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◇药物与临床◇

依诺肝素钠预防高危产妇剖宫产术后静脉血栓形成疗效分析

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摘要:目的　探析依诺肝素钠预防高危产妇剖宫产术后静脉血栓形成的临床疗效。**方法**　选取2017年1月至2018年12月于宁德市医院住院,并予行子宫下段横切口剖宫产术终止妊娠的高危产妇136例,抽签分为研究组与对照组,每组68例。两组病人均指导其术后6 h后开始床上翻身,活动双下肢,术后第1天辅助其适当下床活动。研究组在上述基础上于术后第1天给予依诺肝素钠4 000 U皮下注射,每天1次,持续7 d。比较两组病人静脉血栓栓塞情况及凝血功能改变。**结果**　两组病人年龄与孕周比较,差异无统计学意义($P>0.05$)。对照组有10例(14.71%)病人静脉血栓形成,明显高于研究组(0例)($P<0.05$)。两组病人剖宫产术前凝血功能[D-二聚体、纤维蛋白原(FIB)、凝血酶原时间(PT)、活化部分凝血酶时间(APTT)]比较,差异无统计学意义($P>0.05$)。而术后第5天复查,研究组病人D-二聚体、FIB显著下降,PT、APTT值明显上升;而对照组D-二聚体、FIB、PT、APTT值均有所上升。两组病人分别与各自术前比较,均差异有统计学意义($P<0.05$)。术后第5天复查凝血功能,研究组病人D-二聚体、FIB明显低于对照组,PT、APTT均显著高于对照组,均差异有统计学意义($P<0.05$)。**结论**　依诺肝素钠能有效地预防高危病人剖宫产术后静脉血栓形成,可在临床中应用推广,并为国内高危产妇抗凝治疗选择提供依据。

关键词:依诺肝素;　剖宫产术;　手术后并发症;　静脉血栓形成;　妊娠,高危

Effect of enoxaparin sodium on preventing venous thrombosis in high-risk pregnant women after cesarean section

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Abstract: Objective　To explore the clinical effect of enoxaparin sodium in preventing venous thrombosis in high-risk pregnant women after cesarean section. **Methods**　A total of 136 high-risk pregnant women who were hospitalized in Ningde City Hospital from January 2017 to December 2018 and underwent cesarean section of transverse incision at the lower section of uterus were selected and randomly assigned into study group and control group by drawing lots, with 68 cases in each group. Patients in both groups were instructed to start turning over in bed 6 h after surgery and to move their lower limbs. On the 1st day after surgery, they were assisted to get out of bed properly. Additionally, the research group received 4 000 U of enoxaparin sodium subcutaneously once daily for 7 days after the surgery. The venous thromboembolism and the change of coagulation function were compared between the two groups. **Results**　There were no significant differences in age and weeks of gestational between the two groups ($P>0.05$). Venous thrombosis occurred in 10 patients (14.71%) in the control group, which was significantly higher than that in the study group (0 case) ($P<0.05$). Comparison of coagulation function [D-dimer, fibrinogen (FIB), prothrombin time (PT), activated partial thrombin time (APTT)] between the two groups before cesarean section showed no statistically significant difference ($P>0.05$). On the 5th day after the surgery, the levels of D-dimer and FIB of the patients in the study group were significantly decreased, while the levels of PT and APTT were significantly increased. The levels of D-dimer, FIB, PT and APTT in the control group were all increased. There were statistical difference between preoperative and postoperative levels in both groups ($P<0.05$). The coagulation function was rechecked on the 5th day after the surgery. The levels of D-dimer and FIB in the study group were significantly lower than those in the control group, while the levels of PT and APTT were significantly higher than those in the control group, which both showed statistically significant differences ($P<0.05$). **Conclusion**　Enoxaparin sodium can effectively prevent venous thrombosis in high-risk patients after cesarean section, which can be widely used in clinical practice, and provides reference for the option of anticoagulant treatment for high-risk pregnant women in China.

