接受治疗的148例施行冠状动脉搭桥术的冠心病患者, 根据不同治疗方式分为对照组($n=73$)和试验组($n=75$)。两组患者施行冠状动脉搭桥术后均常规给予阿司匹林、酒石酸美托洛尔等常规药物治疗。对照组术前7 d及术后第2天给予阿托伐他汀钙片口服, 每次20 mg, 每晚1次。试验组在对照组的基础上于术后第2天加用富马酸伊布利特注射液, 1 mg加0.9%氯化钠注射液20 mL, 10 min内静脉推注给药。静推过程中若患者转为窦性心律, 则停止推注。静推后10 min若患者仍未转为窦性心律, 则间隔30 min再次给予富马酸伊布利特注射液1 mg, 若仍房颤, 则镇静后, 给予200 J同步直流电复律。两组术后均常规抗凝, 疗程7 d。术后7 d比较两组患者的临床疗效、术后房颤发生情况, 分别于给药前、第1次给药后30 min及第1次给药后24 h测定患者左心房内径、血清肌钙蛋白I (CTnI)、P波离散度, 观察治疗期间两组患者不良反应发生情况。**结果** 治疗后, 试验组总有效率为93.33%, 显著高于对照组的73.97%, 两组比较差异有统计学意义($P<0.05$)。两组术后房颤起始时间比较差异无统计学意义($P>0.05$); 试验组最大心室率、单次房颤持续时间均显著低于对照组, 差异有统计学意义($P<0.05$)。治疗前, 两组左心房内径、CTnI水平比较差异无统计学意义($P>0.05$); 第1次给药后30 min, 两组左心房内径、CTnI水平均显著升高($P<0.05$), 但两组左心房内径、CTnI水平比较差异无统计学意义($P>0.05$); 第1次给药后24 h, 两组左心房内径、CTnI水平均低于治疗前($P<0.05$), 试验组恢复程度优于对照组, 差异有统计学意义($P<0.05$)。治疗前, 两组P波最大值、P波宽度水平比较差异无统计学意义($P>0.05$); 第1次给药后30 min, 两组P波最大值、P波宽度水平均显著升高($P<0.05$), 但两组P波最大值、P波宽度水平比较差异无统计学意义($P>0.05$); 第1次给药后24 h, 两组P波最大值、P波宽度水平均低于治疗前($P<0.05$), 试验组恢复效果优于对照组, 差异有统计学意义($P<0.05$)。两组用药期间不良反应发生情况差异无统计学意义($P>0.05$)。**结论** 伊布利特联合阿托伐他汀可有效预防冠脉搭桥术后房颤的发生, 可有效控制心房内径增大, 延缓心肌重构。

关键词: 伊布利特; 阿托伐他汀; 冠状动脉搭桥术; 冠心病; 围术期; 房颤

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Preventive effect of ibutilide combined with atorvastatin on atrial fibrillation during perioperative period of coronary artery bypass grafting

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Abstract: Objective To investigate the preventive effect of ibutilide combined with atorvastatin on atrial fibrillation during perioperative period of coronary artery bypass grafting. **Methods** A retrospective analysis was performed on 148 patients with coronary heart disease who received coronary artery bypass grafting in Anhui Provincial Hospital from January 2020 to December 2020. According to different treatment methods, the patients were divided into control group ($n=73$) and experimental group ($n=75$). Patients in both groups were routinely given aspirin, metoprolol tartrate and other conventional drugs after coronary artery bypass grafting. The control group was given Atorvastatin Calcium Tablets orally, 20 mg each time, once a night, 7 days before surgery and 2 days after surgery. On the basis of the control group, the experimental group was additionally given Ibutilide Fumarate Injection, 1 mg plus 0.9% Sodium Chloride Injection 20 mL, intravenously within 10 min. If the patient changes to sinus rhythm

