doi: 10.13241/j.cnki.pmb.2019.16.022

硝酸甘油联合甲基多巴治疗重度子痫前期的效果研究 *

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摘要 目的:探讨硝酸甘油联合甲基多巴治疗重度子痫前期的临床效果及对围产结局的影响。**方法:**选取 2015 年 5 月 ~2018 年 6 月我院收治的重度子痫前期患者 81 例作为研究对象,根据患者入院先后顺序分为对照组(40 例)和观察组(41 例),对照组给予常规治疗,观察组在对照组的基础上给予硝酸甘油联合甲基多巴治疗。比较两组患者的临床治疗效果、治疗前后平均动脉压(MAP)、24h 尿蛋白(24 pro)和心率(HR)水平的变化及围产结局。**结果:**治疗后,观察组患者的总有效率显著高于对照组(95.12% vs. 80%,*P<0.05*),两组 MAP、24 pro 和 HR 水平均较治疗前显著下降,且观察组的 MAP 和 24 pro 水平显著低于对照组(*P<0.05*);观察组患者的产后出血、胎盘早剥、胎儿窘迫和新生儿窒息的发生率显著低于对照组,自然分娩率显著高于对照组(*P<0.05*),两组的低体重儿的发生率相比无统计学差异(*P>0.05*)。**结论:**硝酸甘油联合甲基多巴可有效降低重度子痫前期患者的血压和 24 pro 水平,提高自然分娩率,改善围产结局,显著提高临床效果。

关键词:硝酸甘油;甲基多巴;重度子痫前期;临床效果

中图分类号:R714.244 **文献标识码:**A **文章编号:**1673-6273(2019)16-3115-04

Effect of Nitroglycerine Combined with Methyldopa in the Treatment of Severe Preeclampsia*

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ABSTRACT Objective: To explore the clinical efficacy of nitroglycerine combined with methyldopa in the treatment of severe preeclampsia and its effect on the perinatal outcome. **Methods:** 81 cases of patients with severe preeclampsia admitted to our hospital from May 2015 to June 2018 were selected and divided into the control group(40 cases) and the observation group(41 cases) according to the sequence of admission. The control group was treated with routine treatment. The observation group was treated with nitroglycerin combined with methyldopa on the basis of control group. The treatment effect, changes of MAP, 24 pro and HR level before and afterand perinatal outcome were compared between the two groups. **Results:** The total efficiency of observation group was higher than that of the control group (95.12% vs. 80%, *P<0.05*), the MAP, 24 pro and HR levels of both groups were significantly decreased than those before treatment, and the MAP and 24 pro levels of observation group were significantly lower than those of the control group (*P<0.05*). The incidence of postpartum hemorrhage, placental abruption, fetal distress and neonatal asphyxia in the observation group was significantly lower than that of the control group, and the incidence of natural childbirth was significantly higher than that of the control group (*P<0.05*). **Conclusion:** The combination of nitroglycerin and methyldopa can effectively reduce blood pressure and 24 pro in patients with severe preeclampsia, increase the rate of natural childbirth, improve the perinatal outcomes and increase the efficiency of treatment.

Key words: Nitroglycerine; Methyldopa; Severe preeclampsia; Clinical effect

Chinese Library Classification(CLC): R714.244 Document code: A

Article ID: 1673-6273(2019)16-3115-04

前言

子痫前期是妊娠期常见的一种并发症,是指孕前血压处于正常水平的孕妇在妊娠 20 周后出现高血压、尿蛋白和水肿等症状,是妊娠高血压疾病之一,发病率约为 3.0%~5.0%[1-3]。子痫前期分为早发型和晚发型, 早发型子痫前期是孕妇在孕 20 周后 34 周前发生,发病越早对母婴的危害越大[4-6]。早发型重度子痫前期的患者处于高凝状态、纤溶酶的活性降低,容易形成血栓,且大多伴有高血脂、微循环障碍等,导致机体重要的脏器功能缺血缺氧[7-9]。而子宫蜕膜及肌层血管出现动脉粥样硬化,胎盘灌流和功能降低,极易出现胎儿宫内窘迫,增加早产的发生率,甚至出现胎盘早剥、心力衰竭等严重的并发症,危及产妇和胎儿的生命,是产妇和胎儿死亡的重要原因之一[10-12]。

子痫前期综合征的发病机制主要是由于孕期血管痉挛收缩而引起血压升高,血流量降低,导致组织缺血坏死。目前临床治疗以控制血压、解痉和镇静治疗为主,改善患者心、脑、肾、子

