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【临床研究】

硝苯地平和低分子肝素钙联合治疗对早发型重度子痫前期患者氧化应激、血压及母婴结局的影响

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摘要: 目的 探讨硝苯地平和低分子肝素钙联合治疗对早发型重度子痫前期(EOSP)患者氧化应激、血压及母婴结局的影响。**方法** 选择 2020 年 1 月至 2022 年 1 月三门峡市中心医院产科二病区收治的 160 例 EOSP 患者为研究对象,根据治疗方法将患者分为观察组和对照组,每组 80 例。2 组患者均给予硫酸镁解痉、纠正低蛋白血症、持续低流量吸氧、加强营养等常规对症支持治疗。在常规治疗基础上,对照组患者给予硝苯地平治疗,观察组患者给予硝苯地平和低分子肝素钙联合治疗,2 组患者均治疗 1 周。治疗后评估 2 组患者的临床疗效;分别于治疗前后采用黄嘌呤氧化酶法检测血清超氧化物歧化酶(SOD)和谷胱甘肽过氧化物酶(GSH-Px)活性,采用硫代巴比妥酸法检测血清丙二醛(MDA)、脂质过氧化物(LPO)水平,使用血压检测仪测定 2 组患者的收缩压(SBP)和舒张压(DBP);治疗后对所有患者进行随访,记录 2 组患者不良妊娠结局的发生情况。**结果** 观察组和对照组患者治疗总有效率分别为 92.50%(74/80)、81.25%(65/80),观察组患者治疗总有效率显著高于对照组($\chi^2=4.440$,$P<0.05$)。治疗前 2 组患者血清 SOD、GSH-Px、MDA、LPO 水平比较差异无统计学意义($P>0.05$);2 组患者治疗后的血清 SOD、GSH-Px 水平显著高于治疗前,血清 MDA、LPO 水平显著低于治疗前($P<0.05$);治疗后,观察组患者血清 SOD、GSH-Px 水平显著高于对照组,血清 MDA、LPO 水平显著低于对照组($P<0.05$)。治疗前 2 组患者的 SBP、DBP 比较差异无统计学意义($P>0.05$),2 组患者治疗后的 SBP、DBP 显著低于治疗前($P<0.05$);治疗后,观察组患者的 SBP、DBP 显著低于对照组($P<0.05$)。观察组和对照组不良妊娠结局发生率分别为 6.25%(5/80)、18.75%(15/80),观察组不良妊娠结局发生率显著低于对照组($\chi^2=5.714$,$P<0.05$)。**结论** 硝苯地平和低分子肝素钙联合治疗可以有效改善 EOSP 患者的氧化应激状态,控制血压,降低不良妊娠结局发生率。

关键词: 早发型重度子痫前期;低分子肝素钙;硝苯地平;超氧化物歧化酶;谷胱甘肽过氧化物酶;血压;母婴结局
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Effect of nifedipine combined with low molecular weight heparin calcium on oxidative stress, blood pressure and maternal and infant outcome in patients with early-onset severe preeclampsia

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Abstract: Objective To investigate the effect of nifedipine combined with low molecular weight heparin calcium on oxidative stress, blood pressure and maternal and infant outcome in patients with early-onset severe preeclampsia (EOSP). **Methods** A total of 160 EOSP patients admitted to the Second Obstetrical Ward of Sanmenxia Central Hospital from January 2020 to January 2022 were selected as the study subjects, and the patients were divided into observation group and control group according to the treatment methods, with 80 patients in each group. The patients in the both groups were treated with routine symptomatic support treatment such as magnesium sulfate for spasmolysis, correcting hypoproteinemia, continuous low flow oxygen inhalation, enhancing nutrition, and so on. On the basis of routine treatment, the patients in the control group were treated with nifedipine, while the patients in the observation group were treated with nifedipine and low molecular weight heparin calcium. The patients in the both groups were treated for one week. The clinical efficacy of patients in the two groups was evaluated after treatment. The activities of serum superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) were measured by xanthine oxidase method, the levels of serum malondialdehyde (MDA) and lipid peroxide (LPO) were measured by thiobarbituric acid method, and the systolic blood pressure (SBP) and diastolic blood pressure (DBP) of patients in the two groups were measured by sphygmomanometer before and after treatment. All patients were followed up after treatment to record

