西地那非联合一氧化氮吸入治疗新生儿肺动脉高压的临床观察

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摘　要　目的：观察西地那非联合一氧化氮（NO）吸入治疗新生儿肺动脉高压的临床疗效及安全性。方法：选取肺动脉高压患儿66例，按随机数字表法分为对照组与观察组，各33例。两组患儿均给予多巴胺注射液5 μg/（kg·min），ivgtt。对照组患儿吸入NO 5～20 ppm；观察组患儿在对照组基础上口服或鼻饲枸橼酸西地那非片0.5～1.0 mg/kg，6 h 1次。两组患儿均治疗3 d。观察两组患儿临床疗效及治疗前后动脉血氧分压（PaO_2）、动脉血二氧化碳分压（$PaCO_2$）、动脉血氧饱和度（SaO_2）、肺动脉压（PAP）、NO、血清内皮素（ET-1）、缺氧诱导因子（HIF-1α）、促红细胞生成素（EPO）及Ca^{2+}水平，并比较不良反应发生率。结果：观察组患儿临床总有效率为96.97%，明显高于对照组的75.76%，差异有统计学意义（$P<0.05$）。治疗前，两组患儿PaO_2、SaO_2、NO、PAP、$PaCO_2$、ET-1、HIF-1α、EPO、Ca^{2+}水平比较，差异无统计学意义（$P>0.05$）；治疗后，两组患儿PaO_2、SaO_2、NO、Ca^{2+}水平较治疗前明显升高，$PaCO_2$、PAP、EPO、HIF-1、ET-1较治疗前明显降低，且观察组显著优于对照组，差异有统计学意义（$P<0.05$）。两组患儿均未见明显不良反应发生。结论：NO联合西地那非治疗新生儿肺动脉高压疗效显著，能有效改善患儿肺动脉高压体征及血气指标，且安全性较好。

关键词　一氧化氮；西地那非；新生儿肺动脉高压；疗效

Clinical Observation of Sildenafil Combined with Nitric Oxide in the Treatment of Neonatal Pulmonary Hypertension

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ABSTRACT　OBJECTIVE: To observe clinical efficacy and safety of nitric oxide (NO) combined with sildenafil in the treatment of neonatal pulmonary hypertension. METHODS: 66 cases of neonatal pulmonary hypertension were selected and randomly divided into observation group and control group, with 33 cases in each group. 2 groups of patients were given Dopamine injection 5 μg/(kg·min), ivgtt. Control group was given NO 5-20 ppm; observation group received oral or nasal feeding of Citric acid sildenafil tablets, 0.5-1.0 mg/kg, 96 h, on the basis of control group. Both group received 3 d of treatment. Clinical efficacy of 2 groups were observed as well as the level of PaO_2, $PaCO_2$, SaO_2, PAP, NO, ET-1, HIF-1α, EPO and Ca^{2+} before and after treatment. The incidence of ADR was compared between 2 groups. RESULTS: Total effective rate of observation group was 96.97%, which was significantly higher than that of control group (75.76%), with statistical significance ($P<0.05$). There was no statistical significance in the levels of PaO_2, $PaCO_2$, SaO_2, PAP, NO, ET-1, HIF-1α, EPO and Ca^{2+} between 2 groups before treatment ($P>0.05$); compared to before treatment, PaO_2, SaO_2, No and Ca^{2+} levels of 2 groups increased significantly after treatment, while $PaCO_2$, PAP, EPO, HIF-1, ET-1 significantly lowered and the observation group was better than the control group, with statistical significance ($P<0.05$). No obvious ADR was found in 2 groups. CONCLUSIONS: Sildenafil combined with NO is effective in the treatment of neonatal pulmonary hypertension and can effectively improve pulmonary hypertension and blood gas indexes with good safety.

