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HFOV 联合 PS 对治疗新生儿 ALI/ARDS 的疗效及对肺动态顺应性的影响 *

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摘要 目的:探讨高频振荡通气(HFOV)联合肺表面活性物质(PS)对治疗新生儿急性肺损伤/急性呼吸窘迫综合征(ALI/ARDS)的疗效及对肺动态顺应性的影响。**方法:** 选择 2018 年 1 月至 2020 年 12 月我院新生儿科收治的 160 例 ALI/ARDS 患儿进行研究,按照随机数表法分为观察组和对照组,每组 80 例。对照组患儿给予常频通气(CMV)模式联合 PS 治疗,观察组患儿给予 HFOV 模式联合 PS 治疗。比较两组患儿一般治疗情况、治疗前后肺动态顺应性、动脉血氧分压(PaO_2)、动脉二氧化氮分压($PaCO_2$)、氧合指数(OI)、血清肿瘤坏死因子 -α(TNF-α)、白细胞介素(IL)-6、IL-10 的变化,以及治疗期间并发症发生情况。**结果:**观察组胸片恢复正常时间、机械通气时间、氧暴露时间、ICU 停留时间、住院时间结果均明显短于对照组($P<0.05$),两组患儿病死率相比较,无统计学意义($P>0.05$);治疗后 12 h、24 h、48 h 时,观察组肺动态顺应性及 PaO_2、OI 结果明显高于对照组,$PaCO_2$ 明显比对照组低,差异有统计学意义($P<0.05$);治疗后 48 h 时,观察组血清 TNF-α、IL-6 水平均明显低于对照组,IL-10 明显比对照组高,差异有统计学意义($P<0.05$);两组治疗期间,呼吸机相关性肺损伤、颅内出血、气漏、呼吸道感染的总发生率比较,无统计学意义($P>0.05$)。**结论:**HFOV 联合 PS 治疗新生儿 ALI/ARDS 疗效明显,可有效改善患儿肺动态顺应性,促进血气分析指标恢复,且可降低炎症因子的表达,值得推广应用。

关键词:新生儿;急性肺损伤;急性呼吸窘迫综合征;高频振荡通气;肺表面活性物质;肺动态顺应性
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Effect of HFOV Combined with PS in Treatment of Neonatal ALI/ARDS and Its Effects on Dynamic Lung Compliance*

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ABSTRACT Objective: To study the effect of high frequency oscillatory ventilation (HFOV) combined with pulmonary surfactant (PS) in treatment of neonatal acute lung injury/acute respiratory distress syndrome (ALI / ARDS) and its effects on dynamic lung compliance. **Methods:** 160 children with ALI/ARDS in our hospital from January 2018 to December 2020 were selected, they were randomly divided into observation group and control group, 80 cases in each group. The control group was treated with constant frequency ventilation (CMV) mode combined with PS, and the observation group was treated with HFOV mode combined with PS. The general treatment, the changes of the pulmonary dynamic compliance, arterial partial pressure of oxygen (PaO_2), arterial partial pressure of nitrogen dioxide ($PaCO_2$), oxygenation index (OI), serum blood gas tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-10 before and after treatment, and complications during treatment were compared between the two groups. **Results:** The results of chest X-ray recovery time, mechanical ventilation time, oxygen exposure time, ICU stay time and hospitalization time in the observation group were significantly shorter than those in the control group($P<0.05$); There was no statistical significance in the mortality rate between the two groups ($P>0.05$); At after treatment 12 h, 24 h and 48 h, the results of pulmonary dynamic compliance, PaO_2 and OI in the observation group were significantly higher than those in the control group, and $PaCO_2$ in the observation group was significantly lower than that in the control group, with statistically significant ($P<0.05$); At after treatment 48 h, the serum TNF-α and IL-6 levels in the observation group were significantly lower than those in the control group, and the IL-10 levels in the observation group were significantly higher than those in the control group with statistically significant($P<0.05$); There was no statistical significance in the total incidence of ventilator-related lung injury, intracranial hemorrhage, air leakage and respiratory tract infection in the two groups($P>0.05$). **Conclusion:** HFOV combined with PS have

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obvious curative effect in the treatment of neonatal ALI/ARDS, which can effectively improve the dynamic compliance of lung, promote the recovery of blood gas analysis indexes, and reduce the expression of inflammatory factors, which is worthy of popularization and application.

