

doi: 10.13241/j.cnki.pmb.2019.18.027

维生素 E 联合尼莫地平治疗妊娠期高血压综合征的效果观察 *

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摘要 目的:研究维生素 E 联合尼莫地平治疗妊娠期高血压综合征的临床效果和可能机制。**方法:**选择 2016 年 1 月~2018 年 12 月我院收治的 200 例妊娠期高血压综合征患者并将其随机分为两组。对照组患者口服维生素 E 治疗,每次 50 mg,每天 3 次;观察组联合口服尼莫地平治疗,每次 30 mg,每天 2 次。检测和比较两组治疗前后的血清肽素、皮质醇、一氧化氮及内皮素、血清 C 反应蛋白(C-reactive protein, CRP)、白介素-12(Interleukin-12, IL-12)和肿瘤坏死因子- α (Tumor necrosis factor- α , TNF- α)水平的变化,记录患者的妊娠结局:胎盘早剥、产后出血、胎儿窘迫、剖宫产、低体重儿以及新生儿窒息的发生情况。**结果:**治疗后,观察组的总有效率明显高于对照组(91% vs. 73%, $P<0.05$);两组的血清肽素、皮质醇及内皮素水平均较治疗前明显降低,血清一氧化氮水平较治疗前明显升高,且观察组的以上指标水平均明显优于对照组(均 $P<0.05$)。两组治疗后的血清 CRP、IL-12 和 TNF- α 水平均较治疗前明显降低,且观察组以上指标均明显低于对照组(均 $P<0.05$)。观察组的胎盘早剥率、产后出血率、胎儿窘迫率、剖宫产率、低体重儿率以及新生儿窒息率均明显低于对照组($P<0.05$)。**结论:**维生素 E 联合尼莫地平能明显改善妊娠期高血压综合征的妊娠结局,可能与其降低血清 CRP、IL-12、TNF- α 、皮质醇及和肽素水平有关。

关键词:维生素 E;尼莫地平;妊娠期高血压综合征;皮质醇;和肽素;血管内皮功能

中图分类号:R714.246 **文献标识码:**A **文章编号:**1673-6273(2019)18-3523-04

Effect of Vitamin E Combined with Nimodipine in the Treatment of Pregnancy Induced Hypertension Syndrome*

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ABSTRACT Objective: To study the clinical effect and possible mechanism of vitamin E combined with nimodipine in the treatment of pregnancy-induced hypertension syndrome. **Methods:** 200 patients with pregnancy-induced hypertension syndrome who were treated in our hospital from January 2016 to December 2018 were randomly divided into two groups. The control group was given oral vitamin E treatment, 50 mg each time, three times a day, the observation group was treated with oral nimodipine, 30 mg each time, twice a day. The changes of serum copeptin, cortisol, NO and endothelin, CRP, IL-12 and TNF- α levels before and after treatment were detected and compared between the two groups. And the pregnancy outcome: placental abruption, postpartum hemorrhage, fetal distress, cesarean section, low birth weight and neonatal asphyxia were recorded. **Results:** After treatment, the total effective rate of observation group was significantly higher than that of the control group (91% vs. 73%, $P<0.05$). After treatment, the levels of serum peptide, cortisol and endothelin in the two groups were significantly lower than those of the control group, while the levels of serum nitric oxide were significantly higher, and the above indicators in the observation group were significantly better than those of the control group (both $P<0.05$). After treatment, the levels of serum CRP, IL-12 and TNF- α in the two groups were significantly decreased, and the the above indexes in the observation group were significantly lower than those in the control group (all $P<0.05$). The rates of placental abruption, postpartum hemorrhage, fetal distress, cesarean section, low birth weight and neonatal asphyxia in the observation group were significantly lower than those in the control group ($P<0.05$). **Conclusion:** Vitamin E combined with nimodipine can significantly improve the pregnancy outcome of hypertensive syndrome in pregnancy, it may be related to the decrease of serum CRP, IL-12 and TNF- α , cortisol, peptide, and levels.

