doi: 10.13241/j.cnki.pmb.2019.21.042

硝苯地平联合拉贝洛尔治疗妊娠期高血压的综合疗效及对血清 UⅡ、PTM、Apelin 水平影响 *

王 君[1] 周 蕾[1△] 贺同强[1] 肖 瑾[1] 刘 丹[2]

（1 西北妇女儿童医院 陕西 西安 710061；2 西安交通大学第一附属医院 陕西 西安 710061）

摘要 目的：研究硝苯地平联合拉贝洛尔治疗妊娠期高血压的综合疗效及对血清尾加压素Ⅱ(UⅡ)、血浆血栓蛋白(PTM)、Apelin 水平的影响。**方法：**选取我院 2015 年 8 月到 2016 年 8 月收治的妊娠期高血压患者 500 例为研究对象，采用随机数字法将其分为对照组和观察组，每组各 250 例。对照组患者给予静脉滴注硫酸镁治疗，观察组患者在对照组基础上加用硝苯地平联合拉贝洛尔治疗。比较两组患者的治疗总有效率、母婴不良围生结局的发生情况以及治疗前后血清 UⅡ、PTM、Apelin 水平的变化。**结果：**治疗后，观察组的总有效率(91.60%)明显高于对照组(77.60%)(P=0.000)；观察组患者的血清 UⅡ、PTM、Apelin 水平明显低于对照组(P<0.01)，胎盘早剥、胎儿窘迫、新生儿窒息、终止妊娠、产后出血、低体重儿等不良围生结局发生率均明显低于对照组(P<0.05)。**结论：**硝苯地平、拉贝洛尔及硫酸镁三联治疗妊娠期高血压的临床疗效显著，能有效改善母婴围生结局，可能与其有效减低血清 UⅡ、PTM、Apelin 水平有关。

关键词：硝苯地平；拉贝洛尔；妊娠期高血压；尾加压素Ⅱ；血浆血栓蛋白；Apelin

中图分类号：R544.1；R714.252 **文献标识码：**A **文章编号：**1673-6273(2019)21-4184-04

Curative Efficacy of Nifedipine Combined with Labetalol in the Treatment of Gestational Hypertension and Its Effects on the Serum UⅡ, PTM, Apelin Levels*

WANG Jun[1], ZHOU Lei[1△], HE Tong-qiang[1], XIAO Jin[1], LIU Dan[2]

(1 Northwest Women and Children's Hospital, Xi'an, Shaanxi, 710061, China;

2 The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, 710061, China)

ABSTRACT Objective: To study Curative efficacy of Nifedipine combined with labetalol in treatment of Gestational hypertension and its effects on Tail vasopressin Ⅱ (UⅡ), blood clots in the blood plasma protein (PTM), Apelin impact. **Methods:** 500 patients with gestational hypertension admitted to our hospital from August 2015 to August 2016 were selected as research objects, they were divided into control group and observation group by random number method, with 250 cases in each group. Patients in the control group were treated with intravenous magnesium sulfate, and patients in the observation group were treated with nifedipine combined with rabelol on the basis of the control group. Compare two groups of the treatment of patients with total effective rate, and the occurrence of adverse perinatal outcomes and before and after treatment serum UⅡ, PTM, Apelin level changes. **Results:** After treatment, the total effective rate of the observation group (91.60%) was significantly higher than that of the control group (77.60%)(P=0.000). The observation group of patients with serum UⅡ, PTM, Apelin levels significantly lower than the control group (P<0.01), placental abruption, fetal distress and neonatal asphyxia, termination of pregnancy, postpartum hemorrhage and the incidence of adverse perinatal outcomes, such as low birth weight were significantly lower than the control group (P<0.05). **Conclusion:** Nifedipine, labetalol and magnesium sulfate sanlian clinical curative effect of treatment of gestational hypertension significantly, mother-to-child can effectively improve the perinatal outcome, to effectively reduce serum UⅡ, PTM, Apelin levels.