* 基金项目:陕西省自然科学基础研究计划项目(81200418)

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(收稿日期:2018-12-06 接受日期:2018-12-30)

宫及胎盘等重要器官的血液循环,同时降低围产期母婴并发症的发生,尽可能延长妊娠时间,提高新生儿的成活率[13-15]。临床对于该病的治疗尚未有统一规范的治疗方案，常规的控制血压、解痉和镇静等治疗效果欠佳。因此,本研究主要探讨了硝酸甘油联合甲基多巴治疗重度子痫前期的临床效果,旨在为临床用药提供参考。

1 资料与方法

1.1 临床资料

选取 2015 年 5 月 ~2018 年 6 月我院收治的重度子痫前期患者 81 例,纳入标准:① 符合《妇产科学》(第 7 版)中关于重度子痫前期的诊断标准;② 伴有不同程度的头晕、上腹胀、头痛、胸闷和视物模糊等临床症状;③ 孕妇为单胎妊娠;④ 早发型重度子痫前期。排除标准:① 合并糖尿病等其他妊娠并发症者;② 合并严重肝肾疾病者;③ 合并颅内高血压患者;④ 对本研究所用药物过敏者。根据患者入院先后顺序分为两组,对照组给予常规治疗,观察组在对照组的基础上给予硝酸甘油联合甲基多巴治疗。对照组 40 例,年龄 26~31 岁,平均 28.95± 3.12 岁;孕次 1~2 次，平均 1.56± 0.32 次；孕周 28~31 周，平均 30.56± 1.22 周,初产妇 32 例,经产妇 18 例。观察组 41 例,年龄 27~31 岁,平均 29.33± 3.25 岁;孕次 1~3 次,平均 1.68± 0.41 次;孕周 30~32 周,平均 31.02± 1.31,初产妇 34 例,经产妇 17 例。两组患者的一般资料相比无统计学差异(*P>0.05*),具有可比性。

1.2 治疗方法

对照组:所有患者入院后均给予硝苯地平控制血压,小剂量硫酸镁解痉,地西泮镇静等常规治疗,同时嘱患者卧床休息,严密监测母胎情况。观察组在对照组的基础上给予硝酸甘油联合甲基多巴治疗,硝酸甘油(山东圣鲁制药有限公司,国药准字 H20058649,1 mL: 5 mg)以 1.5 mL/h 静脉滴注,根据患者的血压变化情况进行调整，调节为 6 μg/15min，最高用量应小于 120 μg/min。甲基多巴(湖南尔康湘药制药有限公司,国药准字 H43021077,0.25 g)250~500 mg/ 次,2~4 次 /d。两组均为 7d 一个疗程。

1.3 观察指标

① 比较两组患者的治疗效果。显效:症状消失,血压恢复正常,尿蛋白下降;有效:症状改善,血压有所下降,尿蛋白有所下降;无效:症状无改善,血压无变化,尿蛋白下降不明显。总有效率 = 显效率 + 有效率。② 比较两组患者治疗前后的平均动脉压(MAP)、24h 尿蛋白(24 pro)和心率(HR)。采用心电监测仪测量患者的血压及心率，采用免疫吸附法检测患者治疗前后 24 pro。③ 比较两组患者的围产结局。

1.4 统计学方法

采用 SPSS 20.0 软件处理数据,计量资料用 $\bar{x}\pm s$ 表示,组间比较行 t 检验;计数资料采用例和%表示,组间比较行 x^2 检验,以 *P<0.05* 为差异有统计学意义。

2 结果

2.1 两组患者临床疗效的比较

治疗后,观察组患者的总有效率为 95.12%,对照组患者的总有效率为 80.00%,观察组显著高于对照组(*P<0.05*),见表 1。

表 1 两组患者临床疗效比较[n(%)]

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

Groups	n	Excellent	Effective	Invalid	Total effective rate
Control Group	40	18(37.50)	14(35.00)	8(20.00)	32(80.00)
Observation Group	41	24(58.54)	15(36.59)	2(4.88)	39(95.12)
x^2	-				4.278
P	-				0.048

2.2 两组患者治疗前后的 MAP、24 pro 和 HR 比较

两组患者治疗前的 MAP、24 pro 和 HR 水平无统计学差异(*P>0.05*),两组治疗后 MAP、24 pro 和 HR 水平均较治疗前显著下降，且观察组的 MAP 和 24 pro 水平显著低于对照组 (*P< 0.05*),见表 2。