Key words: Vitamin E; Nimodipine; Pregnancy induced hypertension syndrome; Cortisol; Peptide; Vascular endothelial function

Chinese Library Classification(CLC): R714.246 **Document code:** A

Article ID: 1673-6273(2019)18-3523-04

* 基金项目:陕西省缺血性心血管疾病重点实验室项目(18JS103)

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(收稿日期:2019-05-07 接受日期:2019-05-29)

前言

妊娠期高血压综合征的发病率在全部妊娠孕妇中高达 10%,且占有妊娠相关死亡中的 10%~16%,是导致孕妇死亡的第二大原因^[1,2]。目前多项研究显示妊娠期高血压综合征的发生可能与胎儿胎盘着床较浅、孕妇的免疫功能、血管内皮损伤、胰岛素功能降低以及遗传因素等相关^[3-5]。针对妊娠期高血压综合征的治疗,临床上目前以解痉、吸氧、降压、合理补充血容量以及镇静为主,且积极预防相关的并发症^[6,7]。

维生素 E 作为一种脂溶性的抗氧化剂,能调节氧化应激状态,降低脂质氧化,调节脂质代谢,有效保护血管内皮细胞^[8,9]。尼莫地平能有效阻断钙离子,使全身的血管得以扩张,抑制平滑肌发生收缩,从而明显降低血压,使外周的循环得到有效的改善,并且不会经胎盘屏障而对胎儿造成损伤^[10,11]。本研究将维生素 E 以及尼莫地平两种药物联用,分析其对妊娠期高血压综合征患者血清皮质醇、和肽素、血管内皮功能和炎症因子水平的影响,结果报道如下。

1 资料与方法

1.1 一般资料

选择 2016 年 1 月~2018 年 12 月我院收治的 200 例妊娠期高血压综合征患者,纳入标准:①符合《妇产科学》中的诊断标准;②无其他的产科并发症;③无原发性高血压、急慢性肾炎、冠心病、恶性肿瘤和糖尿病病史;④对本项研究知情同意;⑤入选本研究前 1 个月没有服用过其他降压药物;⑥意识比较清楚。排除标准:⑦伴有严重的感染性疾病、过敏性疾病和自身免疫性疾病患者;⑧合并有肾动脉狭窄、原发性高血压和肾上腺肿瘤者;⑨有肝、心、脾、肾和肺等脏器病变患者;⑩存在维生素 E 以及尼莫地平用药禁忌症的患者;⑪有认知功能和语言障碍,无法正常进行沟通的患者。用抽签法将患者随机分为两组。观察组 100 例,年龄 21~42 岁,平均(29.47±3.92)岁;孕周 27~40 周,平均(35.38±2.47)周。对照组 100 例,年龄 20~41 岁,平均(29.36±3.59)岁;孕周 27~39 周,平均(35.42±2.73)

周。两组的基线资料比较差异均无统计学意义($P>0.05$),具有可比性。

1.2 治疗方法

两组均采取低钠饮食调节、卧床休息、利尿、吸氧、扩容和心理疏导等。对照组:口服维生素 E (批号:国药准字 H43021652,生产厂家:湖南中和制药,规格:50 mg/粒),每次 50 mg,每天 3 次。观察组:联合口服尼莫地平(批号:国药准字 H14022821,生产厂家:亚宝药业公司,规格:20 mg/片),每次 30 mg,每天 2 次。观察组维生素 E 的服用方法与对照组相同。均持续治疗直至分娩。

1.3 观察指标

评估疗效的标准:①显效:无蛋白尿和水肿症状,血压降低至小于 140/90 mmHg;②有效:伴有微量的蛋白尿,水肿程度比较轻,血压降低至 140/90~150/100 mmHg;③无效:被迫终止妊娠,症状体征无改善。

于治疗前后空腹取 4 mL 的肘静脉血,采取放射免疫法检测血清内皮素水平,采取 ELISA 法检测血清肽素以及皮质醇水平,采取硝酸还原酶法检测血清一氧化氮水平,试剂盒均购自成都安普诺生物公司。并且采取 ELISA 法检测血清 C 反应蛋白(C-reactive protein, CRP)、白介素-12(Interleukin-12, IL-12)和肿瘤坏死因子- α (Tumor necrosis factor- α , TNF- α)水平,试剂盒购自上海朝瑞生物公司。记录患者的妊娠结局:胎盘早剥、产后出血、胎儿窘迫、剖宫产、低体重儿以及新生儿窒息的发生情况。

