DOI:10.13210/j.cnki.jhmu.20170810.020
网络出版地址:http://kns.cnki.net/kcms/detail/46.1049.R.20170810.1042.040.html

低分子肝素治疗妊娠期高血压疾病后母体内皮损伤及胎盘病理损伤的评估

董 珊
(四川省自贡市第一人民医院妇产科,四川 自贡 643000)

[摘要] **目的**:探讨低分子肝素治疗对妊娠期高血压疾病后母体内皮损伤及胎盘病理损伤的影响。**方法**:选择2014年9月~2016年5月间在本院接受治疗的妊娠期高血压疾病患者70例,按照随机数表法将其分为对照组、观察组,各35例。对照组患者接受常规治疗,观察组患者接受低分子肝素联合常规治疗,均持续至分娩前,对比两组患者血清中内皮损伤指标,胎盘组织碾磨液中氧化应激指标含量、凋亡分子表达量的差异。**结果**:治疗后,两组患者血清中内皮素(ET)、血管细胞黏附分子-1(VCAM-1)的含量低于治疗前,一氧化氮(NO)、前列腺素E(PGE)含量高于治疗前,且观察组患者血清中ET、VCAM-1的含量低于对照组患者,NO、PGE的含量高于对照组患者,差异均有统计学意义($P<0.05$);分娩后,胎盘组织碾磨液中晚期氧化蛋白产物(AOPP)、丙二醛(MDA)的含量显著低于对照组患者,超氧化物歧化酶(SOD)、谷胱甘肽过氧化物酶(GSH-Px)的含量高于对照组患者,差异均有统计学意义($P<0.05$);胎盘组织碾磨液中Fas、p53、caspase-3 mRNA的表达量低于对照组患者,Bcl-2、bax mRNA的表达量高于对照组患者,差异均有统计学意义($P<0.05$)。**结论**:妊娠期高血压疾病患者接受低分子肝素辅助治疗,有助于减轻母体内皮损伤、减轻全身氧化应激程度、抑制胎盘细胞凋亡。

[关键词] 妊娠期高血压疾病;低分子肝素;内皮损伤;氧化应激;细胞凋亡
[中图分类号] R714.2 [文献标识码] A [文章编号] 1007-1237(2017)15-2120-03

Effect of low molecular weight heparin therapy on maternal endothelial injury and placental pathological injury after hypertensive disorder complicating pregnancy

DONG Shan
(*Obstetrics and Gynecology Department, Zigong First People's Hospital in Sichuan Province, Zigong City, Sichuan Province*, 643000)

[*Foundation Project*]: *This project is supported by Application Foundation of Science and Technology Department in Sichuan Province (grant No. 2012jy0081).*
[*Author*]: *DONG Shan (1982-), Male, Sichuan Zigong, M.B., Attending Physician, Tel*: 0813-2121123, 13778597705, *E-mail*: 402028830@qq.com.
Received: 2017-07-19 *Revised*: 2017-07-24 *JHMC*, 2017;23(15):2120-2122

View from specialist: It is creative, and of certain scientific and educational value.

[ABSTRACT] **Objective**: To study the effect of low molecular weight heparin therapy on maternal endothelial injury and placental pathological injury after hypertensive disorder complicating pregnancy. **Methods**: A total of 70 patients with hypertensive disorder complicating pregnancy who were treated in the hospital between September 2014 and May 2016 were divided into control group and observation group according to the random number table method, 35 cases in each group. Control group received conventional therapy, the observation group received low molecular weight heparin combined with conventional therapy, and both therapies lasted until delivery. The differences in the levels of endothelial injury indexes in serum as well as the expression of oxidative stress indexes and apoptosis molecules in the placental grinding fluid were compared between the two groups of patients. **Results**: After treatment, serum ET and VCAM-1 levels of both groups of patients were significantly lower than

