doi: 10.13241/j.cnki.pmb.2014.20.011

·临床研究·

负荷量阿托伐他汀对稳定型冠心病患者非心脏手术围手术期保护作用的研究 *

夏经钢[1#] 曲 杨[2#] 胡少东[1] 许 骥[1] 尹春琳[1] 徐 东[1]

(1 首都医科大学宣武医院心脏科 北京 100053;2 首都医科大学附属北京胸科医院病理科 北京 101149)

摘要 目的:探讨负荷量阿托伐他汀对稳定型冠心病患者非心脏的择期外科手术围手术期主要不良心脏事件的保护作用。**方法:**将拟行非心脏外科手术的 60 名稳定型冠心病患者随机分为负荷量阿托伐他汀组(n=30)和对照组(n=30),其中负荷量阿托伐他汀治疗组在术前 12 小时给予阿托伐他汀 80 mg 顿服,术前 2 小时阿托伐他汀 40 mg 顿服,且每晚服用阿托伐他汀 40 mg,对照组术前每晚服用阿托伐他汀 20 mg,而后进行非心脏的外科手术(主要病种为慢性胆囊结石胆囊炎、慢性阑尾炎、消化性溃疡、疝气),术后负荷量组给予每晚服用阿托伐他汀 40 mg,对照组每晚服用阿托伐他汀 20 mg。比较两组围手术期主要不良心脏事件(包括心脏性猝死,急性心肌梗死,非计划性血运重建)的发生情况。**结果:**对照组出现 1 例急性前壁 ST 段抬高型心肌梗死并行急诊前降支介入再灌注治疗和 7 例无症状型心肌梗死,负荷量阿托伐他汀组出现 1 例无症状型心肌梗死,围手术期心肌梗死发生率较对照组明显降低(P<0.05)。**结论:**负荷量阿托伐他汀可显著降低稳定型冠心病患者非心脏的择期外科手术围手术期主要不良心脏事件如心肌梗死,特别是无症状型心肌梗死的发生率,但该结果尚需大样本多中心随机对照临床试验进一步证实。

关键词: 阿托伐他汀;主要不良心脏事件;稳定型冠心病;非心脏手术;心肌梗死

中图分类号:R541.1 **文献标识码:**A **文章编号:**1673-6273(2014)20-3844-05

Research on the Protective Effect of Loading Dose of Atorvastatin on the Perioperative Period of Patients with Stable Coronary Artery Disease Undergo Noncardiac Surgery*

XIA Jing-gang[1#], QU Yang[2#], HU Shao-dong[1], XU Ji[1], YIN Chun-lin[1], XU Dong[1]

(1 Department of Cardiology, Xuanwu HospitalCapital Medical University, Beijing, 100053, China;

2 Deparment of pathology, Beijing Chest Hospital, Capital Medical University, Beijing, 101149, China)

ABSTRACT Objective: To explore the protective effect of loading dose of atorvastatin on the perioperative period of patients with stable coronary artery disease undergoing noncardiac surgery. **Methods:** 60 patients with stable coronary artery disease undergoing elective noncardiac surgery were randomly divided into the loading dose of atorvastatin group (n=30) and control group (n=30). In the loading dose of atorvastatin treatment group, patients were given atorvastatin 80 mg, 12 hours before surgery, atorvastatin 40 mg two hours before surgery, and atorvastatin 40 mg every night before surgery. In control group, patients were given atorvastatin 20 mg every night before surgery, and after noncardiac surgery (gallstone disease and chronic cholecystitis, chronic appendicitis, peptic ulcer, hernia), in the loading dose group patients were given atorvastatin 40 mg every night, in control group atorvastatin 20 mg. The occurrence of perioperative major adverse cardiac events (including sudden cardiac death, acute myocardial infarction, unplanned revascularization) were compared between the two groups. **Results:** In control group, 1 patient suffered myocardial infarction with acute anterior ST-segment elevation and was given emergency left anterior descending artery interventional reperfusion therapy, 7 patients suffered myocardial infarction with non-ST-segment elevation. In the loading dose of atorvastatin group, 1 patient suffered myocardial infarction with acute non-ST-segment elevation, the incidence rate of perioperative acute myocardial infarction reduced significantly compared with control group (P<0.05). **Conclusion:** Loading dose of atorvastatin significantly reduced the incidence of perioperative major adverse cardiac events such as myocardial infarction, especially asymptomatic myocardial infarction in patients with stable coronary artery disease undergoing elective non-cardiac surgery, but the results still need to be further confirmed by large multicenter randomized controlled clinical trials.