表 2 两组患者治疗前后的 MAP、24 pro 和 HR 比较($\bar{x}\pm s$)

Table 2 Comparison of the MAP, 24 pro and HR before and after treatment between the two groups($\bar{x}\pm s$)

Groups	n	MAP(mmHg)		24 pro(g/L)		HR(times/min)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control Group	40	126.85± 11.32	111.02± 9.32*	3.21± 0.86	1.32± 0.54*	114.32± 21.31	104.25± 20.15*
Observation Group	41	127.74± 11.65	98.56± 8.54*	3.19± 0.74	0.71± 0.21*	115.89± 22.14	99.25± 19.41*
t	-	-0.349	6.276	0.112	6.669	-0.325	-1.137
P	-	0.728	＜0.001	0.911	＜0.001	0.746	0.259

Note: Compared with before treatment, **P<0.05*.

2.3 两组患者围产结局的比较

观察组患者的产后出血、胎盘早剥、胎儿窘迫和新生儿

窒息的发生率显著低于对照组，自然分娩显著高于对照组($P<0.05$)，两组的低体重儿的发生率无统计学差异($P>0.05$)，见表 3。

表 3 两组患者围产结局的比较[例(%)]

Table 3 Comparison of the perinatal outcome between the two groups[n(%)]

Groups	n	Postpartum blood loss	Natural Childbirt	Placental abruption	Low birth weight	Fetal distress	Asphyxia neonatorum
Control Group	40	7(17.50)	16(40.00)	5(12.50)	5(12.50)	8(20.00)	7(17.50)
Observation Group	41	1(2.44)	31(75.61)	0(0.00)	1(2.44)	2(4.88)	1(2.44)
x^2	-	5.160	10.541	5.462	2.988	4.278	5.160
P	-	0.029	0.001	0.026	0.109	0.048	0.029

3 讨论

重度子痫前期是危害母婴健康的妊娠期特发性疾病，容易并发严重的并发症而导致孕产妇死亡，一经确诊，应当进行积极的治疗[16-18]。终止妊娠是治疗子痫前期最有效的方法，但终止妊娠后仍有部分患者的血压不能明显下降，且病情继续加重，甚至发生产后子痫，心血管意外等，危及产妇的生命，且对于没有足月的胎儿影响其成活率[19-21]。妊娠高血压最基本的病理为血管内皮受损、全身细小动脉痉挛，硫酸镁可预防重度子痫前期患者发展为子痫，能够改善脑细胞的缺氧状态，降低颅内压，具有解痉和控制子痫前期的作用，具有良好的临床效果，但单纯使用在降低血压、减少尿蛋白和改善症状方面仍然有一定的不足，且镁离子在血液中的浓度过高会导致呼吸及肝肾功能损害，甚至发生猝死[22,23]。因此，本研究在硫酸镁等常规治疗的基础上联合硝酸甘油和甲基多巴对重度子痫前期患者进行治疗。

重度子痫前期患者临床表现主要为血压持续上升，肾功能损伤，尿蛋白和血肌酐增加等，患者全身小动脉痉挛，导致 SBP/DBP 上升，胎盘动脉粥样硬化，血流灌注减少，引起系列并发症，并常常伴有中枢神经系统、心血管系统、肝肾功能等多器官功能受损[24,25]。还有研究认为重度子痫前期与患者体内 NO 水平下降有关[26,27]。硝酸甘油进入体内后可迅速脱去硝基形成具有活性的 NO，通过内源性刺激生成前列腺素而直接松弛血管平滑肌，可扩张动静脉血管，降低体内循环的阻力，从而降低血压，尤其对于外周血管痉挛性疾病有效[28]。甲基多巴的代谢产物可阻断中枢α 受体，抑制对心、肾和周围血管输出交感冲动，降低周围血管阻力和血浆肾素，从而发挥降压作用[29]，是肾病合并高血压和妊娠期高血压患者的首选治疗药物。本研究结果显示在常规治疗的基础上联合应用可显著降低患者的 MAP 和 24 pro 水平，提高临床治疗有效率。另外，硝酸甘油还可显著降低患者的回心血量，减轻心脏负荷而减少心肌耗氧量，从而降低血压，并保证患者的血容量[30]。本研究中，硝酸甘油联合甲基多巴治疗重度子痫前期患者产后出血、胎盘早剥、胎儿窘迫和新生儿窒息的发生率显著低于常规治疗，且自然分娩率升高，可能是由于硝酸甘油和甲基多巴不仅具有较好的降压作用，还均具有减弱内皮素和血栓素的作用，确保母体供给胎儿的血流量，使得胎儿能够得到充分的氧气和营养[31]。