[基金项目] 四川省科技厅应用基础项目(2012jy0081)
[作者简介] 董珊(1982-),女,四川自贡人,主治医师,学士,电话:0813-2121123,13778597705,Email: 402028830@qq.com。
[收稿日期] 2017-07-19 [修回日期] 2017-07-24 网络出版时间:2017-08-10 10:42:07

those before treatment while NO and PGE levels were higher than those before treatment, and serum ET and VCAM-1 levels of observation group were significantly lower than those of control group while NO and PGE levels were higher than those of control group ($P<0.05$); after delivery, AOPP and MDA levels in placental grinding fluid were significantly lower than those of control group while SOD and GSH-Px levels were higher than those of control group ($P<0.05$); Fas, p53 and caspase-3 mRNA expression in placental grinding fluid were significantly lower than those of control group while Bcl-2 and bax mRNA expression were higher than those of control group ($P<0.05$). **Conclusion**: Adjuvant low molecular weight heparin therapy can help to reduce the maternal endothelial injury, reduce the systemic oxidative stress and suppress the placental cell apoptosis in patients with hypertensive disorder complicating pregnancy.

[KEY WORDS] Hypertensive disorder complicating pregnancy; Low molecular weight heparin; Endothelial injury; Oxidative stress; Apoptosis

妊娠期高血压疾病的发生率占全部妊娠的5%～10%,其所致产妇死亡约占总妊娠死亡人数的10%～16%,需早期接受积极干预以优化母婴结局[1,2]。既往研究报道,随妊娠期高血压病情加剧,严重子痫前期、子痫孕妇可出现血液黏滞度增高,凝血及纤溶功能发生改变,最终可导致弥散性血管内凝血(DIC),是导致患者死亡的主要原因之一[3]。常规硫酸镁解痉、拉贝洛尔降压可缓解妊娠期高血压疾病患者的全身小血管痉挛,但对血液黏度的影响较小,较多学者推荐加入低分子肝素进行辅助干预。低分子肝素通过影响纤维蛋白溶解系统而发挥作用,已经在较多高凝性疾病的治疗中获得成功应用[4,5],本次研究将其作为辅助用药加入妊娠期高血压疾病患者的治疗,从血清学及胎盘病理损伤等方面对其作用进行阐述,现报道如下。

1 资料与方法

1.1 病例资料

选择2014年9月～2016年5月间在本院接受治疗的妊娠期高血压疾病患者70例,患者本人签署知情同意书。按照随机数表法将其分为对照组、观察组,各35例,对照组患者年龄24～38岁,确诊时孕周20～26周,平均(23.17±2.09)周,胎次1～4胎,平均(2.41±0.35)胎,产次1～2次,平均(1.27±0.24)次;观察组患者年龄23～39岁,确诊时孕周20～25周,平均(23.31±2.52)周,胎次1～3胎,平均(2.24±0.37)胎,产次1～2次,平均(1.22±0.27)次。两组患者的年龄、确诊时孕周、胎次、产次等的分布差异无统计学意义($P>0.05$),研究获医院伦理委员会批准。

1.2 入组及排除标准

入组标准:(1)首次确诊妊娠期高血压疾病、院外未接受自主治疗;(2)单胎;(3)全程配合治疗且顺利分娩。排除标准:(1)合并前置胎盘、胎盘早剥等危险妊娠情况;(2)合并基础性凝血功能异常;(3)合并全身感染性疾病。

1.3 治疗方法

对照组患者接受临床妊娠期高血压疾病患者常规治疗,包括硫酸镁(国药准字H12020994,天津金耀药业有限公司)解痉、拉贝洛尔(海南灵康制药有限公司,国药准字H20052264)降血压。观察组患者在常规治疗基础上加入低分子肝素治疗,具体如下:低分子肝素5 000 IU皮下注射,2次/d,持续至妊娠结束。

1.4 观察指标

1.4.1 内皮损伤指标 治疗前、治疗后(分娩前24 h),抽取两组患者的空腹肘静脉血2.0 mL,抗凝、离心取上层血清,采用酶联免疫吸附法测定血清中内皮损伤指标内皮素(ET)、一氧化氮(NO)、前列腺素E(PGE)、血管细胞黏附分子-1(VCAM-1)的含量。