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the occurrence of adverse pregnancy outcomes. **Results** The total effective rate of patients in the observation group and the control group was 92.50% (74/80) and 81.25% (65/80), respectively. The total effective rate of patients in the observation group was significantly higher than that in the control group ($\chi^2 = 4.440$, $P < 0.05$). There was no significant difference in serum SOD, GSH-Px, MDA and LPO levels between the two groups before treatment ($P > 0.05$). Compared with before treatment, the levels of serum SOD and GSH-Px of patients in the two groups were significantly increased after treatment, while the levels of serum MDA and LPO were significantly decreased ($P < 0.05$). After treatment, the levels of serum SOD and GSH-Px of patients in the observation group were significantly higher than those in the control group, and the levels of serum MDA and LPO were significantly lower than those in the control group ($P < 0.05$). There was no significant difference in SBP and DBP of patients between the two groups before treatment ($P > 0.05$). The SBP and DBP of patients in the two groups after treatment were significantly lower than those before treatment ($P < 0.05$). After treatment, the SBP and DBP of patients in the observation group were significantly lower than those in the control group ($P < 0.05$). The incidence of adverse pregnancy outcomes of patients in the observation group and the control group was 6.25% (5/80) and 18.75% (15/80), respectively. The incidence of adverse pregnancy outcomes of patients in the observation group was significantly lower than that in the control group ($\chi^2 = 5.714$, $P < 0.05$). **Conclusion** The combined treatment of nifedipine and low molecular weight heparin calcium can effectively improve the oxidative stress state, control blood pressure, and reduce the incidence of adverse pregnancy outcomes in patients with EOSP.

Key words: early-onset severe preeclampsia; low molecular weight heparin calcium; nifedipine; superoxide dismutase; glutathione peroxidase; blood pressure; maternal and infant outcome

早发型重度子痫前期(early-onset severe preeclampsia, EOSP)多发生于妊娠 34 周前,是妊娠期高血压疾病的常见类型[1]。EOSP 发病时间早,病情严重,随着妊娠周期的延长,患者的血压、蛋白尿会持续升高,若不及时有效干预,常造成不良妊娠结局,甚至导致母婴死亡,且约 40% 的患者再次妊娠时会复发[2]。EOSP 的临床治疗尚无统一标准,多给予保守治疗,通过药物进行降血压、解痉,直至安全分娩。硝苯地平属于钙通道阻滞剂,可降低血管阻力,降低血压,且对脑组织、冠状动脉和肾血流量无明显影响,是临床治疗妊娠高血压的常用药物之一[3]。有研究发现,EOSP 的发生发展与患者血液高凝状态密切相关[4]。因此,在控制血压的同时,保持 EOSP 患者血流动力学稳定对于提高自然分娩率、保证母婴安全具有重要意义。低分子肝素钙具有抗凝作用,可保护机体血管内皮细胞,改善机体血液高凝状态[5]。本研究旨在探讨硝苯地平和低分子肝素钙联合治疗对 EOSP 患者氧化应激、血压及母婴结局的影响,为临床治疗 EOSP 提供参考。

1 资料与方法

1.1 一般资料 选择 2020 年 1 月至 2022 年 1 月三门峡市中心医院产科二病区收治的 EOSP 患者为研究对象。病例纳入标准:(1)符合 EOSP 诊断标准[6];(2)年龄≤35 岁,孕周≤34 周,均为单胎妊娠;(3)入院前未服用过相关治疗药物。排除标准:(1)有低分子肝素钙、硝苯地平等药物过敏史;(2)患有原发性高血压疾病;(3)合并凝血功能障碍、重要器官功能障碍;(4)合并全身感染性疾病、自身免疫性疾病、内分泌疾病;(5)合并妊娠期心脏病、糖尿病等其他妊娠期疾病。本研究共纳入 EOSP 患者 160 例,根据治疗方法将患者分为观察组和对照组,每组 80 例。对照组患者年龄 23 ~ 35(27.71 ± 4.54)岁,孕周 25 ~ 34(31.89 ± 1.50)周;初产妇 57 例,经产妇 23 例。观察组患者年龄 22 ~ 35(28.63 ± 4.37)岁,孕周 26 ~ 33(32.05 ± 1.41)周;初产妇 55 例,经产妇 25 例。2 组患者的年龄、孕周、产次比较差异无统计学意义($P > 0.05$),具有可比性。本研究经医院伦理委员会审批通过,所有患者和(或)家属签署知情同意书。

1.2 治疗方法 2 组患者均给予硫酸镁解痉、纠正低蛋白血症、持续低流量吸氧、加强营养等常规对症支持治疗,在常规治疗基础上,对照组患者给予硝苯地平片(石药集团欧意药业有限公司,国药准字 H20223238)30 mg,口服,每日 1 次;观察组患者在对照组治疗基础上给予低分子肝素钙注射液(深圳赛保尔生物药业有限公司,国药准字 H20060191)5 000 IU,皮下注射,每日 1 次。2 组患者均治疗 1 周。

