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间苯三酚联合拉贝洛尔治疗妊娠高血压疾病的疗效研究*

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摘要 目的:研究间苯三酚联合拉贝洛尔治疗妊娠高血压疾病的临床效果及可能机制。**方法:**选择 2015 年 12 月-2018 年 12 月我院收治的 180 例妊娠高血压疾病患者,并将其根据入院的顺序,随机数字表法均分为两组,每组 90 例。对照组静脉滴注间苯三酚 200 mg,连续给药 7 d,观察组联合静脉滴注拉贝洛尔 100 mg,当患者的血压降至目标期值后,将给药方法改为口服拉贝洛尔片,每次 50 mg,每天 3 次,直至分娩前。比较两组胎盘早剥、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,治疗前后的收缩压(Systolic blood pressure,SBP)、平均动脉压(Mean arterial pressure,MAP)、舒张压(Diastolic blood pressure,DBP)以及血清半胱氨酸蛋白酶抑制剂 C(Serum cysteine protease inhibitor C, Cys-C)、高迁移率蛋白-1(High mobility protein-1, HMGB1)、同型半胱氨酸(Homocysteine, Hcy)水平的变化。**结果:**治疗后,观察组的总有效率为 92.22%,明显高于对照组(74.44%, $P<0.05$);观察组的胎盘早剥率、产后出血率、胎儿窘迫发生率、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($P<0.05$);两组治疗后的 SBP、MAP 和 DBP、血清 Hcy、HMGB1 和 Cys-C 水平均较治疗前明显降低 ($P<0.05$),且观察组以上指标均明显低于对照组 ($P<0.05$)。**结论:**间苯三酚联合拉贝洛尔能显著降低妊娠高血压不良分娩结局的发生率,控制血压效果理想,其作用机制可能与降低患者血清 Hcy、HMGB1 和 Cys-C 水平有关。

关键词:间苯三酚;拉贝洛尔;妊娠高血压疾病;分娩结局

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Therapeutic Effect of Phloroglucinol Combined with Labetalol on the Hypertensive Disorder Complicating Pregnancy*

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ABSTRACT Objective: To investigate the clinical effect of phloroglucinol combined with labetalol in the treatment of pregnancy induced hypertension and its possible mechanisms. **Methods:** 180 cases of patients with hypertensive disorder complicating pregnancy who were treated in our hospital from December 2015 to December 2018, according to the order of admission, the random number table method is divided into two groups with 90 cases in each group. The control group was given phloroglucinol 200 mg intravenously for 7 days. The observation group was combined with intravenous drip of 100 mg of labetalol. When the patient's blood pressure dropped to the target period, the administration method was changed to oral labetalol tablets, 50 mg each time, three times a day, until before delivery. The outcomes of delivery (placental abruption, postpartum hemorrhage, fetal distress, cesarean section, low birth weight infants and neonatal asphyxia) and the changes of systolic blood pressure (SBP), mean arterial pressure (MAP), diastolic blood pressure (DBP), serum cysteine protease inhibitor C (Cys-C), high mobility protein-1 (HMGB1) and homocysteine (Hcy) levels before and after treatment were compared between the two groups. **Results:** After treatment, the total effective rate of observation group (92.22%) was significantly higher than that of the control group (74.44%, $P<0.05$). 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 ($P<0.05$). After treatment, the SBP, MAP and DBP of both groups were significantly decreased ($P<0.05$), which were more obvious decreased in the observation group ($P<0.05$). The levels of SBP, MAP and DBP, serum Hcy, HMGB1 and Cys-C in the two groups were significantly lower than those before treatment ($P<0.05$), and the above indicators in the observation group were significantly lower than the control group ($P<0.05$). **Conclusion:** The combination of phloroglucinol and labetalol can significantly reduce the incidence of adverse delivery outcomes in pregnancy-induced hypertension and control blood pressure. The mechanism may be related to the reduction of serum Hcy, HMGB1 and Cys-C levels.