1.4.2 胎盘损伤指标 留取两组患者分娩后的胎盘组织标本,经碾磨后高速离心留取上层液体,采用ELISA检测其中氧化应激指标的含量,包括晚期氧化蛋白产物(AOPP)、丙二醛(MDA)、超氧化物歧化酶(SOD)、谷胱甘肽过氧化物酶(GSH-Px)。采用荧光定量PCR试剂盒测定碾磨液中凋亡分子mRNA的表达量,包括Fas、Bcl-2、p53、bax、caspase-3。

1.5 统计学处理

内皮损伤指标、氧化应激指标、凋亡分子等属于计量资料,以均数±标准差表示,比较采用t检验。统计软件选择SPSS24.0,$P<0.05$为差异有统计学意义。

2 结果

2.1 内皮损伤指标

两组患者治疗前后血清中内皮损伤指标ET(ng/mL)、NO(μmol/L)、PGE(nmol/L)、VCAM-1(μg/mL)含量的比较如下:治疗前,两组患者血清中ET、NO、PGE、VCAM-1含量的差异无统计学意义($P>0.05$)。治疗后,两组患者血清中ET、VCAM-1的含量低于治疗前,NO、PGE的含量高于治疗前,且观察组患者血清中ET、VCAM-1的含量低于对照组患者,NO、PGE的含量高于对照组患者,差异有统计学意义($P<0.05$)。见表1。

表1 两组治疗前后血清内皮损伤指标含量的比较($n=35,\bar{x}\pm s$)

组别	时间	ET	NO	PGE	VCAM-1
对照组	治疗前	68.92±9.16	32.17±4.09	0.83±0.09	2.84±0.37
	治疗后	60.81±7.25*	40.53±5.12*	1.25±0.23*	1.76±0.25*
观察组	治疗前	68.64±9.24	32.35±4.12	0.85±0.09	2.81±0.35
	治疗后	51.26±5.83*#	51.27±6.32*#	1.98±0.26*#	0.92±0.14*#

注:与组内治疗前比较,*$P<0.05$;与对照组治疗后比较,#$P<0.05$。

2.2 氧化应激指标

分娩后,两组患者胎盘组织碾磨液中氧化应激指标AOPP(nmol/L)、MDA(nmol/L)、SOD(U/L)、GSH-Px(U/L)含量的比较如下:分娩后,观察组患者胎盘组织碾磨液中AOPP、MDA的含量显著低于对照组患者,SOD、GSH-Px的含量高于对照组患者。两组患者分娩后胎盘组织碾磨液中氧化应激指标AOPP、MDA、SOD、GSH-Px含量的差异有统计学意义($P<0.05$)。见表2。

表 2 两组分娩后胎盘组织碾磨液氧化应激指标含量比较($n=35, \bar{x}\pm s$)

组别	AOPP	MDA	SOD	GSH-Px
对照组	24.18±3.09	89.72±9.81	76.32±8.17	41.09±5.26
观察组	15.09±2.17	38.65±4.87	109.25±14.38	72.64±8.72
t	8.982	15.214	12.172	10.972
P	<0.05	<0.05	<0.05	<0.05

2.3 凋亡分子

分娩后，两组患者分娩后胎盘组织碾磨液中凋亡分子表达 Fas、Bcl-2、p53、bax、caspase-3 mRNA 表达量的比较如下：分娩后，观察组患者胎盘组织碾磨液中 Fas、p53、caspase-3 mRNA 的表达量低于对照组患者，Bcl-2、bax mRNA 的表达量高于对照组患者。两组患者分娩后胎盘组织碾磨液中凋亡分子 Fas、Bcl-2、p53、bax、caspase-3 mRNA 表达量的差异有统计学意义($P<0.05$)。见表 3。

表 3 两组分娩后胎盘组织碾磨液凋亡分子表达量比较($n=35, \bar{x}\pm s$)

