

主动脉瓣机械瓣置换术后患者妊娠期抗凝治疗的前瞻性研究

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【摘要】 目的:研究主动脉瓣机械瓣置换术后患者妊娠期的抗凝方案。 方法:将 2013 年 1 月至 2017 年 1 月在长海医院进行产检的主动脉瓣机械瓣置换术后妊娠患者 120 例随机分为 4 组,分别选用不同的抗凝方案:A 组全孕期口服国产华法林;B 组孕 12 周前皮下注射低分子肝素钙,孕 12 周后口服国产华法林;C 组全孕期口服进口华法林;D 组孕 12 周前皮下注射低分子肝素钙,孕 12 周后口服进口华法林。各组患者国际标准化比值均控制在 1.5~2.0。 结果:(1)C 组和 D 组服用华法林的剂量明显低于 A 组和 B 组。(2)4 组产妇流产、早产、产后出血、血栓栓塞性疾病、死亡的发生率差异无统计学意义。(3)4 组新生儿畸形、颅内出血、死亡的发生率差异无统计学意义。 结论:无血栓形成高危因素的主动脉瓣机械瓣置换术后患者妊娠期使用华法林安全有效。

【关键词】 主动脉瓣置换术;机械瓣;妊娠;华法林

doi:10.3969/j.issn.1673-6583.2018.01.014

Prospective study for anticoagulant therapy throughout pregnancy in patients after mechanical aortic valve replacement XUE Qing, LI Ning, CHU Heng, HAN Lin, XU Zhiyun. *Department of Cardiovascular Surgery, Changhai Hospital, Second Military Medical University, Shanghai 200433, China*

【Abstract】 Objective: To explore and discuss the anticoagulant therapy throughout pregnancy in patients with mechanical aortic valve replacement. **Methods:** 120 pregnant patients after mechanical aortic valve replacement were randomly divided into 4 groups according to different anticoagulant therapy projects from January 2013 to January 2017. Patients in the group A were given oral domestic warfarin throughout pregnancy, and those in the group B were given the low molecular weight heparins calcium injection and then oral domestic warfarin after 12 weeks of pregnancy, and those in the group C were given oral imported warfarin throughout pregnancy, and those in the group D were given the low molecular weight heparins calcium injection and then oral imported warfarin after 12 weeks of pregnancy. The administration of warfarin was controlled aiming for an international normalized ratio of 1.5 to 2.0. **Results:** (1) There was significant difference on the warfarin dose between group C/D and group A/B. (2) There was no significant difference on the incidence of spontaneous abortion, premature delivery, postpartum hemorrhage, thrombotic complication and death between 4 groups. (3) There was no significant difference on the incidence of neonatal abnormality, intracranial hemorrhage and death between 4 groups. **Conclusions:** Oral warfarin throughout pregnancy in patients without high risk factors of thrombosis after mechanical aortic valve replacement is safe and effective.

【Key words】 Aortic valve replacement; Mechanical heart valve prosthesis; Pregnancy; Warfarin

基金项目:国家科技部重点研发计划(2016YFC1100900);国家自然科学基金(81770383)

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近年来,主动脉瓣疾病的发病年龄呈现年轻化趋势^[1],一些女性患者在生育前已行机械瓣置换术,需要终生抗凝,而应用抗凝药物对母胎均有一定风险^[2-3]。

对于机械瓣置换术后的患者,目前仍无理想的妊娠期抗凝标准^[4-5]。长海医院心血管外科与产科合作,对主动脉瓣机械瓣置换术后患者妊娠期的抗凝药物使用进行了全孕期指导,取得了一定经验,现介绍如下。

1 对象与方法

1.1 研究对象

选择 2013 年 1 月至 2017 年 1 月在长海医院产科门诊进行产检的主动脉瓣机械瓣置换术后患者,

排除伴有血栓形成高危因素,如心房颤动、高血压、高脂血症、糖尿病、吸烟等^[6]的患者。本研究经长海医院伦理委员会通过,所有患者均签署知情同意书。最终入选 120 例患者,随机分为 4 组,每组 30 例,分别选用不同的抗凝方案。A 组患者全孕期口服国产华法林(上海信谊,2.5 mg/片);B 组患者孕 12 周前皮下注射低分子肝素钙(葛兰素史克,0.4 mL/支)0.4 mL/12 h,孕 12 周后口服国产华法林;C 组患者全孕期口服进口华法林(芬兰奥立,3 mg/片);D 组患者孕 12 周前皮下注射低分子肝素钙 0.4 mL/12 h,孕 12 周后口服进口华法林。4 组患者第一次产检时的年龄、体质量指数、左室射血分数等组间差异均无统计学意义,见表 1。

表 1 4 组患者第 1 次产检时各指标比较

指标	A 组	B 组	C 组	D 组	F 值	P 值
年龄/岁	26.95±2.62	26.72±3.23	26.55±2.91	27.12±3.14	0.212	0.888
体质量指数/kg·m ⁻²	28.67±1.66	29.21±1.45	28.33±1.76	28.78±1.67	1.472	0.226
左室射血分数/%	56.23±5.03	56.65±4.31	56.73±5.24	56.85±5.01	0.091	0.965

1.2 方法

4 组患者服用华法林期间,每 2 周监测 1 次国际标准化比值(INR),孕 36 周后每周监测 1 次 INR。根据 INR 调整华法林剂量,INR 控制在 1.5~2.0。根据既往文献报道经验^[7-8],结合本院产科实际情况,选择孕 36~40 周剖宫产终止妊娠。记录各组产妇流产、早产、产后出血、血栓栓塞性疾病、死亡的发生率和新生儿畸形、颅内出血、死亡的发生率。