Key words: Enoxaparin;　Cesarean section;　Postoperative complications;　Venous thrombosis;　Pregnancy, high-risk

妊娠因为生理和病理的改变,肝、肾、心脏等脏器功能的变化,血液高凝,极易发生易栓症[1],静脉血栓栓塞(venous thromboembolism, VTE)是孕产妇主要死亡原因之一。国外有报道其占孕产妇死亡

的24%[2]。VTE主要包括深静脉血栓形成和肺栓塞,如果不及时诊断和治疗,15%~24%的深静脉血栓形成病人将发展为肺栓塞病人,是孕产妇发生猝死主要原因之一[3]。随着2016年1月我国全面二孩政策开放以来,高龄、辅助生殖、子痫前期、免疫系统疾病(如系统性红斑狼疮、抗磷脂综合征等)、妊娠期糖尿病、肥胖等高危孕产妇明显增多,这类病人是产后发生深静脉血栓甚至肺栓塞的高危人群,因此,产褥期预防VTE,减少不良围产结局的发生显得尤为重要。本研究在高危产妇行剖宫产术后,应用依诺肝素钠抗凝治疗,观察病人VTE情况及凝血功能变化,现报告如下。

1 资料与方法

1.1 一般资料 选取2017年1月至2018年12月于宁德市医院住院,并予行子宫下段横切口剖宫产术终止妊娠的高危产妇136例,抽签分为研究组与对照组,每组68例。纳入标准:有发生VTE风险的高危产妇,合并症或并发症包括高血压、妊娠期糖尿病、妊娠合并心脏病、自身免疫性疾病、肥胖、高龄、辅助生殖。本研究符合《世界医学协会赫尔辛基宣言》相关要求,病人或其近亲属对研究方案签署知情同意书。

1.2 研究方法 两组病人均指导其术后6 h后开始床上翻身,活动双下肢,术后第1天辅助其适当下床活动。研究组在上述基础上于术后第1天同时给予依诺肝素钠(国药准字H20064066)4 000 U皮下注射,每天1次,用药期间观察有无依诺肝素钠可能引起出血的不良反应(如阴道出血明显增多,牙龈出血、皮肤瘀点瘀斑等),指导临床是否继续用药,持续7 d。

1.3 观察指标 ①VTE临床症状:下肢疼痛、酸胀感;双下肢不对称肿大、压痛明显;②双下肢静脉彩超;③术前及术后第5天凝血功能比较:D-二聚体、纤维蛋白原(FIB)、凝血酶原时间(PT)、活化部分凝血酶时间(APTT)。

1.4 统计学方法 研究结果统计数据应用SPSS 17.0进行分析,计量资料以$\bar{x} \pm s$表示,采用t检验,计数资料以例数表示,采用Fisher确切概率法,以$P<0.05$为差异有统计学意义。

2 结果

2.1 两组病人基本情况 研究组年龄(33.50±4.25)岁,范围为22~43岁,孕周(38.4±0.7)周;对照组年龄(32.38±4.06)岁,范围为23~40岁,孕周(38.5±0.5)周。两组病人年龄、孕周比较,均差异无统计学意义($t=1.59$,$P=0.12$;$t=0.75$,$P=0.46$)。

2.2 两组病人VTE情况比较 研究组病人均无下肢疼痛、酸胀感,双下肢不对称肿大、压痛明显等临床症状,行双下肢静脉彩超检查未见血栓形成,无VTE,而对照组有9例病人感一侧下肢疼痛、酸胀感,1例病人一侧下肢肿胀,伴有压痛,这10例病人行双下肢静脉彩超提示静脉血栓形成,其VTE发生率(14.71%)明显高于研究组($P<0.05$)。见表1。

表1 两组剖宫产术后高危产妇静脉血栓栓塞(VTE)情况比较/例

组别	例数	下肢深静脉血栓	小腿肌间静脉血栓	股静脉血栓	髂静脉血栓	总发生
对照组	68	4	5	1	0	10
研究组	68	0	0	0	0	0[a]

注:a为采用Fisher确切概率法,与对照组比较,$P=0.001$

2.3 两组病人凝血功能改变比较 两组病人均无明显出血倾向。研究组与对照组术后5 d总共阴道出血量差异无统计学意义[(31.20±3.25)mL比(28.48±4.06)mL,$t=1.68$,$P=0.17$]。研究组与对照组剖宫产术前凝血功能(D-二聚体、FIB、PT、APTT)比较差异无统计学意义($P>0.05$)。术后第5天复查,研究组D-二聚体、FIB较术前下降,PT、APTT上升;而对照组D-二聚体、FIB、PT、APTT值均较术前上升($P<0.05$)。两组比较,研究组D-二聚体、FIB明显低于对照组,PT、APTT均显著高于对照组($P<0.05$)。见表2。

