低分子肝素预防原发性肝癌切除术后静脉血栓形成的临床观察

单文刚[1],饶建华[1],成旭昱[2] 吕 凌[1],王 平[1],王学浩[1],成 峰[1*]

([1]南京医科大学第一附属医院肝脏外科,肝脏移植中心,江苏 南京 210029;[2]南京医科大学基础医学院,江苏 南京 211166)

[摘 要] **目的**:评价低分子肝素在原发性肝癌切除术后预防静脉血栓形成的疗效及安全性。**方法**:将 105 例行原发性肝癌切除治疗的患者随机分为抗凝组 48 例,术后第 2~7 天每天皮下注射低分子肝素 5 000 U;非抗凝组 57 例,术后未行皮下注射低分子肝素治疗。统计两组患者术后静脉血栓(venous thromboemolism,VET)形成发生率、腹腔出血发生率、切口渗血及切口周围皮肤瘀斑发生率,监测术后第 1 天和第 6 天血红蛋白量变化及术后第 6 天凝血功能,统计术后腹腔引流液总量,行统计学分析。**结果**:抗凝组术后未见 VTE 发生(0/48);非抗凝组术后发生 5 例 VTE,发生率 8.87%(5/57);抗凝组 VTE 术后发生率较非抗凝组显著降低(P=0.043)。抗凝组和非抗凝组术后腹腔活动性出血发生率、血红蛋白变化量、腹腔引流总量、凝血功能、出现切口渗血及切口周围皮肤瘀斑等指标之间无显著性统计学差异(P>0.05)。**结论**:原发性肝癌切除术后易伴发 VTE,低分子肝素预防原发性肝癌切除术后 VTE 疗效确切且安全。

[关键词] 原发性肝癌;肝硬化;低分子肝素;静脉血栓形成;出血
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The clinical preventive effectcs of low molecular weight heparin as prophylaxis against venous thromboembolism after primary hepatocellular carcinoma surgery

Shan Wengang[1], Rao Jianhua[1], Cheng Xuyu[2], Lü Ling[1], Wang Ping[1], Wang Xuehao[1], Cheng Feng[1*]

(Department of Liver Surgery/ Liver Transplantation Center, the First Affiliated Hospital of NJMU, Living Liver Transplantation Center of National Health and Family Planning Commission, Nanjing 210029; School of Basic Medical Sciences, NJMU, Nanjing 211166, China)

[Abstract] **Objective:** To investigate the efficacy and security of low molecular weight heparin (LMWH) as prophylaxis against venous thromboembolism (VTE) after primary hepatocellular carcinoma (PHC) surgery. **Methods:** One hundred and five patients who received PHC surgery were randomly designated to either anticoagulation therapy group (48 cases) or non-anticoagulation therapy group (57 cases). In the anticoagulation therapy group, the patients were subcutaneously injected with LMWH 5 000 U per day from 2nd day to 7th day after operations; however the patients in the non-anticoagulant therapy group were not received the anticoagulant therapy of LMWH after operation. The incidence of postoperative VTE, intra-abdominal hemorrhage, incision bleeding and skin ecchymosis around incision of the two groups were counted. Coagulation function in the 6th day and hemoglobin on the 1st and 6th day after operations were collected. The total abdominal drainage of the two groups was calculated after operation. Finally, a statistical comparison was made between two groups. **Results:** In the anticoagulant therapy group, there was no patients suffering from VTE (0/48). However, there were 5 patients suffering from VTE in the non-anticoagulant therapy group (5/57), which indicated the incidence of VTE was 8.87%. LMWH significantly decreased the incidence of VTE (P=0.043). Furthermore, there are no significantly statistical differences on the aspects of intra-abdominal hemorrhage, hemoglobin variation, abdominal drainage, coagulation function, incision bleeding and skin ecchymosis around incision between the two groups(P>0.05). **Conclusion:** Our study indicates that PHC surgery often leads VTE, which could be effectively and safely treated by LMWH.