KEYWORDS　Nitric oxide; Sildenafil; Neonatal pulmonary hypertension; Therapeutic efficacy

新生儿肺动脉高压是一种新生儿常见的肺部疾病并发症，主要是由于患儿肺小动脉发生病变导致患儿肺动脉高压[1]，可继发右心功能衰竭，并且可导致肺部血管病变，诱发肺炎、窒息、呼吸窘迫综合征等，患儿致死率、致残率极高。临床建议对于新生儿肺动脉高压应及时纠正患儿低氧血症、酸中毒等症状，并迅速降低患儿肺动脉血压指标[2]，通过扩张血管、改善患儿肺部局部微循环增加脏器血流量，可有效遏制、预防缺氧引发的诸多损伤[3]。一氧化氮（NO）在治疗新生儿肺动脉高压中得到广泛应用，但在NO停用后肺动脉高压易反弹。西地那非能改善局部微循环。因此，本研究观察了NO联合西地那非治疗新生儿肺动脉高压的临床疗效及安全性。

1　资料与方法

1.1　纳入与排除标准

纳入标准：（1）确诊为肺动脉高压；（2）符合《新生儿急救学》[4]中相关诊断标准；（3）年龄≤7 d。排除标准：（1）先天性肺发育畸形、气胸者；（2）先天性心脏病者。

1.2　研究对象

选取2014年1月－2015年12月我院收治的肺动脉高压患儿66例，按随机数字表法分为对照组和观察组，各33例。两组患儿一般资料比较，差异无统计学意义（$P>0.05$），具有可比性，详见表1。本研究方案经医院医学伦理委员会批准，患儿家属知情同意并签署知情同意书。

1.3　治疗方法

两组患儿均给予多巴胺注射液5 μg/（kg·min），ivgtt。对照组患儿吸入NO 5～20 ppm；观察组患儿在对照组基础上口服或鼻饲枸橼酸西地那非片（辉瑞药业有限公司，批准文号：国药准字H20020526，规格：25 mg/片）0.5～1.0 mg/kg，6 h 1次。两组患儿均治疗3 d。

1.4　观察指标

（1）观察两组患儿临床疗效，疗效评价参考《新生儿急救

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表1　两组患儿一般资料比较($\bar{x}\pm s$)

Tab 1　Comparison of general information between 2 groups($\bar{x}\pm s$)

组别	n	性别,例		年龄,d	平均年龄,d	体质量指数,kg/m^2
		男	女			
对照组	33	18	15	0.3~7	2.6±0.7	14.5±0.6
观察组	33	20	13	0.5~7	2.5±0.5	15.2±0.5
t/χ^2		0.745		1.322	1.102	2.034
P		>0.05		>0.05	>0.05	>0.05

学》制定。显效:患儿治疗后临床症状与体征明显缓解,各项指标明显改善;有效:患儿治疗后青紫、气促、呻吟等一般临床症状与体征有所缓解,各项肺动脉指标等有所改善;无效:治疗前后体征、症状与相关参数比较无显著差异。总有效率=(显效例数+有效例数)/总例数×100%。(2)观察两组患者治疗前后血氧分压(PaO_2)、动脉血二氧化碳分压($PaCO_2$)、动脉血氧饱和度(SaO_2)、肺动脉压(PAP)、NO、血清内皮素(ET-1)、缺氧诱导因子(HIF-1α)、促红细胞生成素(EPO)及Ca^{2+}水平。(3)观察两组患者不良反应发生情况。

1.5　统计学方法

采用SPSS 19软件对数据进行统计学分析。计量资料以$\bar{x}\pm s$表示,采用t检验;计数资料以率表示,采用χ^2检验。$P<0.05$为差异有统计学意义。

2　结果

2.1　两组患儿临床疗效比较

观察组患儿临床总有效率明显高于对照组,差异有统计学意义($P<0.05$),详见表2。

表2　两组患儿临床疗效比较[例(%)]

Tab 2　Comparison of clinical efficacy between 2 groups [case(%)]

组别	n	显效	有效	无效	总有效
对照组	33	10(30.30)	15(45.45)	8(24.24)	25(75.76)
观察组	33	14(42.42)	18(54.55)	1(3.03)	32(96.97)

2.2　两组患儿治疗前后血气指标比较

治疗前,两组患儿PaO_2、$PaCO_2$、SaO_2、PAP、EPO指标比较,差异无统计学意义($P>0.05$);治疗后,两组患儿PaO_2、SaO_2水平明显升高,$PaCO_2$、PAP、EPO明显降低,且观察组显著优于对照组,差异有统计学意义($P<0.05$)。两组患儿治疗前后血气指标比较见表3(1 mm Hg=0.133 kPa)。

表3　两组患儿治疗前后血气指标比较($\bar{x}\pm s$)

Tab 3　Comparison of blood gas indexes between 2 groups before and after treatment($\bar{x}\pm s$)