Key words: Phloroglucinol; Labetalol; Hypertensive disorder complicating pregnancy; Delivery outcome

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前言

妊娠高血压疾病是产科特有的疾病,病情较轻的妊娠高血压患者会发生轻度的恶心呕吐、头晕头痛、蛋白尿和水肿等症状,病情严重者会出现明显水肿,蛋白尿增多,甚至出现昏迷及抽搐等^[1-3]。妊娠高血压会使患者的动静脉发生痉挛、血液的黏度增加以及胎盘功能异常等,可能造成腹中的胎儿发生早产、发育迟缓和缺氧等不良后果^[4-7]。临床对于妊娠高血压疾病的治疗方法包括解痉、降压、吸氧、镇静、抗癫痫以及补液等,治疗方案尚未形成统一的标准,部分患者在产后血压水平可基本恢复正常,但有一部分患者产后血压仍然居高不下,因而需要采取更全面、更系统的降压治疗^[8]。

间苯三酚是常用于保胎治疗的解痉药,其对痉挛肌肉具有较高的亲和性,但不会影响正常的平滑肌^[9,10]。拉贝洛尔作为水杨酸氨的一种衍生物,能对于 α 和 β 肾上腺素能受体发挥竞争性拮抗作用,从而扩张外周血管,发挥降压作用^[11,12]。本研究将间苯三酚和拉贝洛尔联合用于治疗妊娠高血压,分析了其疗效和可能的作用机制。

1 资料与方法

1.1 一般资料

选择2015年12月-2018年12月我院收治的180例妊娠高血压疾病患者,纳入标准:①舒张压 >85 mmHg或者收缩压 >130 mmHg,②单胎妊娠,③依从性良好,④均知情同意,且自愿参加本研究。排除标准:①合并有严重肝肾肺以及心脑血管等器官组织疾病的患者,②对间苯三酚以及拉贝洛尔过敏的患者,③合并恶性肿瘤患者,④由于主动脉关闭不全、甲状腺功能亢进、肾动脉狭窄、库欣综合征、系统性红斑狼疮、嗜铬细胞瘤以及滋养细胞疾病等引发的高血压患者。用抽签法将所有患者随机分为两组。观察组90例,年龄20~42岁,平均 (29.13 ± 1.37) 岁;孕周31~40周,平均 (36.44 ± 2.13) 周;身体质量指数平均为 (27.83 ± 2.46) kg/m²;对照组90例,年龄21~40岁,平均 (29.08 ± 1.42) 岁;孕周31~39周,平均 (36.27 ± 1.94) 周;身体质量指数平均为 (27.94 ± 3.17) kg/m²。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

两组入院后均保持侧卧位卧床休息,适量补充维生素和钙质,限制每日钠盐的摄入量以及活动量,且给予解痉和镇静治疗。对照组:给予间苯三酚(湖北午时药业股份有限公司,国药准字H20060385,规格:40 mg/支),200 mg与500 mL的5.0%葡萄糖溶液混合后静脉滴注,连续治疗7 d。观察组联合拉贝洛尔(江苏迪赛诺制药有限公司,国药准字H32026122,规格:2 mL:25 mg),100 mg与250 mL的5.0%葡萄糖溶液混合后静脉滴注治疗,当患者的血压降至目标值后,将给药方法改为口服拉贝洛尔片(河南科伦药业有限公司,国药准字H41025249,规格:50 mg/片),每次50 mg,每天3次,直至分娩。

1.3 观察指标

疗效标准:①显效:血压明显降低,症状明显改善;②有效:血压有一定程度的降低,症状有所缓解;③无效:未达到上述标准。

分娩结局:包括胎盘早剥、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。

记录两组治疗前后的收缩压(Systolic blood pressure, SBP)、平均动脉压(Mean arterial pressure, MAP)、舒张压(Diastolic blood pressure, DBP),并进行比较。