Key word: Nifedipine; Rabelor; Hypertension during pregnancy; The tail vasopressin Ⅱ; Plasma thrombus protein; Apelin

Chinese Library Classification(CLC): R544.1; R714.252 Document code: A

Article ID: 1673-6273(2019)21-4184-04

前言

妊娠期高血压是妊娠期妇女特有的病症，常发生在妊娠 20 周以后，以高血压、蛋白尿、水肿为主要临床表现，重者可出现恶心呕吐、头昏眼花、持续腹痛等，易发生脑水肿、急性心衰等严重并发症[1]。据统计，全球范围内妊娠期高血压发病率在

* 基金项目：西安市卫生局科技攻关项目(J2013108)

作者简介：王君(1978-)，女，本科，住院医师，研究方向：孕产妇的重症治疗方面，电话 18392506390，E-mail：quanl123@163.com

△ 通讯作者：周蕾(1982-)，女，本科，主管护师，研究方向：孕产妇重症疾病治疗与护理

(收稿日期：2019-04-12 接受日期：2019-05-07)

7.0%~12.0%,而我国发病率约为 9.4%[2],是孕妇死亡的第二大病因,同时可导致胎儿生长受限、胎儿窘迫、新生儿窒息等不良围生儿结局,甚至可导致胎儿的死亡,对母婴生命安全均构成极大威胁。控制和预防子痫,降低高血压对靶器官损害,从而改善母婴围生结局,是目前治疗妊娠期高血压的首要目标。其中,解痉、扩容、降压、镇静、利尿及终止妊娠是常规治疗方法[3],但治疗整体效果欠佳,同时易出现相关不良反应。临床上,通常使用硫酸镁进行治疗,但其降压速度较慢,用于临产等紧急状态下时,无法达到满意疗效[4]。因此,寻求多药联合治疗方案已成为临床研究重点。

硫酸镁联合降压药拉贝洛尔治疗妊娠期高血压已有大量报道,且证实能够提高治疗整体疗效。硝苯地平是 Ca^{2+} 通道阻断剂,能够松弛血管平滑肌、扩张血管,且药量小,但药效时间长,用于妊娠期高血压的疗效明显且副作用低[5]。UⅡ是血管舒张及收缩的相关指标,在血管内皮中的影响也较大;TM 是血管内皮细胞合成并位于细胞表面的凝血酶受体,其脱落与血中可引起 PTM 浓度上升,是血管内皮细胞损伤的标志物之一;Apelin 是胎盘组织分泌的小分子活性多肽,直接作用血管平滑肌细胞的 APJ 受体,发挥升血压效应,在妊娠期中呈高表达,加重患者病情。三种指标在妊娠期高血压中均有表达,但具体意义需进一步探讨。因此我们结合治疗疗效、UⅡ、PTM、Apelin 及母婴围生结局进行研究,现报告如下。

1 资料与方法

1.1 一般资料

选取我院 2015 年 8 月至 2016 年 8 月收治的妊娠期高血压患者 500 例,纳入标准[6]:① 符合 2012 版《妇产科学》中妊娠期高血压诊断标准;② 检查无双胎妊娠;③ 无合并严重的心脏、脑血管、肝肾肺等器官组织疾病;④ 无合并糖尿病等其他妊娠期严重疾病。排除标准:① 原发性高血压者;② 合并心肌损害、II 和 III 度房室传导阻滞等严重心脏疾病者;③ 合并凝血功能障碍、免疫系统或内分泌系统疾病者;④ 合并精神类或神经系统疾病者。

采用随机数字法将其分为两组,每组各 250 例。对照组患者年龄在 21~40 岁,平均年龄为(29.97± 3.46)岁,孕周在 30~36 周,平均孕周为(33.14± 2.06)周,其中初产妇 130 例、经产妇 120 例,病情程度:中度 119 例、重度 131 例;观察组患者年龄在 22~43 岁,平均年龄为(30.86± 3.92)岁,孕周在 28~35 周,平均孕周为(32.76± 2.11)周,其中初产妇 121 例、经产妇 129 例,病情程度:中度 122 例、重度 128 例。两组患者比较差异无统计学意义(P>0.05),具有可比性。