表2 两组剖宫产前后高危产妇凝血功能比较/$\bar{x} \pm s$

组别	例数	D-二聚体/(mg/L)	FIB/(g/L)	PT/s	APTT/s
对照组	68				
术前		2.93±0.20	4.87±0.09	12.37±0.18	32.93±0.58
术后第5天		3.05±0.18[a]	5.50±0.14[a]	12.59±0.19[a]	33.45±0.43[a]
研究组	68				
术前		3.16±0.61	4.89±0.34	12.04±0.34	33.08±0.42
术后第5天		1.60±0.51[ab]	3.95±0.28[ab]	12.80±0.31[ab]	34.69±0.40[ab]
t值		30.90	58.95	16.68	14.48
P值		<0.001	<0.001	<0.001	<0.001

注:FIB为纤维蛋白原,PT为凝血酶原时间,APTT为活化部分凝血酶时间。t、P值为研究组治疗前后的差值与对照组治疗前后的差值比较。与同组术前比较,[a]$P<0.05$;与对照组术后第5天比较,[b]$P<0.05$

3 讨论

孕妇在正常妊娠过程中静脉血液淤滞、血管壁损伤均导致妊娠期血液属于高凝状态,使妊娠期女性发生血管栓塞性疾病风险较非孕期女性增加5~6倍,但同时这种生理改变亦使产后胎盘剥离面血管内血栓快速形成,是预防产后出血的另一重要机制[4-5]。但当孕妇出现肥胖、高龄、高血压、糖尿病、心脏病等合并症或并发症时,便会打破这种平衡,容易引发孕产妇深静脉血栓的形成。在国外发达国家,VTE是孕产妇死亡的主要原因[6-7],我国等发

展中国家尚未有相关多中心研究及大数据来评估静脉血栓栓塞性疾病的发病率及孕产妇病死率。在本研究中对照组68例孕妇中,有10例病人发生VTE,发生率为14.71%,但尚未发现肺栓塞的病例及死亡病例,这可能跟本研究样本量少有关。

国外研究表明病人在产后,尤其是产后第1周发生静脉血栓风险最高,这些研究结果表明产褥期发生深静脉血栓形成的风险是孕期的2.5倍,且行剖宫产的产妇发生静脉血栓形成风险明显多于顺产病人[8-10]。Blondon等[11]做了一项Meta分析,发现剖宫产术后病人发生VTE概率是0.3%,而顺产病人发病率仅为其1/4。本研究的136例病人均为剖宫产术后病人,剖宫产病人静脉血栓形成发生率高于顺产病人可能跟麻醉、手术创伤、切口疼痛、术后活动受限有关。

临床上对于剖宫产术后开始抗凝治疗的时间一直存在争议,Leffert等[12]推荐于剖宫产术后6~12 h开始抗凝治疗,这样不易继发产后出血。本研究在病人剖宫产术后第1天,间隔时间约12~24 h之间给予依诺肝素钠预防性抗凝治疗,两组病人术后5 d总共阴道出血量差异无统计学意义($P>0.05$)。同时,本研究中应用依诺肝素钠抗凝治疗后,研究组中产妇均无VTE。而对照组有10例病人发生VTE,发生率为14.71%(10/68)。

虽然VTE对于高危产妇是一种致命性疾病,但仍然可以采用一些方法进行预防或降低其危害[13-15],低分子肝素钠是目前多学科抗凝药物的首要选择[16]。2015年英国皇家妇产科医师学会(RCOG)的《妊娠及产褥期静脉血栓栓塞性疾病诊治指南》建议:低分子肝素是产后,尤其针对合并或并发妊娠期高血压、妊娠期糖尿病、肥胖、高龄、双胎等高危因素的产妇预防VTE的首选药物。本研究中研究组病人于术后第1天开始应用依诺肝素钠,并于术后第5天复查凝血功能,其结果表明D-二聚体、FIB明显下降,而PT、APTT均不同程度上升。另外,与对照组相比较,研究组D-二聚体、FIB显著低于对照组,但PT、APTT值较对照组高。由此可见,依诺肝素钠抗凝效果、纤溶效果显著,明显改善产妇术后凝血功能,降低高凝状态,有效预防VTE。