分别于治疗前后空腹抽取4 mL外周静脉血,采用分光光度计法测定同型半胱氨酸(Homocysteine, Hcy)水平,试剂盒购自成都安普诺生物科技有限公司;采用ELISA测定迁移率蛋白-1(High mobility protein-1, HMGB1)水平,试剂盒购自北京普华仕科技发展有限公司;采用免疫比浊法测定血清半胱氨酸蛋白酶抑制剂C(Serum cysteine protease inhibitor C, Cys-C)水平。均严格按照试剂盒说明书操作。

1.4 统计学分析

数据采用SPSS22.0软件进行统计学分析,计量资料组间比较行t检验,计数资料组间比较行 χ^2 检验,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组临床疗效的比较

治疗后,观察组总有效率为92.22%,明显高于对照组(74.44%, $P<0.05$),见表1。

表1 两组临床疗效比较[例(%)]

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

Groups	n	Effective	Valid	Invalid	Total effective rate
Control group	90	35 (38.89)	32 (35.56)	23 (25.56)	67(74.44)
Observation group	90	43 (47.78)	40 (44.44)	7 (7.78)	83(92.22)*

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

2.2 两组的分娩结局的比较

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2。

2.3 两组治疗前后SBP、MAP和DBP的对比

两组治疗后的SBP、MAP和DBP均较治疗前明显降低($P<0.05$),且观察组以上指标均明显低于对照组($P<0.05$),见表3。

2.4 两组治疗前后血清Hcy、HMGB1和Cys-C水平的对比

两组治疗后的血清Hcy、HMGB1和Cys-C水平均较治疗前明显降低,且观察组以上指标均显著低于对照组($P<0.05$),见表4。

3 讨论

妊娠高血压疾病患者会出现蛋白尿、高血压、水肿昏迷、肾功能衰竭以及抽搐等临床特点,严重时会造成胎儿和产妇死亡^[13]。该病的发病机制非常复杂,与免疫、子宫胎盘缺血、前列

腺素缺乏及遗传等因素相关,多胎妊娠、羊水过多等因素会使宫腔内压力升高,血流量降低,导致胎盘缺氧,严重者可出现视力模糊、凝血功能障碍、头晕、抽搐及肾功能衰竭等症状^[14-16]。妊娠期高血压疾病的基本病理改变为血管内皮细胞受到损伤,对

一氧化氮的敏感性降低、对血管紧张素的敏感性升高,导致血压升高以及全身小动脉痉挛,病情严重者可甚至会发生昏迷、抽搐和视网膜血管痉挛等^[17-19]。因而,寻找有效且安全的治疗药物极为重要。

表 2 两组的分娩结局的对比[例(%)]

Table 2 Comparison of the delivery outcome between two groups [n (%)]

Groups	n	Placental abruption	Postpartum hemorrhage	Fetal distress	Cesarean section	Low birth weight	Neonatal asphyxia
Control group	90	6(6.67)	12(13.33)	8(8.89)	32(35.56)	19(21.11)	9(10.00)
Observation group	90	0(0.00)*	3(3.33)*	1(1.11)*	17(18.89)*	8(8.89)*	1(1.11)*

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

表 3 两组治疗前后 SBP、MAP 和 DBP 的对比($\bar{x}\pm s$, mmHg)

Table 3 Comparison of the SBP, MAP, DBP between two groups before and after treatment($\bar{x}\pm s$, mmHg)

Groups	n		SBP	MAP	DBP
Control group	90	Before treatment	143.48 $\pm$ 12.39	113.58 $\pm$ 10.94	96.48 $\pm$ 8.97
		After treatment	138.57 $\pm$ 10.42 [#]	105.21 $\pm$ 10.54 [#]	89.24 $\pm$ 7.25 [#]
Observation group	90	Before treatment	144.27 $\pm$ 11.59	113.63 $\pm$ 11.28	97.61 $\pm$ 9.53
		After treatment	132.42 $\pm$ 8.67**	99.56 $\pm$ 7.32**	84.28 $\pm$ 6.94**

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

表 4 两组治疗前后的血清 Hcy、HMGB1 和 Cys-C 水平的比较($\bar{x}\pm s$)

Table 4 Comparison of the serum levels of Hcy, HMGB1 and Cys-C between two groups before and after treatment ($\bar{x}\pm s$)