组别	n	时期	PaO_2,mm Hg	$PaCO_2$,mm Hg	SaO_2,%	PAP,mm Hg	EPO,U/ml
对照组	33	治疗前	35.56±10.57	55.49±9.56	50.54±14.36	62.16±7.59	27.25±8.36
		治疗后	74.25±12.33*	43.54±6.59*	89.11±5.34*	29.49±8.34*	15.36±4.39*
观察组	33	治疗前	36.81±9.25	56.22±8.49	51.34±15.36	61.45±8.33	26.49±6.54
		治疗后	82.66±11.26$^{*\#}$	35.11±8.34$^{*\#}$	96.48±3.49$^{*\#}$	25.44±6.25$^{*\#}$	11.71±3.49$^{*\#}$

注:与治疗前比较,$^*P<0.05$;与对照组比较,$^\#P<0.05$

Note: vs. before treatment, $^*P<0.05$; vs. control group, $^\#P<0.05$

2.3　两组患儿实验室检查指标比较

两组患儿治疗前ET-1、HIF-1α、NO、Ca^{2+}水平比较,差异无统计学意义($P>0.05$);两组患儿治疗后ET-1、HIF-1α显著降低,NO、Ca^{2+}显著升高,且观察组显著优于对照组,差异有统计学意义($P<0.05$)。两组患儿实验室检查指标比较见表4。

2.4　不良反应

两组患儿治疗过程中均未见严重不良反应发生。

3　讨论

新生儿肺动脉高压的病理基础为肺小动脉的病变以及其

表4　两组患儿实验室检查指标比较($\bar{x}\pm s$)

Tab 4　Comparison of lab indexes between 2 groups before and after treatment($\bar{x}\pm s$)

组别	n	时期	ET-1,pg/ml	HIF-1α,pg/ml	NO,μmol/l	Ca^{2+},mmol/l
对照组	33	治疗前	237.55±43.16	769.55±115.25	13.97±9.55	1.44±0.15
		治疗后	78.64±22.35*	386.26±62.48*	21.24±12.28*	1.95±0.18*
观察组	33	治疗前	240.65±45.22	775.36±120.18	14.35±10.32	1.54±0.15
		治疗后	46.17±30.33$^{*\#}$	305.64±48.34$^{*\#}$	26.74±15.32$^{*\#}$	2.03±0.16$^{*\#}$

注:与治疗前比较,$^*P<0.05$;与对照组比较,$^\#P<0.05$

Note: vs. before treatment, $^*P<0.05$; vs. control group, $^\#P<0.05$

他肺部疾病或心血管疾病并发症,因此新生儿肺动脉高压与患儿的心功能同样具有密切联系,同时肺动脉高压可导致心房、动脉水平由右向左进行分流,可直接导致右心房进行性衰竭的发病,威胁新生儿生命健康及生长发育的安全性[5]。

本研究结果显示,观察组患儿临床总有效率明显高于对照组,血气指标、验室检查指标改善效果明显优于对照组,差异均有统计学意义($P<0.05$)。分子学角度的研究认为,肺动脉高压基础病例的缺氧性肺小动脉内皮损伤可导致患儿血清细胞因子以及相关血管活性物质分泌的异常,其中HIF-1α是重要的蛋白调节因子,主要参与细胞缺氧时的特异性反应[6],因此肺动脉高压时患儿HIF-1α水平明显升高,而ET-1可在机体缺氧条件下由HIF-1α诱导表达[7],受HIF-1α影响,当发生肺动脉高压时,ET-1水平同样升高;而EPO是机体在缺氧条件下产生的保护因子,可增加红细胞数量,改善缺氧情况[8]。

西地那非是一种具有显著的磷酸二酯酶活性抑制作用的药物,能松弛患儿肌细胞,并扩张肺部血管,改善局部微循环,同时可有效降低患儿肺动脉血压;而多巴胺则具有α、β受体激动作用[1],对肺动脉高压新生儿可扩张肺、肾血管,增加肺部血流量,扩张血管,降低血管阻力,同样可改善肺部局部微循环[9]。1992年,美国学者首先应用并报道了采用NO吸入治疗新生儿肺动脉高压,并且取得良好的疗效以及安全性。NO作为一种内皮依赖性血管舒张因子,具有较强的血管扩张作用,并且已有临床研究证实,机体在急性缺氧状态下内源性NO的产生将迅速减少并且肺血管的松弛能力逐渐减弱,当机体发生慢性缺氧时同样可导致NO的长期减少,进而导致患者肺血管组织发生病变,如内皮增厚导致的慢性肺动脉高压等症状[10-11]。而在应用NO吸入治疗中发现,新生儿肺动脉高压吸入NO能够选择性降低肺动脉压力,并且对于新生儿正常的体循环基本无影响,尤其是因缺氧导致的肺动脉高压患儿疗效更为显著。但在实际临床应用中应注意NO吸入的副作用,如高铁血红蛋白血症、肺损伤、血小板破坏等,应根据患儿的呼吸功能及时调节NO的吸入浓度以及吸入时间,提高NO治疗的安全性。