组别	Fas	Bcl-2	p53	bax	caspase-3
对照组	99.17±10.73	101.53±13.47	97.62±10.28	102.88±13.47	98.64±10.15
观察组	61.35±7.09	140.28±15.71	64.83±8.15	145.19±17.62	75.13±8.27
t	14.392	15.981	13.264	10.988	11.427
P	<0.05	<0.05	<0.05	<0.05	<0.05

3 讨论

妊娠期高血压疾病属于妊娠常见病，可严重危害母体及胎儿健康，寻求高效合理的治疗方案改善患者病情、优化母婴结局，是目前产科研究的重点。常规硫酸镁治疗主要是利用解除痉挛的机制，抑制运动神经末梢释放乙酰胆碱、松弛子宫平滑肌、增加胎盘血流量；拉贝洛尔等降压治疗通过阻断肾上腺受体而减少外周血管阻力，两者均有助于妊娠期高血压疾病病情缓解，但部分孕妇远期仍发生血管栓塞性疾病[6,7]。低分子肝素是一种典型的抗凝剂，因分子量小故组分相对均一，生物利用度高达 90%，通过抗凝血活酶(AT)而增加对凝血因子 Ⅹa 的抑制，是改善凝血功能的常用药物，也被认为有望进一步优化妊娠期高血压疾病的内环境稳态[8,9]。

全身小动脉痉挛是妊娠期高血压疾病的根本病理基础，长期血管壁压力增高可损伤内皮细胞并激活血小板功能，导致局部血液粘度增加，甚至可发生血栓性事件及 DIC[10,11]。本次研究中观察组患者接受低分子肝素辅助治疗，对照组患者接受常规西医治疗，首先对比两者治疗前后血清中内皮损伤指标含量的差异，发现：与治疗前比较，两组患者血清中血管内皮收缩指标 ET、VCAM-1 的含量降低，血管内皮舒张指标 NO、PGE 的含量增高；进一步与对照组比较，观察组患者治疗后血清中 ET、VCAM-1 的含量较低，NO、PGE 的含量较高，证实低分子肝素辅助治疗可有效优化妊娠期高血压疾病患者的血管内皮收缩/舒张平衡、减少血管痉挛所致病情加剧。

全身小动脉痉挛、血液黏滞度增加时，胎盘循环血量迅速下降，胎盘组织处于缺氧状态，同时缺血-再灌注损伤可刺激滋养细胞并使线粒体产生大量氧自由基，进一步启动脂质过氧化过程，加速胎盘发育异常[11-13]。胎盘组织氧耗/抗氧化平衡状态可客观反映妊娠期高血压疾病及治疗效果，本次研究对比两组患者胎盘组织碾磨液中氧化指标 AOPP、MDA，抗氧化指标 SOD、GSH-Px 表达量的差异，发现：与对照组比较，观察组患者治疗后胎盘组织碾磨液中氧化指标 AOPP、MDA 的含量较低；抗氧化指标 SOD、GSH-Px 的含量较高，证实低分子肝素辅助治疗可有效抑制患者的氧化应激状态，主要与其改善血液黏度增加胎盘血流量相关。

胎盘滋养细胞异常凋亡可直接造成胎盘功能不良、胎儿发育异常[14]。Fas 可引起细胞凋亡，Bcl-2 则是细胞凋亡的重要抑制分子；p53 是 Bcl-2 的上游调控基因，可下调 Bcl-2 表达并促使细胞发生凋亡。Bax 同样受 p53 调控，其表达上调可抑制细胞凋亡活性[15,16]。caspase-3 是介导凋亡发生的重要分子，是细胞凋亡的执行者[17]。本次研究对比两组患者胎盘组织碾磨液中上述凋亡调节分子的表达量差异，发现：与对照组比较，观察组患者治疗后胎盘组织碾磨液中促凋亡分子 Fas、p53、caspase-3 的 mRNA 表达量较低，抗凋亡分子 Bcl-2、bax mRNA 的表达量较高，证实低分子肝素辅助治疗可有效调节妊娠期高血压疾病患者胎盘组织的细胞凋亡活性，抑制滋养细胞的过度凋亡。

妊娠期高血压疾病患者接受低分子肝素辅助治疗，可有效减轻血管内皮损伤，降低胎盘组织氧化应激及凋亡程度，值得在日后临床实践中推广应用。

参考文献

1 Wang Y, Liu RX, Liu H. Association of adiponectin gene polymorphisms with hypertensive disorder complicating pregnancy and disorders of lipid metabolism [J]. Genet Mol Res, 2015, 14(4): 15213-15223.