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during static pushing, the injection is stopped. After 10 min of static delay, if the patient still did not revert to sinus rhythm, Ibutilide Fumarate Injection 1 mg was given again 30 min later. If the patient still had atrial fibrillation, synchronous dc cardioversion was given 200 J after sedation. Conventional anticoagulation was performed in both groups. The clinical efficacy and incidence of postoperative atrial fibrillation were compared between the two groups. The left atrial inner diameter, serum troponin I (cTnI) and P wave dispersion were measured before administration, 30 min after the first administration and 24 h after the first administration, respectively, and the incidence of adverse reactions in the two groups during treatment was observed. **Results** After treatment, the total effective rate of the experimental group was 93.33%, significantly higher than 73.97% of the control group. There was significant difference between two groups ($P < 0.05$). There was no significant difference in the onset time of atrial fibrillation between two groups ($P > 0.05$). The maximum ventricular rate and duration of single atrial fibrillation in the experimental group were significantly lower than those in control group ($P < 0.05$). Before treatment, there was no significant difference in left atrial diameter and cTnI level between two groups ($P > 0.05$). 30 minutes after the first administration, the left atrial diameter and cTnI level were significantly increased in two groups ($P < 0.05$), but there was no significant difference in the left atrial diameter and cTnI level between two groups ($P > 0.05$). 24 hours after the first administration, the left atrial diameter and cTnI level in two groups were lower than those before treatment ($P < 0.05$), and the recovery degree in the experimental group was better than that in control group ($P < 0.05$). Before treatment, there was no significant difference in P wave maximum and P wave width between two groups ($P > 0.05$). 30 minutes after the first administration, the maximum value and width of P wave in two groups were significantly increased ($P < 0.05$), but there was no significant difference between two groups ($P > 0.05$). At 24 hours after the first administration, the maximum value and width of P wave in two groups were lower than those before treatment ($P < 0.05$). The recovery effect of the experimental group was better than that of the control group, and the difference was statistically significant ($P < 0.05$). There was no significant difference in adverse reactions between two groups ($P > 0.05$). **Conclusion** Ibutilide combined with atorvastatin can effectively prevent atrial fibrillation after coronary artery bypass grafting, effectively control the increase of atrial diameter and delay myocardial remodeling.

Key words: ibutilide; atorvastatin; coronary bypass; coronary heart disease; perioperative period; atrial fibrillation

冠状动脉搭桥术是目前治疗冠心病最有效的方法,可有效降低患者死亡率,改善患者生活质量^[1]。有研究显示,冠状动脉搭桥术可使心脏的应激反应增高,增加患者并发症的发生,其中房颤是冠状动脉搭桥术最常见的并发症之一^[2]。房颤的发生可导致患者心脏结构和机体血流动力学出现不同程度障碍,导致心室充盈受损,增加肾功能不全、心肌梗死、脑卒中等并发症的发生,危及患者生命,因此,冠状动脉搭桥术后房颤的预防和治疗具有重要意义^[3]。阿托伐他汀具有调节血脂、抑制内皮细胞损伤等作用,同时还能降低冠心病患者血运重建后心血管事件的发生率,是目前预防房颤发生的常用药物,但其单独使用效果不佳^[4]。伊布利特是一种新型Ⅲ类抗心律失常药物,起效迅速,能快速治疗新发房颤。目前临床对于伊布利特预防房颤多使用单药的治疗方案,与其他药物联合治疗的报道较少,因此,本研究旨在探讨伊布利特联合阿托伐他汀对冠状动脉搭桥围术期房颤的预防效果,为临床治疗提供参考。

1 资料与方法

1.1 一般资料

回顾性选择2020年1月—2020年12月在安徽省立医院接受治疗的冠心病并施行冠状动脉搭桥

术的148例患者为研究对象,其中男性85例,女性63例;年龄54~75岁,平均 (65.50 ± 3.18) 岁;冠心病病程1~10年,平均 (5.35 ± 1.26) 年。