综上所述，硝酸甘油联合甲基多巴可有效降低重度子痫前期患者的血压和 24 pro 水平，提高自然分娩率，改善围产结局，显著提高临床效果。

参 考 文 献(References)

[1] Rolnik D L, Wright D, Poon L C, et al. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia[J]. N Engl J Med, 2017, 73(7): 613-622

[2] Roberge S, Nicolaides K, Demers S, et al. The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis [J]. American Journal of Obstetrics & Gynecology, 2016, 216(2): 110-120

[3] Gammill H S, Roberts J M. Emerging concepts in preeclampsia investigation[J]. Front Biosci, 2016, 12(1): 2403-2411

[4] Chen Q, De S J, Snowise S, et al. Reduction in the severity of early onset severe preeclampsia during gestation may be associated with changes in endothelial cell activation: A pathological case report[J]. Hypertension in Pregnancy, 2016, 35(1): 32-41

[5] Bokslag A, Teunissen P W, Franssen C, et al. Effect of early-onset preeclampsia on cardiovascular risk in the fifth decade of life [J]. American Journal of Obstetrics & Gynecology, 2017, 216 (5): 523. e1-523e7

[6] Simard J F, Arkema E V, Nguyen C, et al. Early-onset Preeclampsia in Lupus Pregnancy [J]. Paediatric & Perinatal Epidemiology, 2016, 31 (1): 29-36

[7] Lala P K, Nandi P. Mechanisms of trophoblast migration, endometrial angiogenesis in preeclampsia: the role of decorin[J]. Cell Adhesion & Migration, 2016, 10(1-2): 111-125

[8] Biró O, Nagy B, Rigó J R. Identifying miRNA regulatory mechanisms in preeclampsia by systems biology approaches [J]. Clinical & Experimental Hypertension Part B Hypertension in Pregnancy, 2016, 36(1): 90-99

[9] Gardiner C, Vatish M. Impact of haemostatic mechanisms on pathophysiology of preeclampsia[J]. Thrombosis Research, 2017, 151 Suppl 1: S48-S52

[10] Nomura Y, John R M, Janssen A B, et al. Neurodevelopmental consequences in offspring of mothers with preeclampsia during pregnancy: underlying biological mechanism via imprinting genes[J]. Archives of Gynecology & Obstetrics, 2017, 295(6): 1319-1329

[11] Jafri S, Ormiston M L. Immune regulation of systemic hypertension, pulmonary arterial hypertension and preeclampsia: shared disease

mechanisms and translational opportunities [J]. Am J Physiol Regul Integr Comp Physiol, 2017, 313(6): R693-R705

[12] Chávez J A, Cavalli R C. Preeclampsia: Vascular Pathophysiological Mechanism and the Basis for Early Diagnosis and Treatment [J]. Rev Bras Ginecol Obstet, 2016, 38(8): 369-372

[13] Brownfoot F C, Hastie R, Hannan N J, et al. Metformin as a prevention and treatment for preeclampsia: Effects on soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin secretion, and endothelial dysfunction [J]. American Journal of Obstetrics & Gynecology, 2016, 214(3): 356

[14] Wang Y A, Chughtai A A, Farquhar C M, et al. Increased incidence of gestational hypertension and preeclampsia after assisted reproductive technology treatment [J]. Fertility & Sterility, 2016, 105 (4): 920-926.e2

[15] Vigilde G P, Ludmir J. Perinatal and Hemodynamic Evaluation of Sildenafil Citrate for Preeclampsia Treatment: A Randomized Controlled Trial[J]. Obstetrics & Gynecology, 2016, 128(5): 1181-1182

[16] Zheng J J, Wang H O, Huang M, et al. Assessment of ADMA, estradiol, and progesterone in severe preeclampsia [J]. Clinical & Experimental Hypertension, 2016, 38(4): 347-351

[17] Marchetti T, De M P, Gris J C. Antiphospholipid antibodies and the risk of severe and non-severe preeclampsia: the NOHA case-control study[J]. Journal of Thrombosis & Haemostasis, 2016, 14(4): 675-684

[18] Baghbahadorani F K, Miraj S. The impact of Silymarin on improvement of platelet abnormalities in patients with severe preeclampsia[J]. Electronic Physician, 2016, 8(5): 2436-2442