Key words: Acute lung injury; Acute respiratory distress syndrome; High frequency oscillatory ventilation; Pulmonary surfactant; Pulmonary dynamic compliance

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前言

急性肺损伤 / 急性呼吸窘迫综合征(ALI/ARDS)属于新生儿中的一种急危重症,发病机制较为复杂[1,2]。主要是由于新生儿的肺部发育尚不成熟,在感染、创伤、休克、中毒等因素的刺激下,极易造成急性肺部弥漫性损伤,导致该病发生[3,4]。若得不到有效的治疗,严重者甚至出现多器官功能衰竭,增加病死率,威胁着患儿的生命安全[5,6]。目前针对新生儿 ALI/ARDS 的治疗主要包括机械通气、应用肺表面活性物质(PS)等方案,在改善患儿预后、减少病死率方面有重要价值[7,8]。而在机械通气的选择上,临床上应用较多的是常频通气(CMV)、高频振荡通气(HFOV)两种[9,10]。因此,本研究将 CMV、HFOV 分别联合 PS 应用新生儿 ALI/ARDS 的治疗,旨在对比其疗效及对肺动态顺应性的影响,现报道如下。

1 资料与方法

1.1 一般资料

选择 2018 年 1 月至 2020 年 12 月我院新生儿科收治的 160 例 ALI/ARDS 患儿进行研究。纳入标准[11,12]:① 符合《诸福棠实用儿科学》[13]中新生儿 ALI/ARDS 诊断标准,并经由实验室指标、影像学检查等确诊;② 具有机械通气指征,需接受气管插管通气治疗;③ 胎龄≥ 34 周;④ 患儿家属签署相关研究同意书。排除标准[14,15]:① 合并先天性肺部发育不良、先天性心脏疾病、原发性 PS 缺乏等;② 合并其余先天性畸形;③ 合并严重脑室出血;④ 产前有明确感染情况;⑤ 对研究治疗方式有禁忌症。按照随机数表法分为观察组和对照组,每组 80 例。两组患儿的一般资料情况见表 1,差异无统计学意义($P>0.05$)。研究已经由我院伦理委员会批准实施。

表 1 两组患儿一般资料情况比较[$\bar{x}\pm s$,n(%)]

Table 1 Comparison of the general information between two groups children[$\bar{x}\pm s$, n(%)]

Groups	Gender		Gestational age(wekks)	Birth weight (kg)	Primary disease			
	Male	Femal			Asphyxia	Pneumonia	Meconium aspiration syndrome	The others
Observation group(n=80)	47(58.75)	33(41.25)	37.05± 1.75	2.73± 0.30	30(37.50)	24(30.00)	15(18.75)	11(13.75)
Control group (n=80)	50(62.50)	30(37.50)	36.99± 1.90	2.69± 0.38	26(32.50)	27(33.75)	16(20.00)	11(13.75)

1.2 方法

两组均给予常规处理措施,包括镇静、抗感染、改善微循环、维持机体内环境稳定、营养支持等。并接受机械通气(Stephen Christina 呼吸机)治疗,对照组患儿给予 CMV 模式治疗,初始参数设定如下:吸气峰压设置为 1.8~2.5 kPa,呼气末压设置为 0.4~0.6 kPa,呼吸频率设置为 35~60 次 / 分,吸入氧浓度(FiO_2)范围为 0.30~0.60。观察组患儿给予 HFOV 模式治疗,初始参数设定如下:平均气道压(MAP)为 1.0~1.4 kPa,振荡压力幅度范围为 3.5~4.5kPa,振荡至患儿肚脐部位,频率为 9~11Hz,FiO_2 范围为 0.30~0.60。

两组患儿均同时给予 PS(规格 70 mg,厂家:华润双鹤药业股份有限公司,国药准字 H20052128)治疗,经过气管插管进行一次性给药,剂量为 70~100 mg/kg。治疗期间均密切观察患儿病情变化及血气分析情况,并适当调节呼吸机参数。