综上所述,西地那非联合NO治疗新生儿肺动脉高压疗效显著,能有效改善患儿肺动脉高压体征及血气指标,且安全性较好。但本研究样本较小,有待扩大样本量进一步探讨。

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康复新液治疗小儿手足口病的临床观察

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摘　要　目的:观察康复新液治疗小儿手足口病的临床疗效及安全性。方法:将128例手足口病患儿按随机数字表法分为观察组和对照组,各64例。对照组患儿给予皮肤疱疹及口腔护理,对血象升高提示感染患儿给予抗菌药物治疗,酌情应用补液及非甾体类解热镇痛药物等常规治疗。观察组患儿在对照组基础上口服康复新液,≤3岁者,3 ml,tid;>3岁者,5 ml,tid。观察两组患儿临床疗效及治疗前后C反应蛋白(CRP)、乳酸、免疫球蛋白(Ig)和心肌酶水平,并比较两组患儿治疗后症状体征消失时间及不良反应。结果:观察组患儿总有效率(89.06%)显著高于对照组(70.31%),差异有统计学意义($P<0.05$)。两组患儿治疗前CRP、乳酸、Ig、心肌酶水平及治疗后IgM比较,差异均无统计学意义($P>0.05$);两组患儿治疗后CRP、乳酸、肌酸磷酸酶及乳酸脱氢酶水平明显降低,IgA、IgG水平明显升高,且观察组显著高于对照组,差异均有统计学意义($P<0.05$)。观察组患儿退热时间、手足皮疹消退时间、口腔溃疡愈合时间均明显短于对照组,差异有统计学意义($P<0.05$)。两组患儿治疗期间均未见明显不良反应发生。结论:康复新液治疗小儿手足口病疗效显著,能明显改善患儿CRP、Ig、乳酸、心肌酶水平,且安全性较好。
关键词　康复新液;小儿手足口病;心肌酶谱;C反应蛋白;乳酸;免疫球蛋白

Clinical Observation of Kangfuxin Liquid in the Treatment of Pediatric Hand, Foot and Mouth Disease

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ABSTRACT　OBJECTIVE: To observe clinical efficacy and safety of Kangfuxin liquid in the treatment of pediatric hand, foot and mouth disease. METHODS: 128 children with hand, foot and mouth disease were randomly divided into observation group and control group, with 64 cases in each group. Control group was given routine treatment as herpes and oral care, antibiotics for infective children reflected by hemogram elevation, fluid infusion and non-steroidal analgesic-antipyretic agent based on disease condition. Observation group was additionally given Kangfuxin liquid, 3 ml for below 3 year-old, tid and 5 ml for more than 3 year-old, tid. Clinical efficacy of 2 groups were observed as well as CRP, lactic acid, Ig, the level of myocardial enzyme before and after treatment; the time of symptoms and signs disappearance and ADR were compared between 2 groups after treatment. RESULTS: The total effective rate of observation group (89.06%) was significantly higher than that of control group (70.31%), with statistical significance ($P<0.05$). There was no statistical significance in CRP, lactic acid, Ig and myocardial enzyme before treatment and IgM level after treatment between 2 groups, with statistical significance ($P>0.05$). CRP, lactic acid creatine kinase and lactate dehydrogenase level of 2 groups decreased significantly, while IgA and IgG levels increased significantly, and the observation group was higher than the control group, with statistical significance ($P<0.05$). Antipyretic time, hand foot skin rash subsided time and oral ulcer healing time of observation group were significantly shorter than those of control group, with statistical significance ($P<0.05$). No obvious ADR was found in 2 groups during treatment. CONCLUSIONS: Kangfuxin liquid is effective in the treatment of hand, foot and mouth disease in children, and can effectively improve CRP, Ig, lactic acid, and myocardial enzyme level with good safety.
KEYWORDS　Kangfuxin liquid; Pediatric hand, foot and mouth disease; Myocardial enzyme; CRP; Lactic acid; Immune globulin

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