2 Zhong W, Peng H, Tian A, et al. Expression of miRNA-1233 in placenta from patients with hypertensive disorder complicating pregnancy and its role in disease pathogenesis[J]. Int J Clin Exp Med, 2015, 8(6): 9121-9127.

3 Elzein HO, Muddathir AR, Rida M, et al. Fibrinolysis parameters in Sudanese women with severe preeclampsia [J]. Hypertens Pregnancy, 2016, 35(4): 559-564.

4 McLaughlin K, Baczyk D, Potts A, et al. Low molecular weight heparin improves endothelial function in pregnant women at high risk of preeclampsia [J]. Hypertension, 2017, 69(1): 180-188.

5 McLaughlin K, Drewlo S, Parker JD, et al. Current theories on the prevention of severe preeclampsia with low-molecular weight heparin [J]. Hypertension, 2015, 66(6): 1098-1103.

6 Maged AM, Hashem AM, Gad Allah SH, et al. The effect of loading dose of magnesium sulfate on uterine, umbilical, and fetal middle cerebral arteries Doppler in women with severe preeclampsia: A case control study [J]. Hypertens Pregnancy, 2016, 35(1): 91-99.

(下转第 2126 页)

3 Shen M, Smith GN, Rodger M, et al. Comparison of risk factors and outcomes of gestational hypertension and pre-eclampsia [J]. PLoS One, 2017, 12(4): e0175914.

4 Berhan Y. No Hypertensive Disorder of Pregnancy; No Pre-eclampsia-eclampsia; No Gestational Hypertension; No Hellp Syndrome. Vascular Disorder of Pregnancy Speaks for All [J]. Ethiop J Health Sci, 2016, 26(2): 177-186.

5 Bartnik P, Kosinska-Kaczynska K, Kacperczyk J, et al. Twin Chorionicity and the Risk of Hypertensive Disorders: Gestational Hypertension and Pre-eclampsia [J]. Twin Res Hum Genet, 2016, 19(4): 377-382.

6 苟文丽,宗璐,付晶. 营养干预对妊娠期特发性疾病的防治价值[J]. 中国实用妇科与产科杂志,2014,30(8):587-590.

7 鲁春兰,禹蕾. 孕期有氧运动与妊娠结局的相关性研究[J]. 中华临床医师杂志(电子版),2014,8(22):3990-3993.

8 Egeland GM, Klungsøyr K, θ yen N, et al. Preconception Cardiovascular Risk Factor Differences Between Gestational Hypertension and Preeclampsia: Cohort Norway Study [J]. Hypertension, 2016, 67(6): 1173-1180.

9 Franco RC, Ferreira CR, Vieira CR, et al. Ethnicity, Obesity and Emotional Factors Associated With Gestational Hypertension [J]. J Community Health, 2015, 40(5): 899-904.

10 George EM. New approaches for managing preeclampsia: clues from clinical and basic research [J]. Clin Ther, 2014, 36(12): 1873-1881.

11 杨晓菊,孙玲玲,张萌,等. 糖尿病患者妊娠后胎盘组织缺氧诱导因子-1α及内皮素-1的表达及与妊娠结局关系[J]. 中华实用诊断与治疗杂志,2014,28(1):15-18.

12 Vignini A, Cecati M, Nanetti L, et al. Placental expression of endothelial and inducible nitric oxide synthase and NO metabolism ingestational hypertension: a case-control study [J]. J Matern Fetal Neonatal Med, 2016, 29(4): 576-581.