1.2 治疗方法

对照组患使用硫酸镁注射液(开封制药(集团)有限公司,H41022332,10 mL/2.5 g)治疗,首次剂量:20 mL 25.0%硫酸镁注射液 +100 mL 5.0%葡萄糖混合液 1h 内滴完,继之 60 mL 25.0%硫酸镁注射液 +500 mL 5.0%葡萄糖混合液,持续滴注 1-2 g/h,此后 60 mL 25.0%硫酸镁注射液 +500 mL 5.0%葡萄糖混合液,持续滴注 1-2 g/h,1 次 / 天。在此基础上,观察组患者口服硝苯地平片(国药集团工业有限公司, H11022296)治疗,剂量为 10 mg/ 次,3 次 / 天,同时静脉滴注 50 mg 拉贝洛尔(江苏迪赛诺制药有限公司,H32026121,10 mL/50 mg),1 次 / 天,所有患者均连续治疗 7 天。

1.3 观察指标

于治疗前及治疗后采集所有患者 5 mL清晨空腹静脉血,抗凝后,以 3000 $r\cdot min^{-1}$ 的速度进行离心,时间 10 min,提取上层血清后,置于零下 20℃的冷冻箱内存储以备检测,血清 UⅡ、PTM、Apelin 的测定采用双抗体夹心酶联免疫吸附法(ELISA);比较两组患者的胎盘早剥、胎儿窘迫、新生儿窒息、终止妊娠、产后出血、低体重儿等母婴不良围生结局发生率。

1.4 疗效标准

① 显效:治疗后血压恢复至正常,无严重不良围生结局发生;② 有效:治疗后 SBP 和 DBP 均有所降低,同时临床症状有所缓解,母婴围生结局良好;③ 无效:经治疗后血压、临床症状均未明显改善或加重,同时出现流产、新生儿窒息、产后出血等严重不良围生结局。显效+有效 = 总有效率%。

1.5 统计学方法

以 SPSS18.0 软件包处理数据,计量资料用均数± 标准差($\bar{x}\pm s$)表示,组间比较使用独立样本 t 检验,计数资料以率表示,组间比较采用 x^2 检验,以 P<0.05 为差异具有统计学意义。

2 结果

2.1 两组患者的治疗总有效率比较

治疗后,两组患者总有效率分别 91.60%、77.60%,观察组显著高于对照组(P<0.05),见表 1。

表 1 两组患者的治疗总有效率比较[例(%)]

Table 1 Comparison of the total effective rate between two groups [n(%)]

Groups	Effective	Good	Invalid	Total effective rate(%)
Control group(n=250)	83(33.20)	111(44.40)	56(22.40)	77.60
Observation group(n=250)	132(52.80)	97(38.80)	21(8.40)	91.60
P		-		0.000
x^2		-		18.805

2.2 两组患者治疗前后的血清 UⅡ、PTM、Apelin 水平比较

治疗后,两组患者血清 UⅡ、PTM、Apelin 水平较治疗前均显著降低,且观察组以上指标均显著低于对照组(P<0.01),详情见表 2。

2.3 两组的母婴不良围生结局发生率的比较

观察组的胎盘早剥、胎儿窘迫、新生儿窒息、终止妊娠、产后出血、低体重儿等不良围生结局发生率均明显低于对照组(P<0.05),详情见表 3。

表 2 两组患者治疗前后的血清 UⅡ、PTM、Apelin 水平的比较($\bar{x}\pm s$)

Table 2 Comparison of the serum UⅡ, PTM, Apelin levels between two groups before and after treatment ($\bar{x}\pm s$)

Groups	UⅡ(pmol/L)		PTM(ng/L)		Apelin(ng/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group(n=250)	4.13± 0.45	2.81± 0.37[a]	38.27± 16.25	24.85± 9.52[a]	391.37± 25.82	271.98± 22.75[a]
Observation group(n=250)	4.16± 0.48	1.81± 0.25[a]	38.35± 16.27	18.31± 8.45[a]	390.86± 26.13	218.45± 20.90[a]
P	0.471	0.000	0.956	0.000	0.826	0.000
t	0.721	35.408	0.055	8.254	0.220	26.896

Note: [a] Compared with before treatment, $P<0.05$.