1.4 统计学分析

采用 SPSS 20.0 进行数据分析,两组间计量资料对比用 t 检验,计数资料组间比较采用 χ^2 检验,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组疗效的比较

治疗后,观察组的有效率为 91%,明显高于对照组(73%, $P<0.05$),见表 1。

表 1 两组疗效的比较[例(%)]

Table 1 Comparison of the clinical effect between the two groups[n(%)]

Groups	n	Effective	Valid	Invalid	The total effect rate
Control group	100	43(43.00)	30(30.00)	27(27.00)	73(73.00)
Observation group	100	51(51.00)	40(40.00)	9(9.00)	91(91.00) *

Note: Compared with the control group, * $P<0.05$.

2.2 两组治疗前后血清肽素、皮质醇、一氧化氮及内皮素水平比较

治疗后,两组的血清肽素、皮质醇及内皮素水平均较治疗前明显降低,血清一氧化氮水平较治疗前明显升高,且观察组的以上指标明显优于对照组(均 $P<0.05$),见表 2。

2.3 两组治疗前后血清 CRP、IL-12 和 TNF- α 水平的比较

治疗后,两组的血清 CRP、IL-12 和 TNF- α 水平均较治疗前明显降低,且观察组以上指标水平明显低于对照组(均 $P<0.05$),见表 3。

2.4 两组的妊娠结局的比较

观察组的胎盘早剥率、产后出血率、胎儿窘迫率、剖宫产率、低体重儿率以及新生儿窒息率均明显低于对照组($P<0.05$),见表 4。

3 讨论

妊娠期高血压综合征患者普遍会出现蛋白尿、水肿和高血压等症状,病情严重者会出现头痛、上腹痛以及视力模糊等症状,若治疗不及时,易引发全身性痉挛,甚至会造成昏迷^[12-15]。加

表 2 两组治疗前后的血清肽素、皮质醇、一氧化氮及内皮素水平比较($\bar{x} \pm s$)Table 2 Comparison of the serum peptide, cortisol, nitric oxide and endothelin levels before and after treatment between the two groups($\bar{x} \pm s$)

Groups		Copeptin ($\mu\text{g} \cdot \text{L}^{-1}$)	Cortisol ($\text{nmol} \cdot \text{L}^{-1}$)	NO ($\text{nmol} \cdot \text{L}^{-1}$)	ET-1 ($\text{ng} \cdot \text{L}^{-1}$)
Control group (n=100)	Before treatment	3.13 $\pm$ 0.84	367.42 $\pm$ 29.38	523.46 $\pm$ 49.38	93.21 $\pm$ 14.53
	After treatment	2.03 $\pm$ 0.56 [#]	316.75 $\pm$ 27.43 [#]	713.42 $\pm$ 63.49 [#]	74.25 $\pm$ 12.78 [#]
Observation group (n=100)	Before treatment	3.11 $\pm$ 0.82	368.54 $\pm$ 30.14	524.19 $\pm$ 50.23	94.13 $\pm$ 13.78
	After treatment	1.42 $\pm$ 0.38 ^{*#}	283.56 $\pm$ 23.41 ^{*#}	923.75 $\pm$ 74.82 ^{*#}	55.63 $\pm$ 10.19 ^{*#}

Note: Compared with the control group, ^{*} $P < 0.05$; compared with before treatment, [#] $P < 0.05$.

表 3 两组治疗前后的血清 CRP、IL-12 和 TNF- α 水平比较($\bar{x} \pm s$)Table 3 Comparison of the serum CRP, IL-12 and TNF- α levels before and after treatment between the two groups($\bar{x} \pm s$)

Groups		CRP($\text{mg} \cdot \text{L}^{-1}$)	IL-12 ($\mu\text{g} \cdot \text{L}^{-1}$)	TNF- α ($\mu\text{g} \cdot \text{L}^{-1}$)
Control group (n=100)	Before treatment	8.93 $\pm$ 2.46	36.54 $\pm$ 10.39	76.34 $\pm$ 19.27
	After treatment	6.13 $\pm$ 1.72 [#]	25.43 $\pm$ 7.46 [#]	68.92 $\pm$ 12.45 [#]
Observation group(n=100)	Before treatment	8.94 $\pm$ 2.37	37.16 $\pm$ 11.73	75.63 $\pm$ 21.43
	After treatment	4.32 $\pm$ 1.19 ^{*#}	18.72 $\pm$ 3.45 ^{*#}	52.43 $\pm$ 10.13 ^{*#}

Note: Compared with the control group, ^{*} $P < 0.05$; compared with before treatment, [#] $P < 0.05$.