1.3 观察指标

1.3.1 临床疗效 治疗后评估 2 组患者的临床疗效。显效:血压恢复正常,水肿、蛋白尿等临床症状完全消失或显著改善;有效:临床症状及血压均较治疗前明显改善,蛋白尿弱阳性;无效:临床症状、血压均无改善甚至加重,需及时终止妊娠[7]。总有效率 = (显效例数 + 有效例数)/总例数 × 100%。

1.3.2 氧化应激指标 分别于治疗前和治疗后采集患者晨起空腹肘静脉血 5 mL,3 000 r · min^{-1} 离心 10 min,取上层血清,采用黄嘌呤氧化酶法检测血

清超氧化物歧化酶(superoxide dismutase,SOD)和谷胱甘肽过氧化物酶(glutathione peroxidase,GSH-Px)活性,采用硫代巴比妥酸法检测血清丙二醛(malondialdehyde,MDA)、脂质过氧化物(lipid peroxidation,LPO)水平,试剂盒均购自武汉艾迪抗生物科技有限公司,严格按照试剂盒说明书操作。

1.3.3　血压　分别于治疗前和治疗后使用血压检测仪测定 2 组患者的收缩压(systolic blood pressure,SBP)和舒张压(diastolic blood pressure,DBP)。

1.3.4　妊娠结局　治疗后对所有患者进行随访,记录 2 组患者围产期产后出血、低出生体质量儿、新生儿呼吸窘迫综合征、新生儿窒息等不良妊娠结局的发生情况。

1.4　统计学处理　应用 SPSS 22.0 软件进行数据统计与分析。计量资料经 Bartlett 方差齐性检验与 Shapiro-Wilktest 正态性检验确认具备方差齐性且近似服从正态分布,以均数 ± 标准差($\bar{x} \pm s$)表示,组间比较采用 t 检验;计数资料以例数和百分率表示,组间比较采用 χ^2 检验;采用双侧检验,检验水准 $\alpha = 0.05$。

2　结果

2.1　2 组患者临床疗效比较　观察组患者治疗显效 50 例,有效 24 例,无效 6 例,总有效率为 92.50%(74/80);对照组患者治疗显效 42 例,有效 23 例,无效 15 例,总有效率为 81.25%(65/80);观察组患者治疗总有效率显著高于对照组,差异有统计学意义($\chi^2 = 4.440$,$P < 0.05$)。

2.2　2 组患者氧化应激指标比较　结果见表 1。治疗前 2 组患者血清 SOD、GSH-Px、MDA、LPO 水平比较差异无统计学意义($P > 0.05$);2 组患者治疗后的血清 SOD、GSH-Px 水平显著高于治疗前,血清 MDA、LPO 水平显著低于治疗前,差异有统计学意义($P < 0.05$);治疗后,观察组患者血清 SOD、GSH-Px 水平显著高于对照组,血清 MDA、LPO 水平显著低于对照组,差异有统计学意义($P < 0.05$)。

表 1　2 组患者血清 SOD、GSH-Px、MDA 及 LPO 水平比较

Tab.1　Comparison of serum SOD, GSH-Px, MDA and LPO levels of patients between the two groups　($\bar{x} \pm s$)

组别	n	SOD/(kU · L^{-1})	GSH-Px/(kU · L^{-1})	MDA/(mmol · L^{-1})	LPO/(mmol · L^{-1})
对照组	80				
治疗前		90.22 ± 10.14	92.45 ± 10.17	9.29 ± 1.01	15.22 ± 1.63
治疗后		102.66 ± 11.08[a]	98.85 ± 10.68[a]	7.75 ± 0.83[a]	11.63 ± 1.35[a]
观察组	80				
治疗前		89.87 ± 9.58	93.01 ± 9.88	9.34 ± 0.98	14.94 ± 1.58
治疗后		138.84 ± 14.25[ab]	122.28 ± 13.54[ab]	5.16 ± 0.62[ab]	8.85 ± 0.96[ab]

注:与治疗前比较[a]$P < 0.05$;与对照组比较[b]$P < 0.05$。

2.3　2 组患者血压比较　结果见表 2。治疗前 2 组患者的 SBP、DBP 比较差异无统计学意义($P > 0.05$);2 组患者治疗后的 SBP、DBP 显著低于治疗前,差异有统计学意义($P < 0.05$);治疗后,观察组患者的 SBP、DBP 显著低于对照组,差异有统计学意义($P < 0.05$)。

表 2　2 组患者的 SBP 和 DBP 比较

Tab.2　Comparison of SBP and DBP of patients between the two groups　($\bar{x} \pm s$)