表 3 两组母婴不良围生结局发生率的比较[例(%)]

Table 3 Comparison of the incidence of adverse perinatal outcomes between the two groups[n(%)]

Groups	Placental abruption	Fetal distress	Asphyxia neonatorum	Terminal pregnancy	Postpartum hemorrhage	Low birth weight infant
Control group (n=250)	28(11.20)	49(19.60)	28(11.20)	63(25.20)	35(14.00)	56(22.40)
Observation group (n=250)	0(0.00)	7(2.80)	7(2.80)	14(5.60)	7(2.80)	14(5.60)
P	0.000	0.000	0.000	0.000	0.000	0.000
x^2	29.661	35.473	13.548	36.858	20.379	29.924

3 讨论

妊娠期高血压是产科常见的严重疾病，存在遗传易感、免疫适应不良、胎盘缺血及氧化应激等多种学说，同时各因素可相互作用，共同导致妊娠期高血压发生[8]。研究表明[9]全身小动脉痉挛、抗凝血功能障碍，引起机体持续的高凝状态，最终造成全身各器官损害，是该病发病的主要病理过程。研究证实妊娠期高血压不仅可造成孕妇生活质量降低，且动脉痉挛及多脏器损害，还可造成胎儿宫内严重缺氧状态，影响其正常生长发育，恶化母婴妊娠结局，甚至危及母婴生命安全[11]。目前，临床治疗妊娠期高血压多以解痉、扩张血容量、降低血压、镇静、利尿、控制子痫和终止妊娠等措施可减少血容量和低血压。硫酸镁是临床妊娠期高血压的首选治疗药物，其具有解痉、降压及利尿等多重功效，能够有效预防和控制子痫发作。药理学研究显示硫酸镁中 Mg^{2+} 能有效抑制神经 - 肌肉突触间乙酰胆碱释放，干扰神经化学传递和抑制骨骼肌收缩，促进子宫平滑肌舒张进而治疗早产[12]，同时还能调节细胞内外离子平衡，达到解痉降压作用，改善孕妇及胎儿血氧供给，优化母婴妊娠结局。但单药治疗降压效果不够理想，但是增加用药剂量可能会发生严重的并发症。因此，在治疗中需要和其他降压药物联合使用[13]。

拉贝洛尔是一种甲型肾上腺受体阻断剂，能够放缓窦性心律，减少外周血管阻力。有研究显示拉贝洛尔能够能降低卧位血压和周围血管阻力，用于治疗高血压有较好的效果[14]。临床研究表明硫酸镁联合拉贝洛能达到协同降压的效果，提高降压效果，改善母婴妊娠结局。硝苯地平是钙离子通道阻断剂的一种，能通过血管连接细胞、神经肌肉细胞和骨骼肌抑制乙酰胆碱的释放[15]。在妊娠高血压患者中应用硫酸镁进行治疗可以有效改善患者临床症状，稳定患者血压，且药物副作用少[16]。本研究结果显示联合治疗的总有效率明显高于单药治疗的患者，同时胎盘早剥、胎儿窘迫、产后出血、新生儿窒息等不良母婴妊娠结局发生率明显低于对照组，表明三药联合治疗的降压效果更明显，能更好改善母婴妊娠结局。

UⅡ是最近发现的一种新的血管活性物质，其对血管调节的作用，可以产生较强的血管收缩和血管舒张作用；PTM 是内皮细胞膜型 MT 代谢所产生或血管内皮细胞损伤、炎症时受酶解而脱落下来的完整 MT 的胞膜外部分[17,18]。Apelin 则是由胎盘所分泌的小分子活性多肽，可促进妊娠期孕妇体内 NO 合成，又可激活血管平滑肌细胞 APJ 受体，实现降压和升压双向调控作用[19]。而在妊娠期高血压患者中，Apelin 呈高表达，起升高血压作用，从而恶化患者病情[20]。本研究结果显示联合治疗患者治疗后血清 UⅡ、PTM、Apelin 水平降低更明显，提示其可能是联合治疗的降压机制。

综上所述，硝苯地平、拉贝洛尔及硫酸镁三联治疗妊娠期高血压的临床疗效显著，能有效改善母婴围生结局，可能与其有效减低血清 UⅡ、PTM、Apelin 水平有关。

参 考 文 献(References)

[1] Foo L, Tay J, Lees C C, et al. Hypertension in Pregnancy: Natural History and Treatment Options [J]. Current Hypertension Reports, 2015, 17(5): 1-18