表 4 两组的妊娠结局比较[例(%)]

Table 4 Comparison of the delivery outcome between two groups [n (%)]

Groups	n	Placental abruption	Postpartum hemorrhage	Fetal distress	Cesarean section	Low birth weight infant	Neonatal asphyxia
Control group	100	6(6.00)	10(10.00)	8(8.00)	37(37.00)	22(22.00)	9(9.00)
Observation group	100	0(0.00) [*]	2(2.00) [*]	1(1.00) [*]	19(19.00) [*]	10(10.00) [*]	1(1.00) [*]

Note: Compared with the control group, ^{*} $P < 0.05$.

强评估以及监测妊娠期高血压综合征孕妇的病情,采取一定的措施以确保孕妇有良好的休息和饮食情况,保持平稳的精神状态,进行适当的降压处理,采取针对性的病因治疗,确保妊娠结局良好,同时依照患者的病情特点给予镇静剂、利尿剂、促进肺成熟和纠正低蛋白血症等方法,是现阶段治疗该病的主要手段^[16-18]。但是在实际的诊治过程中,部分患者的精神状态、血压控制以及症状控制效果往往并不满意,部分患者甚至需要采取选择终止妊娠的手段以保证胎儿和孕妇的生命安全,不但会严重威胁孕妇的生命健康,而且不利于早产胎儿后续的生长发育情况。维生素 E 能对机体的氧化应激状态进行改善,使脂质氧化率明显降低,并抑制脂质代谢物累积于血管壁^[19]。

尼莫地平主要通过扩张血管、减弱或者抑制平滑肌收缩而发挥降压的效果,而且能有效调节外周循环以及扩张脑部的血管,但是不会穿透胎盘屏障而导致胎儿受到损伤^[20,21]。血管内皮功能受损是妊娠期高血压比较重要的一种病理改变环节^[22]。内皮素是机体中收缩血管效果最强的一种物质,而一氧化氮是机体中具有明显舒张血管作用的物质^[23]。血清和肽素作为重要的中介物质在妊娠期高血压的发生过程中起着一定的作用^[24]。皮质醇会使新生儿的生长受到限制,其血清水平与围生并发症和疾病程度相关^[25]。本研究结果提示维生素 E 联合尼莫地平治疗妊娠期高血压综合征的有效性明显提高。观察组的血清肽素、皮质醇、一氧化氮及内皮素水平明显优于对照组;表明将维生

素 E 以及尼莫地平联用可以有效提高血管的顺应性,改善血管的内皮功能,改善新生儿及孕妇的结局。

TNF- α 可以启动炎症细胞因子,诱导血管内皮细胞释放大量的炎症递质^[26,27]。正常妊娠孕妇的血清 TNF- α 水平普遍比较低,可有效调节的机体免疫和代谢功能,保持平稳的机体内环境,但是 TNF- α 出现过量表达时,则会导致病理性改变^[28]。有研究表明,TNF- α 水平会随着妊娠期高血压综合征的加重而升高,可以作为诊断的指标^[29]。IL-12 作为一种前炎症细胞因子,能促进免疫平衡发生 Th1 方向极化,从而增强妊娠期高血压综合征患者的细胞免疫反应^[30]。CRP 是炎症反应的一种标志物,TNF- α 可以有效激活分泌颗粒以及中性粒细胞等,能促进 CRP 的大量释放^[31]。本研究中,维生素 E 联合尼莫地平能更明显降低血清 CRP、IL-12 和 TNF- α , 提示维生素 E 联合尼莫地平能够显著降低血液的粘度,增加流动性,减少对内皮细胞的损伤,改善机体的炎症状态,同时又能增强细胞免疫反应,提高妊娠期高血压综合征患者的免疫功能,提高治疗效率。

综上所述,维生素 E 联合尼莫地平能明显改善妊娠期高血压综合征的妊娠结局,可能与其降低血清 CRP、IL-12、TNF- α 、皮质醇及内皮素水平有关。

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