[Key words] primary hepatocellular carcinoma; liver cirrhosis; low molecular weight heparin; venous thromboembolism; bleeding
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* 通信作者(Corresponding author),E-mail: docchengfeng@njmu.edu.cn

静脉血栓栓塞(venous thromboembolism,VTE)是指静脉系统内血凝块形成所致的一类疾病，主要包括下肢深静脉血栓形成 (deep venous thrombnosis,DVT)、肺血栓栓塞 (pulmonary thromboembolism,PTE)、肠系膜静脉血栓形成 (mesenteric venous thrombosis,MVT)等。Virchow 理论认为静脉壁损伤、血液高凝状态和血流缓慢是静脉血栓形成的三大因素,术后发生 VTE 也与这些因素密切相关,围手术期长时间限制活动或卧床可引起血流缓慢，静脉输注刺激性药物或感染等可造成静脉壁损伤，肿瘤患者血液高凝状态等均可引起术后 VTE 形成。有资料显示,普通外科手术患者 DVT 发生率 10%~40%[1]。大型手术患者同时具有多种 VTE 危险因素 (年龄>40 岁、VTE 病史、肿瘤等)时,致死性 PE 发生率高达 5%[2]。肝癌是我国常见恶性肿瘤之一,其死亡率占肿瘤死亡率第 2 位。其中肝细胞性肝癌占我国原发性肝癌的 95%以上,均伴随着不同程度肝硬化。以往认为肝硬化患者由于肝脏凝血因子自我平衡的严重破坏导致机体具有较高的出血倾向，然而最近越来越多的证据表明即使肝硬化患者具有高的国际标准化比率(INR)和自发性抗凝作用也不能完全避免血栓形成的发生[3]。有研究表明 PT 或 APTT 延长已不能作为评估肝硬化患者处于低凝状态的指标；相反地,肝硬化患者被认为处于一种获得性促凝状态,肝硬化患者暴露于危险因素(如手术)中能够增加 VTE 形成的机率[4]。因此,对于原发性肝癌切除术后评估 VTE 形成风险及是否采用预防性抗凝治疗具有重要的临床价值。

1 对象和方法

1.1 对象

2015年 7 月—2016 年 7 月南京医科大学第一附属医院肝脏外科单个医疗小组诊治的 105 例原发性肝癌($T_{1\text{-}2}N_0M_0$)患者。其中男 83 例,女 22 例,年龄 42~79 岁,中位年龄(57.67±9.91)岁。入组标准:①术后病理证实为肝细胞性肝癌；②术前乙型肝炎病毒指数<500,肝硬化程度为轻中度;③既往无血液相关性疾病和血栓性疾病史；④术前未长期口服抗血小板或抗凝药物;⑤血小板计数>80×10^9 个/L,凝血功能和 D-二聚体基本正常;⑥术前评估无严重基础疾病,肝功能 Child-Pugh 分级为 A 级或 B 级。⑦术后均放置腹腔引流管。剔除标准:①术中出血>1 000 mL;②手术时间>5 h。

1.2 方法

1.2.1 处理及分组

根据术后 2~7 d 是否使用低分子肝素(5 000 U,立迈青，合肥兆科药业有限公司）抗凝分成抗凝组(48 例)和非抗凝组(57 例),两组术后常规治疗无差异,术后均建议早期床上活动下肢,早期下床活动。本研究为随机双盲,两组患者的性别、年龄、术前凝血功能、Child-Pugh 分级、手术方式、术中肝硬化程度、手术时间、无肝期时间、术中出血量及输血情况等一般资料差异无统计学意义(P>0.05,表 1,2),术后疗效具有可比性。本研究经医院伦理委员会批准。

表 1 抗凝组和非抗凝组一般资料比较

Table 1 Comparison of baseline between the anticoagulant and non-anticoagulation therapy groups

项目	抗凝组 (n=48)	非抗凝组 (n=57)	χ^2 或 t 值	P 值
性别(例)			0.001	0.978
男	38	45		
女	10	12		
年龄(岁)	58.71±8.60	56.79±10.9	0.988	0.326
术前凝血功能				
PT(s)	12.8±1.15	12.6±1.09	0.872	0.385
APTT(s)	30.12±2.83	30.2±3.98	0.180	0.857
INR	2.43±0.45	2.64±1.18	1.196	0.234
Child-Pugh 分级(例)			0.086	0.769
A 级	39	45		
B 级	9	12		

表2 抗凝组和非抗凝组术中情况比较

Table 2 Comparison of the intraoperative conditions between the anticoagulant and non-anticoagulation therapy groups