[2] Nooij L S, Visser S, Meuleman T, et al. The optimal treatment of severe hypertension in pregnancy: update of the role of nicardipine[J]. Current Pharmaceutical Biotechnology, 2014, 15(1): 64-72

[3] Moser M, Brown C M, Rose C H, et al. Hypertension in Pregnancy: Is it time for a new approach to treatment?[J]. Journal of Hypertension, 2012, 30(6): 1092-1100

[4] Stott D, Bolten M, Paraschiv D, et al. Longitudinal hemodynamics in acute phase of treatment with labetalol in hypertensive pregnant women to predict need for vasodilatory therapy[J]. Ultrasound in Obstetrics & Gynecology, 2017,49(15): 627-635

[5] Matsuura A, Yamamoto T, Arakawa T, et al. Management of severe hypertension by nicardipine intravenous infusion in pregnancy induced hypertension after cesarean section[J]. Water Research, 2015, 3 (1): 28-31

[6] Clark S M, Dunn H E, Hankins G D. A review of oral labetalol and nifedipine in mild to moderate hypertension in pregnancy [J]. Seminars in Perinatology, 2015, 39(7): 548-555

[7] Shi Q, Leng W, Yao Q, et al. Oral nifedipine versus intravenous labetalol for the treatment of severe hypertension in pregnancy[J]. International Journal of Cardiology, 2014, 32(17): 162-164

[8] Sharma K J, Greene N, Kilpatrick S J. Oral labetalol compared to oral nifedipine for postpartum hypertension: A randomized controlled trial [J]. Hypertension in Pregnancy, 2017, 1(6): 1372-1377

[9] Steiner T, Juvela S, Unterberg A, et al.European Stroke Organization Guidelines for the Management of Intracranial Aneurysms and Subarachnoid Haemorrhage [J]. Cerebrovascular Diseases, 2013, 35(2): 93-99

[10] Koren G. Systematic review of the effects of maternal hypertension in pregnancy and antihypertensive therapies on child neurocognitive development[J]. Reproductive Toxicology, 2013, 39(4): 1-5

[11] Morris R, Sunesara I, Darby M, et al. Impedance cardiography assessed treatment of acute severe pregnancy hypertension: a randomized trial[J]. Journal of Applied Ecology, 2014, 29(2): 1-22

[12] Webb T N, Shatat I F, Miyashita Y. Therapy of acute hypertension in hospitalized children and adolescents [J]. Current Hypertension Reports, 2014, 16(4): 1-9

[13] Cannon C M, Levy P, Baumann B M, et al. Intravenous nicardipine and labetalol use in hypertensive patients with signs or symptoms suggestive of end-organ damage in the emergency department: a subgroup analysis of the CLUE trial[J]. Bmj Open, 2013, 3(3): 737-743

[14] Ostrye J, Hailpern S M, Jones J, et al. The efficacy and safety of intravenous hydralazine for the treatment of hypertension in the hospitalized child[J]. Pediatric Nephrology, 2014, 29(8): 1403-1410

[15] Vesoulis Z A, Attarian S J, Zeller B, et al. Minoxidil Associated Anorexia in an Infant with Refractory Hypertension[J]. Pharmacotherapy, 2014, 34(12): 341-344

[16] Vadhera R B, Simon M. Hypertensive emergencies in pregnancy[J]. Critical Care Clinics, 2016, 32(1): 29-35

[17] Brehaut S S, Roche A M. Abstract W P65: Clevidipine Outperforms Other Agents in Emergent Acute Hypertension Treatment in Ischemic Stroke Pre-rt-PA [J]. Journal of the Peripheral Nervous System,2015, 18(1): 64-71

[18] Shawkat E, Myers J E. PMM.76 The effect of ethnicity and different antihypertensives on the 24-hour blood pressure profile during pregnancy[J]. Archives of Disease in Childhood - Fetal and Neonatal Edition, 2014, 39(16): 147-153

[19] Jung Sun K, Eun Joo K, Ok Hee W, et al. The relationship between preeclampsia, pregnancy-induced hypertension and maternal risk of breast cancer: A meta-analysis [J]. Acta Oncologica, 2013, 52(8): 1643-1648