13 Sakar MN, Atay AE, Demir S, et al. Association of endothelial nitric oxide synthase gene G894T polymorphism and serum nitric oxidelevels in patients with preeclampsia and gestational hypertension[J]. J Matern Fetal Neonatal Med, 2015, 28(16): 1907-1911.

14 Altorjay ÁT, Surányi A, Nyári T, et al. Use of placental vascularization indices and uterine artery peak systolic velocity in early detection of pregnancies complicated by gestational diabetes, chronic or gestational hypertension, and preeclampsia at risk[J]. Croat Med J, 2017, 58(2): 161-169.

15 Leaños-Miranda A, Méndez-Aguilar F, Ramírez-Valenzuela KL, et al. Circulating angiogenic factors are related to the severity of gestational hypertension and preeclampsia, and their adverse outcomes[J]. Medicine (Baltimore), 2017, 96(4): e6005.

16 陈学琳. 血管生成失衡与子痫前期关系的研究新进展[J]. 现代妇产科进展,2015,24(8):624-627.

17 Visentin S, Londero AP, Camerin M, et al. A possible new approach in the prediction of late gestational hypertension: The role of the fetal aortic intima-media thickness [J]. Medicine (Baltimore), 2017, 96(2): e5515.

(上接第 2122 页)

7 Anjum S, Rajaram GP, Bano 1. Short-course postpartum (6-h) magnesium sulfate therapy in severe preeclampsia [J]. Arch Gynecol Obstet, 2016, 293(5): 983-986.

8 Groom KM, McCowan LM, Stone PR, et al. Enoxaparin for the prevention of preeclampsia and intrauterine growth restriction in women with a prior history - an open-label randomised trial (the EPPI trial): study protocol [J]. BMC Pregnancy Childbirth, 2016, 16(1): 367.

9 McLaughlin K, Drewlo S, Parker JD, et al. Current theories on the prevention of severe preeclampsia with low-molecular weight heparin [J]. Hypertension, 2015, 66(6): 1098-1103.

10 Thakoordeen S, Moodley J, Naicker T. Serum levels of platelet endothelial cell adhesion molecule-1 (PECAM-1) and soluble vascularendothelial growth factor receptor (sVEGFR)-1 and -2 in HIV associated preeclampsia [J]. Hypertens Pregnancy, 2017,36(2):168-174.

11 Brodowski L, Burlakov J, Hass S, et al. Impaired functional capacity of fetal endothelial cells in preeclampsia [J]. PLoS One, 2017, 12(5): e0178340.

12 Keshavarz P, Nobakht BF, Mirhafez SR, et al. Alterations in lipid profile, zinc and copper levels and superoxide dismutase activities in normal pregnancy and preeclampsia[J]. Am J Med Sci, 2017, 353(6): 552-558.

13 León-Reyes G, Maida-Claros RF, Urrutia-Medina AX, et al. Oxidative profiles of LDL and HDL isolated from women with preeclampsia [J]. Lipids Health Dis, 2017, 16(1): 90.

14 Li J, Chen Z, Zhou X, et al. Imbalance between proliferation and apoptosis-related impaired GPR30 expression is involved in preeclampsia [J]. Cell Tissue Res, 2016, 366(2): 499-508.

15 ReŠi ć Karara J, Zeki ć Tomas S, MaruŠi ć J, et al. Fas and FasL expression in placentas complicated with intrauterine growth retardation with and without preeclampsia [J]. J Matern Fetal Neonatal Med, 2016, 29(7): 1154-1159.

16 Wang A, Liu Q, Zhang J, et al. Berberine alleviates preeclampsia possibly by regulating the expression of interleukin-2/interleukin-10 and Bcl-2/Bax [J]. Int J Clin Exp Med, 2015, 8(9): 16301-16307.

17 Rukoyatkina N, Butt E, Subramanian H, et al. Protein kinase A activation by the anti-cancer drugs ABT-737 and thymoquinone is caspase-3-dependent and correlates with platelet inhibition and apoptosis[J]. Cell Death Dis, 2017, 8(6): e2898.