1.3 统计学分析

采用 SPSS 22.0 对数据进行统计学分析。计量资料以均数±标准差表示,两组间均数比较采用 *t* 检验,多组间均数比较采用 *F* 检验。计数资料以百分数表示,采用 Pearson χ^2 检验。以 *P*<0.05 为差异有统计学意义。

2 结果

2.1 华法林剂量

在维持 INR 1.5~2.0 的情况下,C 组[(2.73±0.69) mg·d⁻¹]和 D 组[(2.79±0.66) mg·d⁻¹]患者每日服用华法林的剂量均低于 A 组[(3.14±

0.56) mg·d⁻¹]和 B 组[(3.21±0.54) mg·d⁻¹],见图 1。

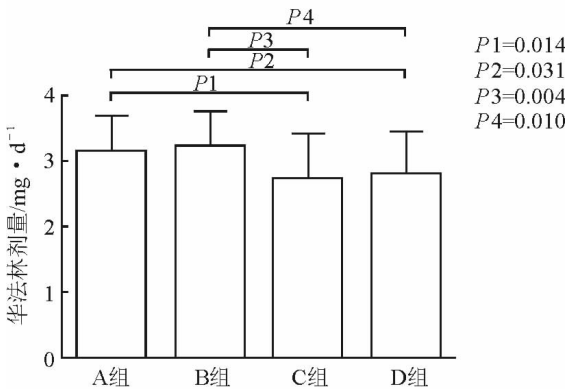


图 1 4 组患者服用华法林剂量比较

2.2 产妇不良结局

4 组产妇流产、早产、产后出血、血栓栓塞性疾病、死亡的发生率差异均无统计学意义,见表 2。

2.3 新生儿不良结局

4 组新生儿畸形、颅内出血、死亡的发生率差异均无统计学意义,见表 3。

表 2 4 组产妇不良结局比较/*n*(%)

指标	A 组	B 组	C 组	D 组	χ^2	<i>P</i> 值
流产	2(6. 7)	1(3. 3)	1(3. 3)	1(3. 3)	0. 626	0. 890
早产	1(3. 3)	2(6. 7)	2(6. 7)	1(3. 3)	0. 702	0. 873
产后出血	4(13. 3)	5(16. 7)	4(13. 3)	5(16. 7)	0. 261	0. 967
血栓栓塞性疾病	0	0	0	0		
死亡	0	0	0	0		

表 3 4 组新生儿不良结局比较/*n*(%)

指标	A 组	B 组	C 组	D 组	χ^2	<i>P</i> 值
畸形	1(3. 3)	0	0	1(3. 3)	2. 034	0. 565
颅内出血	1(3. 3)	1(3. 3)	0	1(3. 3)	1. 026	0. 795
死亡	0	1(3. 3)	0	0	3. 025	0. 388

3 讨论

机械瓣置换术后患者妊娠期的抗凝方案尚存在争论——何时选用何种抗凝药物^[9-10]。时间段主要分为孕 12 周前和孕 12 周后^[11],孕 12 周前是胎儿发育的关键期,药物对胎儿影响较大,而孕 12 周后则相对安全。药物选择主要是华法林和低分子肝素^[12-13]。华法林可透过胎盘进入胎儿体内,有导致流产、早产、致畸等风险,并且风险与剂量呈正相关^[14]。低分子肝素对胎儿致死致畸风险较小,但对处于高凝状态的孕妇,其抗凝效果不如华法林,有血栓风险^[15]。因此,根据既往研究经验,在孕 12 周前使用低分子肝素,孕 12 周后使用华法林是较好方案。

本研究发现,4 组患者妊娠结局无明显差异,全孕期使用华法林抗凝与孕 12 周前使用低分子肝素+孕 12 周后使用华法林抗凝的方案同样安全,而且华法林是口服制剂,使用更方便^[16]。

本研究各组妊娠结局相似,可能与 INR 控制在 1.5~2.0 相关。如果患者伴有血栓形成的高危因素,则需要提高抗凝标准^[17],A 组和 C 组产妇的流产、早产、产后出血风险以及新生儿畸形、颅内出血、死亡风险可能增加,而 B 组和 D 组产妇的血栓栓塞性疾病风险也可能增加。因此,对有血栓形成高危因素的患者,机械瓣置换术后妊娠期的抗凝方案仍有待进一步研究^[18-19]。

A 组和 C 组患者全孕期分别使用国产和进口华法林,最终妊娠结局两组无明显差异,但国产华法林每日所需剂量较大。根据华法林使用风险与

剂量正相关的理论,在相同抗凝效果下服用的药物剂量越小越安全^[20],我们认为进口华法林可能更安全。

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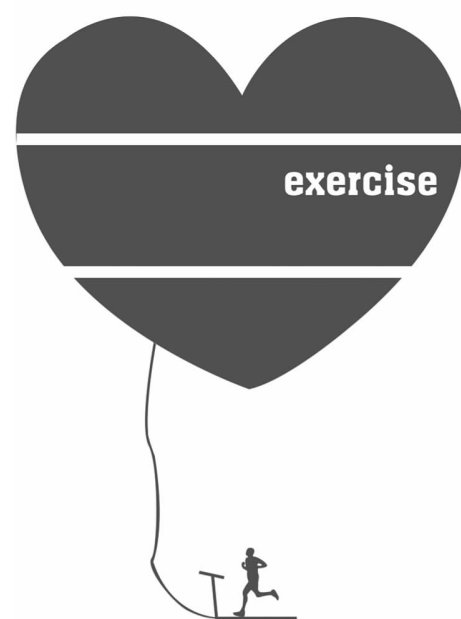
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(收稿:2017-12-03 修回:2017-12-26)

(本文编辑:丁媛媛)



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