1.2 纳入标准与排除标准

1.2.1 纳入标准 (1)符合《冠心病合理用药指南》^[5]中冠心病诊断标准;(2)术前颈动脉超声检查颈动脉无重度狭窄;(3)符合施行冠状动脉搭桥术的冠心病患者;(4)心电图平板实验阳性;(5)超声检查确诊;(6)患者知情同意。

1.2.2 排除标准 (1)对本研究药物过敏者;(2)沟通不便者;(3)有抗凝禁忌或左心房血栓者;(4)有酒精滥用史者;(5)甲状腺机能亢进者;(6)瓣膜病性房颤者;(7)近3个月内已接受过相关治疗的患者;(8)有生命危险者。

1.3 方法

两组患者施行冠状动脉搭桥术后均常规给予阿司匹林、酒石酸美托洛尔等常规药物治疗。对照组术前7d及术后第2天给予阿托伐他汀钙片(辉瑞制药有限公司,国药准字H20051407,规格:每片10mg;批号20191115、20200115)口服,每次20mg,每晚1次,连续治疗7d。试验组在对照组的基础上于术后第2天加用富马酸伊布利特注射液(马鞍山丰原制药有限公司,国药准字H20061029,规格:10mL:1mg,

批号:20191027、20200413),1 mg加0.9%氯化钠注射液20 mL,10 min内静脉推注给药。静推过程中若患者转为窦性心律,则停止推注。静推后10 min若患者仍未转复为窦性心律,则间隔30 min再次给予富马酸伊布利特注射液1 mg,若仍为房颤,则镇静后,给予200 J同步直流电复律。两组术后均给予常规抗凝治疗,疗程7 d。

1.4 观察指标

于给药前、第1次给药后30 min及第1次给药后24 h分别采集两组患者空腹静脉全血5 mL,采用酶联免疫吸附法对血清肌钙蛋白I(CTnI)进行检测,试剂盒购于赫澎(上海)生物科技有限公司;采用动态心电图观察记录术后房颤情况;超声心动图检查左心房内径;心电图检查P波离散度;记录不良反应发生情况。

于术后7 d对患者进行疗效评价,疗效评定标准^[6]:显效:未发生房颤,或偶发房颤但持续时间小于30 s;有效:每天房颤发生次数≤1次,且持续时间≤24 h;无效:临床症状无改善。

总有效率=(显效+有效)例数/总例数

1.5 统计学分析

以SPSS 24.0软件包处理数据,符合正态分布计量资料用 $\bar{x} \pm s$ 表示,组间比较使用独立样本 t 检验,计数资料以百分率表示,行 χ^2 检验, $P < 0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组基线资料比较

根据术后用药情况将患者分为对照组和试验组,对照组73例,男44例,女29例;年龄54~75岁,平均(65.51±3.10)岁;病程1~10年,平均(5.25±1.26)年;单纯主动脉-冠状动脉搭桥47例,搭桥换瓣手术26例。试验组75例,男41例,女34例;年龄55~75岁,平均(65.56±3.12)岁;冠心病病程1~8年,平均(5.12±1.25)年;单纯主动脉-冠状动脉搭桥46例,搭桥换瓣手术29例。两组基线资料差异无统计学意义($P > 0.05$),具有可比性。

2.2 两组临床疗效比较

术后7 d,试验组总有效率为93.33%,显著高于对照组的73.97%,两组比较差异有统计学意义($P < 0.05$),见表1。

2.3 两组术后房颤发生情况比较

两组术后房颤起始时间比较差异无统计学意义($P > 0.05$);试验组最大心室率、单次房颤持续时间均显著低于对照组,差异有统计学意义($P < 0.05$),见表2。