组别	n	SBP/mm Hg	DBP/mm Hg
对照组	80		
治疗前		177.48 ± 18.56	108.85 ± 11.34
治疗后		145.52 ± 12.44[a]	88.46 ± 8.12[a]
观察组	80		
治疗前		179.24 ± 15.64	109.36 ± 10.22
治疗后		136.62 ± 11.12[ab]	81.04 ± 8.87[ab]

注:与治疗前比较[a]$P < 0.05$;与对照组比较[b]$P < 0.05$;1 mm Hg = 0.133 kPa。

2.4　2 组患者不良妊娠结局发生情况比较　观察组发生产后出血 1 例,低出生体质量儿 2 例,新生儿呼吸窘迫综合征 1 例,新生儿窒息 1 例,不良妊娠结局发生率为 6.25%(5/80);对照组发生产后出血 4 例,低出生体质量儿 7 例,新生儿呼吸窘迫综合征 2 例,新生儿窒息 2 例,不良妊娠结局发生率为 18.75%(15/80);观察组不良妊娠结局发生率显著低于对照组,差异有统计学意义($\chi^2 = 5.714$,$P < 0.05$)。

3　讨论

EOSP 可累及患者多个器官组织,严重者可导致产妇和新生儿死亡[8]。目前,EOSP 的发病机制尚未完全明确,多与过度的氧化应激、遗传因素、子宫和胎盘情况、凝血功能异常等有关[9]。临床治疗需要结合发病机制来进行针对性治疗,以改善患者和新生儿结局,降低母婴死亡风险,而探索安全有效的治疗手段一直是临床研究的重要课题之一。

高血压是 EOSP 患者的典型临床症状之一,也是导致产妇死亡的原因之一,因此,控制高血压,使血压维持在相对安全的范围内是治疗 EOSP 的关键[10]。硝苯地平是第 1 代钙拮抗剂,通过选择性抑制细胞膜上的钙离子通道内流,阻止钙离子内流,阻断血管膜上 α-肾上腺能受体和心肌细胞兴奋-收缩偶联,扩张全身血管,降低血压[11]。EOSP 患者需在

住院 48 h 内有效控制血压,单独应用硝苯地平常无法快速平稳达到降压标准,此时需要与其他药物联合应用,以减少对母体胎盘和肾脏等重要脏器功能的影响[12]。低分子肝素钙是一种新型抗凝血酶Ⅲ依赖性抗血栓形成药,抗血栓与抗凝效果较为理想,不仅能有效缓解血流阻力,还能保护血管内皮组织,相较于肝素,其药效及维持时间都更佳[13]。此外,低分子肝素钙能够有效保护血管内皮细胞,可促进酯酶的释放与三酰甘油、胆固醇的降解,从而降低血浆黏度、恢复血流通畅[14]。本研究结果显示,治疗后 2 组患者 SBP、DBP 显著降低,且观察组患者的 SBP、DBP 显著低于对照组;另外,观察组患者的治疗总有效率显著高于对照组;提示硝苯地平和低分子肝素钙联合治疗可进一步加强对血压的控制效果,使孕妇血压维持在一个更安全的水平。

EOSP 发病时,滋养细胞侵入子宫壁过浅,子宫螺旋动脉血管重铸异常,胎盘血流灌注不足,导致胎盘缺血缺氧,机体过氧化物表达异常,引起机体氧化应激性损伤;过度氧化应激反应又会抑制滋养细胞对螺旋动脉的浸润,进一步导致胎盘缺血缺氧,促进 EOSP 的发生与发展[15]。因此,改善 EOSP 患者氧化应激状态意义重大。硝苯地平可通过清除自由基,调节机体新陈代谢,有效调节体内脂质过氧化物水平,从而改善机体氧化应激状态[16]。低分子肝素钙可抗血小板聚集,清除氧自由基,改善机体内环境,有效增加机体脑血流量及冠状动脉血流量,调节机体氧化和抗氧化系统平衡[17]。本研究结果显示,2 组患者治疗后的血清 SOD、GSH-Px 水平显著高于治疗前,血清 MDA、LPO 水平显著低于治疗前;治疗后,观察组患者血清 SOD、GSH-Px 水平显著高于对照组,血清 MDA、LPO 水平显著低于对照组;提示硝苯地平联合低分子肝素钙可以有效改善 EOSP 患者的氧化应激状态。另外,本研究结果显示,观察组不良妊娠结局发生率显著低于对照组。硝苯地平可以有效降低高血压,而低分子肝素钙的应用可及时为孕妇补充钙元素,使孕妇血流动力学趋于正常,进而改善胎儿生长发育,促使孕妇身体恢复,改善妊娠结局,提高母婴安全指数[18]。

综上所述,硝苯地平和低分子肝素钙联合使用可以有效改善 EOSP 患者机体的氧化应激状态,控制血压,降低不良妊娠结局发生率,改善母婴预后。

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