[20] Gordin D, Kaaja R, Forsblom C, et al. Pre-eclampsia and pregnancy-induced hypertension are associated with severe diabetic retinopathy in type 1 diabetes later in life [J]. Acta Diabetologica, 2013, 50(5): 781-787

[21] Leañosmiranda A, Méndezaguilar F, Ramírezvalenzuela K L, et al. Circulating angiogenic factors are related to the severity of gestational hypertension and preeclampsia, and their adverse outcomes [J]. Medicine, 2017, 96(4): e6005

[22] Sonnaville C D, Mol B W, Groen H, et al. 6: The impact of the HYPITAT I trial on obstetric management and outcome for gestational hypertension and preeclampsia in the Netherlands[J]. American Journal of Obstetrics & Gynecology, 2018, 218(1): S5-S6

[23] Kim S J, Ahn H J, Park J Y, et al. The clinical significance of D-dimer concentrations in patients with gestational hypertensive disorders according to the severity[J]. Obstetrics & Gynecology Science, 2017, 60(6): 542-548

[24] Malhotra A S, Goel P, Chaudhary A, et al. Serial profile of flow-mediated dilatation in primigravida for prediction of preeclampsia and gestational hypertension[J]. Hypertension in Pregnancy, 2018, 37(11): 1-8

[25] Jirakittidul P, Sirichotiyakul S, Ruengorn C, et al. Effect of iron supplementation during early pregnancy on the development of gestational hypertension and pre-eclampsia[J]. Archives of Gynecology & Obstetrics, 2018, 298(3): 545-550

[26] Breatnach C R, Monteith C, Mcsweeney L, et al. The Impact of Maternal Gestational Hypertension and the Use of Anti-Hypertensives on Neonatal Myocardial Performance [J]. Neonatology, 2017, 113(1): 21-26

[27] Jeon Y, Lee W I, Kang S Y, et al. Modified Complete Blood Count Indices as Predicting Markers of Preeclampsia from Gestational Hypertension: Neutrophil to Lymphocyte Ratio, Platelet to Lymphocyte Ratio[J]. Clinical Laboratory, 2017, 63(11): 1897-1902

[28] Dasgupta K, Pace R. Dasgupta and Pace Respond to "Gestational Hypertension and Diabetes" [J]. American Journal of Epidemiology, 2017, 186(10): 1129-1130

[29] Eche S, Mackraj I, Moodley J. Circulating fetal and total cell-free DNA, and sHLA-G in black South African women with gestational hypertension and pre-eclampsia[J]. Hypertension in Pregnancy, 2017, 36(2): 1-7

[30] Khaskheli M N, Baloch S, Sheeba A, et al. Labour induction with gestational hypertension: A great obstetric challenge [J]. Pakistan Journal of Medical Sciences, 2017, 33(1): 151-155

（上接第 4179 页）

[25] Gomaa A M S, Abdelhafez A T, Aamer H A. Garlic (Allium sativum) exhibits a cardioprotective effect in experimental chronic renal failure rat model by reducing oxidative stress and controlling cardiac Na^+/K^+-ATPase activity and Ca^{2+} levels[J]. Cell Stress & Chaperones, 2018(Suppl 1): 1-8

[26] Clifforde E L. Chronic renal disease in dogs and cats: anaesthesia considerations[J]. Veterinary Nursing Journal, 2018, 33(5): 131-137

[27] Kobusiakprokopowicz M, Krzysztofik J, Kaaz K, et al. MMP-2 and TIMP-2 in Patients with Heart Failure and Chronic Kidney Disease [J]. Open Medicine, 2018, 13(1): 237-246

[28] Hawkins C L. Protein carbamylation: a key driver of vascular calcification during chronic kidney disease [J]. Kidney International, 2018, 94(1): 12-14

[29] Hu H, Xu S, Hu S, et al. The clinical characteristics of posterior reversible encephalopathy syndrome in patients with chronic renal failure[J]. Experimental & Therapeutic Medicine, 2017, 14(1): 881

[30] Trimble A, Partridge R. Smoke on the water: A case report of chronic renal failure resulting from the ingestion of smoke machine fluid[J]. Journal of the Intensive Care Society, 2017, 18(1): 57-58