[19] Chen Q, De S J, Snowise S, et al. Reduction in the severity of early onset severe preeclampsia during gestation may be associated with changes in endothelial cell activation: A pathological case report[J]. Hypertension in Pregnancy, 2016, 35(1): 32-41

[20] Baghbahadorani F K, Miraj S. The Impact of Silymarin on Improvement of Hepatic Abnormalities in Patients with Severe Preeclampsia: A Randomized Clinical Trial [J]. Electron Physician, 2017, 9(8): 5098-5106

[21] Wibowo N, Kurniawan R H, Irwinda R, et al. Maternal and cord blood cyclophilin A in severe preeclampsia and normal pregnancy and its correlation with vitamin D and zinc [J]. Hypertension in Pregnancy, 2017, 36(4): 283-287

[22] Anjum S, Rajaram G P, Bano I. Short-course postpartum (6-h) magnesium sulfate therapy in severe preeclampsia [J]. Archives of Gynecology & Obstetrics, 2016, 293(5): 983-986

[23] Kashanian M, Koohpayehzadeh J, Sheikhansari N, et al. A comparison between the two methods of magnesium sulfate administration for duration of 12 versus 24 h after delivery in patients with severe preeclampsia [J]. Journal of Maternal-Fetal Medicine, 2016, 29(14): 2282-2287

[24] Kim H J, Yang S H, Yang S H, et al. Extra-adrenal paraganglioma masquerading as severe preeclampsia [J]. Obstetrics & Gynecology Science, 2018, 61(4): 520-523

[25] Benschop L, Duvekot J J, Versmissen J, et al. Blood Pressure Profile 1 Year After Severe Preeclampsia [J]. Hypertension, 2018, 71(3): 491498

[26] Awni B M, Rahal M A, Fontes A B, et al. 145 Systematic delivery approach at 37 weeks of gestation in mild and severe preeclampsia: Maternal and neonatal outcomes:Preeclampsia in low and middle income countries [J]. Pregnancy Hypertension An International Journal of Womens Cardiovascular Health, 2016, 6(3): 251-252

[27] Millen K R, Buhimschi C S, Zhao G, et al. Serum and Urine Thioflavin-T-Enhanced Fluorescence in Severe Preeclampsia [J]. Hypertension, 2018, 71(6): 1185-1192

[28] Buszek R J, Soto D, Dailey J M, et al. Back Cover: Structures and Binding Energies of Nitrate Plasticizers DEGDN, TEGDN, and Nitroglycerine (Prop. Explos. Pyrotech. 2/2018) [J]. Propellants Explosives Pyrotechnics, 2018, 43(2): 216-216

[29] Hoeltzenbein M, Beck E, Fietz A K, et al. Pregnancy Outcome After First Trimester Use of Methyldopa: A Prospective Cohort Study [J]. Hypertension, 2017, 70(1): 201-208

[30] Sasano T, Tomimatsu T, Kanagawa T, et al. Neglected shoulder presentation with foetal death managed by internal podalic version with nitroglycerine and sevoflurane [J]. Journal of Obstetrics & Gynaecology, 2017, 37(1): 1-2

[31] Fukuda S, Nakamura Y, Egi K, et al. Comparison of direct effects of clinically available vasodilators; nitroglycerin, nifedipine, cilnidipine and diltiazem, on human skeletonized internal mammary harvested with ultrasonic scalpel[J]. Heart & Vessels, 2016, 31(10): 1-4

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[27] Chen J, Li T, Hao Y, et al. THU0474 The Influence of Osteoporotic Hip Fracture after Total Knee Arthroplasty: A Propensity-Matched Cohort Study [J]. Annals of the Rheumatic Diseases, 2016, 75(Suppl 2): 363.3-363

[28] Bruyère O, Hiligsmann M, Zegels B, et al. Risk of Hip Fracture in Community-dwelling and Institutionalized Osteoporotic Patients: A 3-year Study [J]. International Journal of Gerontology, 2013, 7(3): 167-170

[29] El-Haj M, Gurt I, Cohen-Kfir E, et al. Reduced Sirtuin1 expression at the femoral neck in women who sustained an osteoporotic hip fracture [J]. Osteoporosis International, 2016, 27(7): 1-6

[30] Diamantopoulos A P, Hoff M, Hochberg M, et al. THU0372 Osteoporosis an Independent Predictor of Mortality in Hip Fracture Patients [J]. Annals of the Rheumatic Diseases, 2013, 72 (Suppl 3): A291-A291