在我国目前对于孕产妇的抗凝治疗尚未形成临床指南或专家共识,抗凝治疗大多参考欧美国家,但人种不一,发病率不同,药物应用剂量或药物选择亦不同。本研究结果可为我国临床孕产妇抗凝治疗提供参考。

参考文献

[1] 张海娟,杨孜.低分子肝素在子痫前期中应用的回顾与展望[J].中国实用妇科与产科杂志,2017,33(7):755-759.

[2] VILLANI M, AGENO W, GRANDONE E, et al. The prevention and treatment ofvenous thromboembolism in pregnancy[J].Expert Rev Cardiovasc Ther,2017,15(5):397-402.

[3] CHEN Y,DAI Y,SONG J,et al.Establishment of a risk assessment tool for pregnancy - associated venous thromboembolism and its clinical application:protocol for a prospective observational study in Beijing[J]. BMC Pregnancy Childbirth,2019,19(1):294.

[4] 谢幸,孔北华,段涛.妇产科学[M].9版.北京:人民卫生出版社,2018:40.

[5] LINNEMANN B, BAUERSACHS R, ROTT H, et al. Treatment of pregnancy – associated venous thromboembolism – position paper of the Working Group in Women's Health of the Society of Thrombosis and Haemostasis (GTH) [J].Vasa,2016,45 (2):103-118.

[6] MCLEAN KC, JAMES AH. Diagnosis and management of VTE in pregnancy[J].Clin Obstet Gynecol,2018,61(2):206-218.

[7] ROSSIGNOL M, MORAU E, DREYFUS M. Maternal death by venousthromboembolic disease [J]. Gynecol Obstet Fertil Senol, 2017,45(12S):S31-S37.

[8] HEIT JA, KOBBERVIG CE, JAMES AH, et al. Trends in the incidence of venous thromboembolism during pregnancy or postpartum:a 30-year population-based study[J].Annals of Internal Medicine,2005,143 (10):697-706.

[9] SULTAN AA, WEST J, TATA LJ, et al. Risk of first venous thromboembolism in and around pregnancy:a population-based cohort study[J].British Journal of Haematology,2012,156 (3):366-373.

[10] EUROPEAN SOCIETY OF GYNECOLOGY (ESG), ASSOCIATION FOR EUROPEAN PAEDIATRIC CARDIOLOGY (AEPC), GERMAN SOCIETY FOR GENDER MEDICINE (DGESGM), et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy:the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC)[J].Eur Heart J,2011,32(24):3147-3197.

[11] BLONDON M, CASINI A, HOPPE KK, et al. Risks of venous thromboembolism after cesarean sections: a meta - analysis [J]. Chest,2016,150(3):572-596.

[12] LEFFERT L, BUTWICK A, CARVALHO B, et al. The society for obstetric anesthesia and perinatology consensus statement on the anesthetic management of pregnant and postpartum women receiving thromboprophylaxis or higher dose anticoagulants [J]. Anesth Analg,2018,126(3):928-944.

[13] FRIEDMAN AM, ANANTH CV. Obstetrical venous thromboembolism: Epidemiology and strategies for prophylaxis [J]. Semin Perinatol,2016,40(2):81-86.

[14] LIEW NC, ALEMANY GV, ANGCHAISUKSIRI P, et al. Asian venousthromboembolism guidelines: updated recommendations for theprevention of venous thromboembolism[J].Int Angiol,2017,36 (1):1-20.

[15] VOON HY, CHAI MC, HII LY, et al. Postpartum thromboprophylaxis in amultireligious cohort: a retrospective review of indications and uptake[J].JObstet Gynaecol,2018,38(4):493-497.

[16] YURDAKÖKM. Fetal and neonatal effects of anticoagulants used in pregnancy:a review[J].Turk J Pediatr,2012,54(3):207-215.

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