两组患儿撤机指征:当患儿临床症状得到明显缓解,可自主呼吸,血气分析指标动脉血氧分压(PaO_2)>60 mmHg,动脉二氧化氮分压($PaCO_2$)<45 mmHg 时,下调呼吸机参数后,血气分析指标结果仍维持正常,则可撤机。

1.3 观察指标

1.3.1 一般治疗情况 记录两组患儿胸片恢复正常时间、机械通气时间、氧暴露时间、ICU 停留时间、住院时间以及病死率。

1.3.2 肺动态顺应性 记录两组患儿通气前(治疗前)、通气后(治疗后)12 h、24 h、48 h 的呼吸机参数上的肺动态顺应性结果。

1.3.3 血气分析指标 分别于治疗前以及治疗后 12h、24h、48 时,使用美国 GEM Premier3000 型血气分析仪检测血气分析指标,包括 PaO_2、$PaCO_2$ 的变化,并计算氧合指数(OI)结果,公式为 PaO_2/FiO_2。

1.3.4 炎症因子指标 采集两组患儿治疗前、治疗后 48 h 的静脉血 2 mL,进行离心处理,转速 3000 r/min,时间 15 min,收集上层血清液并储存于冷冻箱中准备检测,检测指标包括肿瘤坏死因子 -α(TNF-α)、白细胞介素(IL)-6、IL-10,所选择的酶联免疫吸附法(ELISA)试剂盒均购于北京博凌科微生物科技有限公司。

1.3.5 安全性 记录治疗期间并发症的发生情况。

1.4 统计学分析

以 spss18.0 软件包处理实验数据,计量资料用均数± 标准

差($\bar{x}\pm s$)表示，t 检验，计数资料比较采用 x^2 检验，以 $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组患儿一般治疗情况比较

观察组胸片恢复正常时间、机械通气时间、氧暴露时间、ICU 停留时间、住院时间结果均明显短于对照组($P<0.05$)，两组患儿病死率相比较，无统计学意义($P>0.05$)，见表 2。

表 2 两组患儿一般治疗情况比较[$\bar{x}\pm s$，n(%)]

Table 2 Comparison of the general treatment between two groups children[$\bar{x}\pm s$, n(%)]

Groups	Chest X-ray recovery time(h)	Mechanical ventilation time(h)	Oxygen exposure time(h)	ICU stay time(d)	Hospitalization time(d)	Death
Observation group (n=80)	40.82± 6.49*	72.96± 10.12*	81.46± 11.72*	8.39± 2.11*	15.78± 2.64*	2(2.50)
Control group (n=80)	46.02± 6.38	83.48± 13.00	94.25± 10.68	11.23± 2.60	18.92± 2.17	4(5.00)

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

2.2 两组患儿肺动态顺应性情况比较

和治疗前进行比较显示，两组患儿治疗后 12 h、24 h、48 h 肺动态顺应性结果均明显升高，且观察组在上述时间点中，肺动态顺应性结果均高于对照组($P<0.05$)，见表 3。

表 3 两组患儿肺动态顺应性情况比较($\bar{x}\pm s$，mL/cmH_2O)

Table 3 Comparison of the pulmonary dynamic compliance between two groups children($\bar{x}\pm s$, mL/cmH_2O)

Groups	Time	Pulmonary dynamic compliance
Observation group(n=80)	Before treatment	0.28± 0.04
	After treatment 12 h	0.43± 0.05*#
	After treatment 24 h	0.58± 0.07*#
	After treatment 48 h	0.67± 0.05*#
Control group(n=80)	Before treatment	0.27± 0.05
	After treatment 12 h	0.35± 0.04*
	After treatment 24 h	0.49± 0.05*
	After treatment 48 h	0.60± 0.05*

Vs the before treatment, *$P<0.05$; vs the control group, #$P<0.05$.