表1 两组临床疗效比较

Table 1 Comparison on clinical efficacy of two groups

组别	n/例	显效/例	有效/例	无效/例	总有效率/%
对照	73	29	25	19	73.97
试验	75	42	28	5	93.33*

与对照组比较:* $P < 0.05$

* $P < 0.05$ vs control group

表2 两组术后房颤发生情况比较($\bar{x} \pm s$)

Table 2 Comparison of occurrence of postoperative atrial fibrillation between two groups($\bar{x} \pm s$)

组别	n/例	术后房颤 起始时间/d	最大心室 率/(次·min ⁻¹)	单次房颤持 续时间/min
对照	73	2.59±0.48	151.07±25.16	23.05±4.17
试验	75	2.66±0.51	126.04±20.14*	10.01±1.25*

与对照组比较:* $P < 0.05$

* $P < 0.05$ vs control group

2.4 两组左心房内径、CTnI水平比较

治疗前,两组左心房内径、CTnI水平比较差异无统计学意义($P > 0.05$);第1次给药后30 min,两组左心房内径、CTnI水平均显著升高($P < 0.05$),但两组左心房内径、CTnI水平比较差异无统计学意义($P > 0.05$),第1次给药后24 h,两组左心房内径、CTnI水平均低于治疗前,试验组恢复程度优于对照组,差异有统计学意义($P < 0.05$),见表3。

表3 两组左心房内径、CTnI水平比较($\bar{x} \pm s$)

Table 3 Comparison of left atrial diameter and CTnI level between two groups($\bar{x} \pm s$)

组别	n/例	左心房内径/mm			CTnI/(ng·mL ⁻¹)		
		治疗前	第1次给药后30 min	第1次给药后24 h	治疗前	第1次给药后30 min	第1次给药后24 h
对照	73	35.64±5.52	42.40±5.31*	34.46±6.15	0.11±0.04	0.23±0.06*	0.10±0.05
试验	75	35.71±5.48	41.35±5.15*	31.97±5.89**	0.10±0.05	0.22±0.04*	0.08±0.02**

与同组治疗前比较:* $P < 0.05$;与对照组第1次给药后24 h比较:** $P < 0.05$

* $P < 0.05$ vs same group before treatment; ** $P < 0.05$ vs 24 h after first administration of control group

2.5 两组P波离散度比较

治疗前,两组P波最大值、P波宽度水平比较,差异无统计学意义($P>0.05$);第1次给药后30 min,两组P波最大值、P波宽度水平均显著升高,但两组P波最大值、P波宽度水平比较差异无统计学意义($P>0.05$),第1次给药后24 h,

两组P波最大值、P波宽度水平均低于治疗前,试验组恢复效果优于对照组,差异有统计学意义($P<0.05$),见表4。

2.6 两组不良反应情况比较

两组用药期间不良反应发生情况差异无统计学意义($P>0.05$),见表5。

表4 两组P波离散度比较($\bar{x}\pm s$)

Table 4 Comparison of P wave dispersion between two groups ($\bar{x}\pm s$)

组别	n/例	P波最大值/ms			P波宽度/ms		
		治疗前	第1次给药后30 min	第1次给药后24 h	治疗前	第1次给药后30 min	第1次给药后24 h
对照	73	97.67±11.23	130.38±11.75*	96.59±9.89	27.43±5.34	50.98±5.73*	26.98±5.73
试验	75	97.51±11.21	131.25±11.12*	93.15±10.71*#	27.42±5.41	51.26±5.69*	24.15±4.61*#

与同组治疗前比较: * $P<0.05$; 与对照组第1次给药后24 h比较: # $P<0.05$

* $P<0.05$ vs same group before treatment; # $P<0.05$ vs 24 h after the first administration of control group