项目	抗凝组 (n=48)	非抗凝组 (n=57)	χ^2 或 t 值	P 值
手术方式(例)			0.029	0.865
规则肝段、叶切除	21	24		
不规则肝切除	27	33		
肝硬化程度(例)			0.036	0.85
轻度	32	37		
中度	16	20		
手术时间(min)	146.00±39.77	155.26±39.58	1.192	0.236
无肝期时间(min)	24.56±11.67	26.18±10.96	0.729	0.467
术中出血量(mL)	210.21±195.45	258.42±197.18	1.253	0.213
术中输血(例)	8	11	0.122	0.727

1.2.2 疗效观察

观察患者术后有无 VTE 临床表现,如术后出现下肢肿胀、酸痛不适、行走时疼痛、胸痛、胸闷不适、活动后突发血氧饱和度下降、咯血、腹胀、腹痛、长时间不通气、术后早期出现肠梗阻表现、腹膜炎体征等可疑症状,通过彩色多普勒、增强 CT、CTV 等检查确诊 VTE,统计两组术后 VTE 发生率。观察患者术后腹腔引流液的颜色和量,生命体征变化,统计 2 组术后腹腔活动性出血的发生率,当腹腔引流液量小于 50 mL/d 后拔出腹腔引流管。监测术后第 1、6 天血红蛋白量指标,计算两组患者血红蛋白变化量。监测术后第 6 天凝血功能(PT、APTT、INR)。观察患者术后切口渗血及切口周围皮肤瘀斑情况,统计其发生率。

1.3 统计学方法

使用 SPSS 19.0 统计软件进行分析,结果中计量指标采用均数±标准差($\bar{x}$±s)表示,组间比较采用 t 检验;计数资料比较采用 χ^2 检验和 Fisher 精确检验,$P\leqslant0.05$ 为差异有统计学意义。

2 结 果

2.1 术后 VTE 发生率

抗凝组 48 例,均无 VTE 发生;非抗凝组 57 例,发生 VTE 共 5 例,其中 3 例经 B 超检查确诊为下肢 DVT ,1 例经 B 超和胸部增强 CT 确诊为下肢 DVT 伴 PE ,1 例经 CTV 确诊为 MVT ,非抗凝组术后 VTE 发生率 8.87%。抗凝组 VTE 发生率较非抗凝组显著下降,差异有统计学意义($P<0.05$)。

2.2 术后腹腔出血发生率

术后抗凝组和非抗凝组均未发生腹腔活动性出血,且两组在术后切口渗血及切口周围皮肤瘀斑发生率分别为 2/48 和 0/57,统计学上无显著性差异($P>0.05$)。

2.3 术后血红蛋白变化量、腹腔引流总量、凝血功能比较

术后抗凝组和非抗凝组在术后血红蛋白变化量、腹腔引流总量、术后凝血功能(PT、APTT 和 INR)等指标之间无显著性统计学差异($P>0.05$,表3)。

表 3 抗凝组和非抗凝组术后情况比较

Table 3 Comparison of the postoperative conditions between the anticoagulant therapy group and non-anticoagulation therapy group

项目	抗凝组(n=48)	非抗凝组(n=57)	t 值	P 值
血红蛋白变化量(g/L)	16.63±7.10	16.04±6.72	0.437	0.663
腹腔引流总量(mL)	715.00±558.77	601.60±456.80	1.139	0.258
术后凝血功能				
PT(s)	13.23±0.92	13.01±1.11	1.117	0.267
APTT(s)	32.28±2.33	31.31±3.40	1.678	0.096
INR	2.61±0.47	2.48±0.58	1.211	0.229

3 讨 论

VTE 是外科手术后的严重并发症之一,其中深静脉血栓和肺栓塞可能造成患者的死亡[5]。除患者自身因素(年龄、性别、基础疾病、肿瘤等)外,手术是引起术后 VTE 形成的重要因素之一,术中及术后长期卧床可引起下肢静脉血回流速度减慢;术中对局部组织的损伤可引起静脉血管壁损伤和血管内皮细胞缺氧肿胀,血管内皮下胶原和基底膜暴露,继发血液中促凝血因子和组织因子释放,促使血小板聚集并激活凝血系统;术后机体处于应激状态,术后创伤修复,可引起血小板凝集功能增强,纤溶系统功能减弱,使血液处于高凝状态;术后止血药物的使用等多种因素均可促使术后 VTE 发生。DVT 可引起患肢肿胀、疼痛、静脉曲张、股青肿。MVT 早期表现为术后不通气,腹胀不适,随着肠管缺血逐渐加重,肠壁水肿、渗出,继发腹膜炎,出现反跳痛、肌紧张等急腹征需急诊手术治疗。下肢深静脉血栓的栓子脱落随着血流到达肺部血管,可导致肺血管栓塞,引起 PE,患者出现通气功能障碍、呼吸困难、低氧血症等,严重者导致患者死亡。