2.3 两组患儿血气分析指标比较

和治疗前进行比较显示，两组患儿治疗后 PaO_2、OI 指标结果均明显升高，$PaCO_2$ 明显降低，且观察组在上述时间点中，PaO_2、OI 指标结果均明显高于对照组，$PaCO_2$ 明显比对照组低($P<0.05$)，见表 4。

表 4 两组患儿血气分析指标比较($\bar{x}\pm s$)

Table 4 Comparison of blood gas analysis index between two groups children($\bar{x}\pm s$)

Groups	Time	PaO_2(mmHg)	$PaCO_2$(mmHg)	OI
Observation group(n=80)	Before treatment	45.60± 5.71	58.85± 4.32	204.34± 25.77
	After treatment 12 h	62.18± 6.88*#	51.34± 4.04*#	235.91± 26.31*#
	After treatment 24 h	70.83± 6.25*#	45.29± 4.35*	261.83± 21.94*#
	After treatment 48 h	74.29± 6.88*#	41.08± 3.92*#	274.03± 25.62*#
Control group(n=80)	Before treatment	45.31± 6.08	58.50± 4.78	206.11± 20.81
	After treatment 12 h	57.20± 5.37*	55.02± 4.15*	221.84± 23.68*
	After treatment 24 h	65.39± 5.23*	48.09± 3.62*	248.12± 18.76*
	After treatment 48 h	70.02± 5.61*	45.10± 3.77*	260.91± 20.51*

Vs the before treatment, *$P<0.05$; vs the control group, #$P<0.05$.

2.4 两组患儿炎症因子比较

和治疗前进行比较显示，两组患儿治疗后血清 TNF-α、IL-6 水平均明显降低，血清 IL-10 明显升高，且观察组在上述时间点中，血清 TNF-α、IL-6 水平均明显低于对照组，IL-10 明

显比对照组高(P＜0.05),见表 5。

2.5 安全性评价

两组治疗期间,呼吸机相关性肺损伤、颅内出血、气漏、呼吸道感染的总发生率比较,无统计学意义(P＞0.05),见表 6。

表 5 两组患儿炎症因子比较($\bar{x}\pm s$,pg/mL)

Table 5 Comparison of the inflammatory factors between two groups children($\bar{x}\pm s$, pg/mL)

Groups	Time	TNF-α	IL-6	IL-10
Observation group(n=80)	Before treatment	128.34± 36.02	175.92± 32.03	3.90± 0.46
	After treatment 48 h	64.02± 8.36*#	40.94± 4.72*#	8.94± 1.81*#
Control group(n=80)	Before treatment	131.08± 35.21	171.39± 33.62	3.88± 0.51
	After treatment 48 h	80.32± 11.60*	66.81± 7.34*	7.16± 1.42*

Vs the before treatment, *P＜0.05; vs the control group, #P＜0.05.

表 6 两组患儿并发症发生率比较[n(%)]

Table 6 Comparison of the incidence of complications between two groups children[n(%)]

Groups	Ventilator associated lung injury	Intracranial hemorrhage	Air leakage	Respiratory tract infection	Total incidence
Observation group(n=80)	3(3.75)	2(2.50)	6(7.50)	3(3.75)	14(17.50)
Control group(n=80)	4(5.00)	2(2.50)	7(8.75)	3(3.75)	16(20.00)

3 讨论

ALI/ARDS 的发生率在新生儿科中并不少见,属于一种难治性疾病,患儿主要表现出进行性的呼吸困难症状以及难以纠正的低氧血症,具有病情重、预后差等特点[16,17]。发病原因主要是由于各类损伤、感染等因素所诱发的毛细血管内皮细胞、肺上皮细胞损伤等,致使肺部发生水肿、弥漫性损伤,从而导致肺顺应性降低、肺容量减少、通气/血流比例失衡等表现[18,19]。若得不到及时的治疗,极易造成患儿病死,影响预后[20,21]。因此,积极选择一种有效的方案治疗新生儿 ALI/ARDS 显得十分重要。

PS 属于一种肺部保护剂,其用于治疗较多肺损伤疾病中可起到较好的效果,主要作用是对内源性肺表面活性物质的分泌和合成发挥促进作用,从而促进肺上皮细胞再生,起到改善肺顺应性等作用[22,23]。且临床研究也发现,PS 还具有抗氧化、抗感染、调节免疫等效果[24,25]。新生儿 ALI/ARDS 由于体内 PS 物质缺乏,早期给予外源性的 PS 治疗具有重要作用,但也有较多报道指出,在新生儿 ALI/ARDS 中单独使用 PS 的疗效尚有可提升的空间[26,27]。