* 基金项目:首都医学发展科学基金项目(2009-2087)

作者简介:夏经钢(1979-),男,硕士研究生,主治医师,主要研究方向:冠心病介入治疗,

电话:010-83198899-8442, E-mail: xiajinggang@sina.cn;

曲杨(1978-),女,硕士研究生,主治医师,主要研究方向:肺癌的分子机制研究,

电话:13366878686,E-mail:qy834@sina.com

为共同第一作者

(收稿日期:2014-01-22 接受日期:2014-02-20)

Key words: Atorvastatin; Major adverse cardiac events; Stable coronary artery disease; Noncardiac surgery; Myocardial infarction
Chinese Library Classification(CLC): R541.1 Document code: A
Article ID: 1673-6273(2014)20-3844-05

前言

心血管疾病的发病率随着年龄的增长而升高,据估计在美国今后 30 年,大于 65 岁的老年人将增加 25%-30%,将大大增加外科医师手术风险的压力。评估外科手术的心血管风险,降低围手术期不良心脏事件风险一直是外科医师、麻醉科医师和心血管医师共同关心的课题。大规模临床试验证实 3- 羟基 -3- 甲基戊二酰辅酶 A 还原酶抑制剂即他汀类药物具有独立于降脂以外的多种疗效,即他汀多效性,可以显著降低冠心病发病率、心血管病死亡率乃至全因死亡率,在冠心病一级和二级预防中具有基石地位[1-3]。已有大量报道负荷量他汀在冠心病中发挥多效性,但在非心脏的择期外科手术围手术期保护作用方面少见报道。因此,本研究初步探讨了负荷量他汀对稳定型冠心病行择期非心脏手术围手术期的主要不良心脏事件的保护作用。

1 资料与方法

1.1 一般资料

选择 2012 年 1 月 -12 月收入外科拟行择期手术且合并稳定型冠心病的 60 例患者作为研究对象, 主要病种为慢性胆囊结石胆囊炎、慢性阑尾炎、消化性溃疡、疝气。入选标准为外科疾病诊断明确且合并稳定型冠心病患者,纳入标准为:① 年龄 18-75 岁; ②既往临床资料证实患者诊断冠状动脉粥样硬化性心脏病, 且大于 30 天没有心绞痛症状发生; ③心功能 2 级(NYHA 分级)。排除标准为:① 年龄大于 75 岁;② 近 1 年内因急性心肌梗死或心绞痛冠脉植入支架且服用双联抗血小板药物者;③ 近 3 个月有急性脑血管病,包括脑梗死,脑出血,脑栓塞等;④ 严重的肝肾功能不全,谷丙转氨酶和谷草转氨酶大于正常值 3 倍以上,血清肌酐大于 >3 mg/dl;⑤ 心功能 2 级以上(NYHA 分级)或左心室舒张末内径≥60 mm,或左心室射血分数 <40%,⑥ 严重的凝血功能障碍,⑦ 他汀类药物过敏。

60 例患者被随机分为负荷量阿托伐他汀组(n=30)和对照组(n=30)。负荷量他汀治疗组男性 22 例,女性 8 例,平均年龄(56± 10)岁;对照组男性 23 例,女性 7 例,平均年龄(57 ± 11)岁。

1.2 治疗方法

负荷量阿托伐他汀治疗组在术前 12 小时给予阿托伐他汀 80 mg 顿服,术前 2 小时阿托伐他汀 40 mg 顿服,且每晚服用阿托伐他汀 40 mg,对照组术前每晚服用阿托伐他汀 20 mg,而后进行非心脏的外科手术,术后负荷量组给予每晚服用阿托伐他汀 40 mg,对照组每晚服用阿托伐他汀 20 mg。