表5 两组安全性评价

Table 5 Safety evaluation of two groups

组别	n/例	低血压/ 例	心动过 缓/例	室性期前 收缩/例	总发生 率/%
对照	73	3	2	0	6.85
试验	75	1	2	1	5.33

3 讨论

冠状动脉搭桥术是一种急性冠脉综合征的主要血运重建方式,其治疗机制为将病变的冠状动脉与主动脉相连,使动脉血液到达缺血的心肌,从而改善因冠状动脉狭窄所造成的供血不足,是治疗冠心病常用的方法之一^[7]。但有研究显示,冠状动脉搭桥术后可导致房颤的发生,其中70%发生于术后96 h内,严重影响患者预后^[8]。房颤是冠状动脉搭桥术后常见并发症,主要表现为患者快速的心室率,导致患者胸前区不适,以及导致低血压、心力衰竭的出现,增加术后脑栓塞的发生率,因此预防冠状动脉搭桥围术期房颤的发生对患者术后康复具有重要意义^[9]。

房颤的发生机制较为复杂,是由多种因素共同作用导致的,有学者研究发现,术后房颤发生的重要原因包括:心房肌不应期离散导致多源性连续折返;手术后心脏容量变化;炎症反应及氧化应激^[10-11]。目前药物治疗是预防房颤发生的重要方法,阿托伐他汀可通过调节血脂来发挥抗房颤的作用,其通过降低胆固醇和低密度脂蛋白胆固醇来影响心肌细胞膜脂质和蛋白质的含量与分布,从而改善心肌细胞膜的理化性质,另外,其还可通过控制

肾素等系统的功能来阻止心肌细胞的重构,但其单独治疗效果不佳,需与其他药物联合治疗提高临床疗效^[12-13]。伊布利特属于甲基磺酰胺的衍生物,是一种新型抗心律失常药物,具有起效快、疗效好等优势,能促进平台期缓慢 Na^+ 内流和 Ca^{2+} 内流,延长心肌细胞动作电位,发挥其抗心律失常作用^[14-15]。有研究显示,伊布利特增强终止房颤的效果,且其药动学不受患者性别、年龄、左室功能等影响,适合心脏外科围术期、射频消融术中新发房颤等治疗^[6,16]。本研究结果显示,伊布利特联合阿托伐他汀治疗的患者总有效率显著高于对照组,且治疗期间未发生明显不良反应。本研究结果还显示,伊布利特联合阿托伐他汀治疗的患者最大心室率、单次房颤持续时间均显著低于对照组($P<0.05$),结果表明,预防性应用伊布利特联合阿托伐他汀能减少冠状动脉搭桥围术期房颤的发生率。宋卫锋等^[17]研究也显示,伊布利特在心房颤动中能降低心房除颤阈值、减少电转复能量,有利于电复律后窦律的维持。分析其原因可能是因为阿托伐他汀可通过降低胆固醇影响心肌细胞膜脂质分布,改善心肌细胞膜理化性质,从而降低心肌兴奋相关的钙离子通道的通透性;而伊布利特能抑制 K^+ 通道,阻断心肌细胞延迟整流钾通道 I_{Kr} ,延长动作电位时间与心肌细胞有效不应期,从而起预防房颤的作用。本研究结果还显示,第1次给药后30 min患者左心房内径、CTnI水平、P波最大值及P波宽度均显著升高,说明患者经过冠状动脉搭桥术侵入性操作后,术后机体处于应激状态^[18],此时CTnI会显著升高,患者心房各部

位电活动差异增大,则P波离散度增大。第1次给药后24 h,伊布利特联合阿托伐他汀治疗的试验组左心房内径、CTnI水平、P波最大值及P波宽度患者低于对照组($P<0.05$),结果表明,联合伊布利特可有效控制心房内径增大,延缓心肌重构,控制心肌内非均质性电活动的产生。相关研究也显示,伊布利特的应用可定性评估房颤维持基质、增大跨室壁复极离散度,导致透壁性室内折返^[19]。

本研究结果表明,伊布利特联合阿托伐他汀可有效控制冠状动脉搭桥围术期房颤的发生,且并发症较少。但本研究时间较短,样本量不足,今后应加大样本量进一步证实。

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