肝细胞性肝癌作为一种原发性肝癌,在我国绝大多数是由长期肝炎肝硬化引起的,病情发展到肝癌均合并着不同程度肝硬化。以往观点认为,肝硬化患者机体处于低凝状态,具有自发性抗凝作用。然而,近几年有一种新的观念被提出,即“止血重新平衡”,肝硬化肝脏合成的促凝因子和抗凝因子相互作

用会达到新的平衡点,这个平衡不稳定,要么有高的出血倾向,要么容易导致血栓形成[6]。一方面由于肝硬化患者合成促凝因子Ⅱ、Ⅴ、Ⅶ、Ⅹ、Ⅺ、Ⅻ、XIII和纤维蛋白原减少,引起 INR 升高,增加了出血风险;另一方面肝硬化肝脏处于高凝状态是由于合成抗凝因子减少,比如抗凝血酶、蛋白 C、蛋白 S 和血纤维蛋白溶酶原[7-10]。此外,凝血酶、内源性促凝因子如Ⅷ、血管性血友病因子(vWF)和抗磷脂抗体的合成增加也加剧了促凝作用[11]。因此 PT 或 APTT 延长等标准生化指标已不能作为判断肝硬化患者处于低凝状态的指标[12-13],近期有研究数据证明肝硬化患者是完全处于高凝状态[8], 当其暴露于危险因素中能够增加 VTE 形成机率,如门静脉血栓形成在严重肝硬化阶段容易发生,而且合并肝细胞性肝癌的肝硬化患者门静脉血栓形成的机率会明显升高[6]。但目前仍没有明确指标来评估肝硬化患者高凝状态的程度,因此预防 VTE 所带来的出血风险和治疗方法仍然没有明确共识, 包括最新 2012ACCP 指南对于肝硬化病患者如何预防和治疗 VTE 没有给出明确的建议[14]。近来研究表明适量的依诺肝素用于预防肝移植术后门静脉血栓形成时并没有增加出血机率,同时减少细菌移位和呼吸困难的发生[15]。相对于健康人,肝硬化患者需预防深静脉血栓形成,尤其是暴露于危险因素中比如制动、肿瘤或手术患者[16-17]。然而,由于怕有术后出血的风险,预防性抗凝治疗仍没有被用于肝硬化患者。

关于肝癌术后预防 VTE 的相关学术指南尚未建立,且相关报道也较少。本研究中预防性使用低分子肝素抗凝,参照 2016 年发布的《中国普通外科围手术期血栓预防与管理指南》,推荐低分子肝素于术前 12 h 给药,皮下注射,1 次/d,剂量建议参照药品说明书给药。对于肝脏外科手术,除伴有出血性疾病或明显正在出血的患者外,肝脏切除患者应在充分评估出血风险的基础上,考虑应用 VTE 药物预防措施。因此考虑到术前抗凝可能会影响术中肝脏创面的止血,本研究选择从术后第 2 天开始,预防性皮下注射低分子肝素 5 000 U,1 次/d。统计结果表明原发性肝癌患者术后预防性使用低分子肝素抗凝,其 VTE 的发生率较对照组明显下降,且两组在术后腹腔出血发生率、腹腔引流总量、血红蛋白下降幅度、凝血功能、切口渗血及切口周围皮肤瘀斑等方面无明显差异。这说明原发性肝癌患者术后 VTE 仍然有较高发生率,预防性使用低分子肝素抗凝治疗可以降低 VTE 发生率, 且没有增加术后出血的风险,因而低分子肝素抗凝预防肝癌术后 VTE 有效且安全,尤其对于高龄、既往有血栓形成病史等 VTE 高危患者有必要进行术后预防性抗凝治疗。本研究局限于肝癌患者合并轻中度肝硬化, 对于严重肝硬化和血小板明显降低的患者术后预防性抗凝仍需慎重,要权衡好抗凝治疗的利与弊。

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