1.3 观察指标

比较两组患者围手术期, 即住院期间主要不良心脏事件,包括心脏性猝死、急性心肌梗死、非计划性血运重建。两组所有患者术前行心电图检查,心肌标志物检测(肌钙蛋白 I、肌酸激酶同工酶 CK-MB),心脏超声检查,术中及术后 24 小时行心电血压血氧监测,术后即刻,术后 24 小时和 48 小时行心电图检查,并且患者有怀疑心肌缺血症状即刻行心电图检查,术后即刻和术后 6 小时,12 小时,24 小时,48 小时进行心肌标志物检测。根据第三版全球心肌梗死的统一定义的诊断标准[4],患者心肌标志物升高(超过 99%参考值上限)结合下列任何情况之一即可诊断:① 心肌缺血的症状;② 新发缺血性 ECG 表现(缺血性 ST-T 表现或新发完全性左束支传导阻滞;③ ECG 示病理性 Q 波形成;④ 影像学证实新发局部室壁运动异常或存活心肌丢失;⑤ 造影或尸检证实冠脉内血栓。

1.4 统计学方法

采用 SPSS13.0 进行统计学分析,计量资料表示为(均数± 标准差),应用 t 检验。计数资料采用 X^2 检验,以 P<0.05 表示差异有统计学意义。

2 结果

2.1 两组临床基线资料的比较

阿托伐他汀负荷量组和对照组在性别、年龄、既往危险因素史(高血压、糖尿病、高脂血症、吸烟史)、既往心肌梗死病史、冠脉支架植入史(大于 1 年)、冠脉搭桥史、术前心脏超声左心室射血分数、血脂水平、他汀类药物应用情况及心电图方面等比较均无显著差异,具有可比性(P>0.05)。见表 1。

2.2 两组术前疾病种类及麻醉方式的比较

阿托伐他汀负荷量组和对照组在术前疾病种类和麻醉方式、麻醉时间方面比较均无显著差异,具有可比性(P>0.05)。见表 2。

2.3 两组术后主要不良心脏事件发生情况的比较

对照组出现 1 例急性前壁 ST 段抬高型心肌梗死并行急诊造影证实前降支闭塞, 植入支架 1 枚,7 例发生无症状型心肌梗死;负荷量阿托伐他汀组出现 1 例无症状型心肌梗死,两组共 8 例无症状心肌梗死患者心电图均无特异心肌缺血改变,心肌标志物均为 1-2 倍升高,负荷量阿托伐他汀组围手术期心肌梗死特别是无症状心肌梗死的发生率较对照组明显降低(P=0.03)。见表 3。

3 讨论

大规模临床试验证实 3- 羟基 -3- 甲基戊二酰辅酶 A 还原酶抑制剂即他汀类药物具有独立于降脂以外的多种疗效,即他汀多效性,包括减轻炎症反应[9]、抗氧化应激[10]、改善内皮功能[11]、免疫调节、抗血栓形成、参与心血管再生治疗等,可以显著降低冠心病的发病率。美国心脏病学会发布最新心脑血管研究的数据显示[12]:1980 年 -2000 年,全球冠心病死亡率下降 47%,介入治疗和强化冠心病二级预防治疗使冠心病死亡率下降 33%,其中更低的血脂水平可以使冠心病死亡率下降 24%。文献报道对 9251 例冠心病患者且低密度脂蛋白胆固醇低于 130 mg/dL,随机分为阿托伐他汀 80 mg/dL 组和 10 mg/dL,平均随访 4.9 年,结果显示阿托伐他汀高剂量组仍能通过其多效性减

表 1 两组临床基线资料的比较

Table 1 Comparison of the Clinical base-line features between two Groups

Variable	Atorvastatin (n=30)	Placebo (n=30)	P Value
Male sex	22	23	0.8
Age, years old	56 ± 10	57 ± 11	0.7
Diabetes mellitus	13	15	0.8
Systemic hypertension	18	15	0.6
Hypercholesterolemia	8	6	0.8
Stroke	15	13	0.8
Previous myocardial infarction	5	6	1
Previous coronary intervention	8	10	0.7
Previous bypass surgery	3	2	1
Left ventricular ejection fraction,%	54 ± 10	55 ± 11	0.7
Total cholesterol,mmol/L	5.82 ± 0.79	5.78 ± 0.86	0.9
LDL cholesterol, mmol/L	3.99 ± 0.44	3.95 ± 0.39	0.7
HDL cholesterol,mmol/L	1.41 ± 0.23	1.39 ± 0.21	0.7
statin therapy	22	25	0.5
Other medical therapy			
Aspirin	18	20	0.8
Beta-blockers	15	17	0.8
ACE inhibitors or ARBs	28	24	0.3
Nitrates	20	24	0.4
Preoperative 12-lead ECG finding			
Abnormal ECG	15	17	0.8
Q-waves	3	4	1

注:计数资料以病例数表示,计量资料按照均数± 标准差表示。

Note: Values are given as number or mean ± SD.

ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blocker; LDL =low-density lipoprotein; HDL= high-density lipoprotein; ECG= electrocardiogram.

少强化冠心病二级预防后的残余风险[13]。

已有大量文献报道大剂量他汀在冠心病介入治疗[14]和冠脉搭桥[15]治疗中发挥多效性,但其在非心脏的择期外科手术围手术期保护作用方面报道少见,主要集中在血管外科手术[16-19]。血管外科涉及的周围血管疾病仍属于动脉硬化范畴,故本研究对负荷量他汀在稳定型冠心病行择期非心脏手术(以普通外科疾病为主)围手术期主要不良心脏事件的保护作用进行了初步的探讨。根据最新的全球心肌梗死统一定义[4],心肌梗死分为 5 种类型,1 型为由原发冠脉事件(斑块侵蚀 / 破裂、裂隙或夹层)引起的与缺血相关的自发型心肌梗死,2 型为继发于氧耗增加或氧供减少(冠脉痉挛、冠脉栓塞、贫血、心律失常、高血压或低血压)引起缺血的心肌梗死,3 型为突发心脏性死亡和(或)影像学或尸检证实新发血栓,4 型为经皮冠脉介入治疗相关心肌梗死,5 型为冠脉旁路移植术相关心肌梗死, 而外科手术围手术期心肌梗死的发生原因以 1 型和 2 型为常见, 既有由于疼痛,应激,围手术期高凝状态原因导致的冠脉斑块变得不稳定甚至破裂导致心肌梗死[20],又可能由于麻醉,失血等原因导致的氧耗氧供失衡导致心肌梗死[21]。本研究结果显示对照组发生 1 例 1 型心肌梗死和 7 例 2 型心肌梗死,而阿托伐他汀负荷量组可能发生 1 例 2 型心肌梗死。负荷量阿托伐他汀能显著降低择期稳定型冠心病患者围手术期心肌梗死的发生率,特别是单纯以心肌标志物轻度升高,心电图无特异缺血改变而且无明显胸闷痛症状的心肌梗死患者。

总之,负荷量阿托伐他汀可降低稳定型冠心病患者在非心脏的择期外科手术围手术期主要不良心脏事件的发生率,特别是无症状型心肌梗死的发生率。但本研究是对负荷量他汀对外科择期手术患者保护作用的初步探讨,样本量少,且没有进行出院后随访,具有一定的局限性,以后的研究需增加样本量,进行多中心研究,并通过院外随访进一步明确负荷量他汀围手术期的保护作用。

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表 2 两组手术情况比较

Table 2 Comparison of the perioperative features between two groups

Variable	Atorvastatin (n=30)	Placebo (n=30)	P Value
Type of anesthesia			
General	10	13	0.6
Spinal	20	17	0.6
Duration of anesthesia (min)			
Mean	69± 19	72± 15	0.5
Surgery			
Gallstone disease	10	12	0.8
Chronic appendicitis	5	4	1
Peptic ulcer	12	11	1
Hernia	3	3	1

注:计数资料以病例数表示,计量资料按照均数± 标准差表示。

Note: Values are given as number or mean ± SD.

表 3 两组围手术期主要不良心脏事件发生情况的比较

Table 3 Comparison of the incidence of MACE between two groups

Variable	Atorvastatin (n=30)	Placebo (n=30)	P Value
Cardiac death	0	0	NS
Myocardial infarction	1	8	0.03
Silent myocardial infarction	1	7	0.06
Unplanned revascularization	0	1	NS
Total MACE	1	8	0.03

注:计数资料以病例数表示,计量资料按照均数± 标准差表示。

Note: Values are given as number or mean ± SD. MACE =major adverse cardiac events.

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