Groups	n		Hcy ($\mu\text{mol/L}$)	HMGB1 (mg/L)	Cys-C (mg/L)
Control group	90	Before treatment	16.39 $\pm$ 1.54	9.34 $\pm$ 1.72	2.24 $\pm$ 0.69
		After treatment	10.38 $\pm$ 1.42 [#]	4.56 $\pm$ 1.12 [#]	1.39 $\pm$ 0.37 [#]
Observation group	90	Before treatment	16.73 $\pm$ 1.92	9.26 $\pm$ 1.83	2.23 $\pm$ 0.65
		After treatment	6.95 $\pm$ 1.13**	2.03 $\pm$ 0.54**	0.83 $\pm$ 0.22**

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

间苯三酚作为一种新型的解痉止痛药,可以选择性地对机体部分器官(泌尿生殖道及胃肠道)的平滑肌细胞产生直接的松弛效果,而且对正常的平滑肌只会产生极轻微的影响,只作用于已出现痉挛的平滑肌,不良反应少,止痛效果较好^[20-22]。拉贝洛尔通过对交感神经进行抑制,对儿茶酚胺的释放发挥促进作用,使血管发生扩张,具有持久的降压效果。由于拉贝洛尔对于 β 受体的阻滞效果明显强于 α 受体,在降低血压后不会产生反跳现象,且不会导致反射性的心率加快^[23-25]。拉贝洛尔通过阻滞 α 受体能使冠状动脉的血流量显著增加,降低心脏的负荷以及心肌的耗氧量。且拉贝洛尔的降压作用比较快速,可以缓解患者头晕和脑缺血等症状。在安全性方面,拉贝洛尔并不会影响肾脏和胎盘的血液流量,常用的剂量不会导致血压过低,在一定程度上促进胎儿的肺成熟^[26,27]。本研究结果显示间苯三酚联合拉贝洛尔能显著降低妊娠高血压疾病的胎盘早剥率、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,且能更为显著地降低 SBP、MAP 和 DBP,体现了二者联用的临床价值。

Hcy 可促进收血管因子释放入血,使外周小血管阻力升高,引起全身血压升高^[28,29]。研究表明高 Hcy 水平能使妊娠期高

血压疾病的发生危险增加,且与病情炎症程度具有正相关性。HMGB1 能促进炎症因子大量分泌,使上皮细胞通透性增强,使组织水肿和局部渗出加重^[30]。Cys-C 可有效反映妊娠高血压的病情和肾损伤程度^[31,32]。本研究结果显示观察组治疗后的上述指标明显低于对照组,提示间苯三酚联合拉贝洛尔能显著降低血清 Hcy、HMGB1 和 Cys-C 水平。分析其原因可能是拉贝洛尔选择性的与 α 受体竞争性结合扩张血管,降低血管的阻力,增加血管的容量已降低患者的血压,降压速度快,有效保护了血管内皮的损伤,降低氧化自由基的合成,使一氧化氮正常合成,减少内皮素和血管紧张素 II 的合成,同时也可以减轻炎症反应,研究表明炎症因子可以多方面的影响妊娠高血压的发生和发展,随着病情的加重,炎症因子水平也会在增高^[33]。拉贝洛尔应用使得炎症反应得到改善,Hcy、HMGB1 和 Cys-C 的水平降低,Hcy 水平降低能够有效的保护血管内皮未受损伤;HMGB1 水平降低减少了对中性粒细胞趋化作用的刺激,稳定了上皮细胞的通透性;Cys-C 水平降低改善了肾小球滤过膜的通透性,减少肾功能的损伤。通过协同改善患者的血管内皮、上皮细胞的通透性以及肾功能,从而降低血管的阻力,增加血管的容量,降低患者的血压^[34,35],这可能是其发挥作用的机制之一。

综上所述,间苯三酚联合拉贝洛尔能显著降低妊娠高血压疾病不良分娩结局的发生率,控制血压效果理想,其作用机制可能与降低血清 Hcy、HMGB1 和 Cys-C 水平有关。

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