机械通气是新生儿 ALI/ARDS 的重要治疗手段,有助于积极纠正患儿的氧合功能,促进病情恢复[28,29]。CMV 模式是临床上应用较多的一种通气模式,可为患儿提供一定的气道压水平,达到改善呼吸功能、减少病死率的效果[30]。HFOV 是一种新型的通气模式,和传统的机械通气模式原理不同,该模式主要是利用较小的潮气量(1~4 mL/kg)和较高的通气频率(至少是正常呼吸频率的 4 倍数),在低气道压的条件下进行通气,该方式不仅有助于维持机体正常的功能残气量,且可增加机体的摄氧能力[31,32]。有研究显示,和传统的通气方式相比,HFOV 可避免气体滞留、二氧化碳(CO_2)潴留等现象,应用效果会更好[33]。

本研究通过观察显示,采用 HFOV 联合 PS 治疗的患儿在治疗后 12 h、24 h、48 h 时肺动态顺应性结果以及血气分析指标 PaO_2、$PaCO_2$、OI 的改善程度优于采用 CMV 联合 PS 治疗的患者,且胸片恢复正常时间、机械通气时间、氧暴露时间、ICU 停留时间、住院时间均明显更短。通过分析原因是由于,① CMV 模式通气过程中只能将气压水平维持在一定范围,若采用低压力进行通气治疗,则容易发生氧合效果欠佳等现象,若增加压力又容易对肺部造成损伤,而 HFOV 虽然在治疗期间的平均气道压比 CMV 模式更高,但吸气时间更短,一般仅需要 10%~20%的振动压则可进入肺泡,且在治疗时不用调整气压则可增加机体氧合,且在通气期间的压力、振荡幅度、时间等也更加精确稳定,可为患儿提供更好的通气效果;Fischer HS 等[34]研究也显示,在 ARDS 患儿中,采用 HFOV 通气模式功更有助于气体交换,纠正患儿氧合功能,并积极缩短机械通气时间、用氧时间,效果明显。② HFOV 采用低潮气量、高通气频率的方式,在保证通气量的同时,也可为患儿提供肺保护效果,避免肺泡过度扩张,且通过高频率的振荡,有助于促进肺快复张,从而缩短恢复时间,促进患儿病情得到早期恢复。③ PS 也具有稳定肺泡功能、降低肺泡表面张力的作用,可加强肺顺应性,并减少液体由毛细血管渗出的现象,改善肺换气功能,通过和 HFOV 联合,不仅可加速 PS 在肺部的分布情况,还有助于维持其在体内的结构及功能,令 PS 的功效发挥到最大化,进一步提高总体治疗效果。

炎症因子是导致 ALI/ARDS 发病的关键环节,主要原因是由于多种病因所致的大量细胞因子释放,并进一步触发机体炎症瀑布级联反应相关,最终诱发炎症反应的发生[35]。血清 TNF-α、IL-6、IL-10 是反映机体炎症反应程度的重要指标,因此本研究通过检测上述指标来了解患儿炎症情况的变化[36]。本研究结果显示,采用 HFOV 联合 PS 治疗的患儿在治疗后 48 h 时血清 TNF-α、IL-6、IL-10 得到了更明显的改善,且改善程度优于 CMV 联合 PS 治疗的患儿。通过分析原因主要是由于,HFOV 在积极改善患儿氧合、呼吸功能后,有助于修复机体损伤,从而减少了机体炎症因子的释放;Chen Z 等[37]实验中也发现,HFOV 模式联合 PS 治疗可有效降低极低出生体质量儿呼吸窘

迫综合征血清 IL-6 水平的表达，积极缓解机体炎症反应，和本研究具有一定相似性。

本研究中也显示，联合 HFOV 模式治疗的患儿呼吸机相关性肺损伤、颅内出血、气漏、呼吸道感染和对照组比较无明显差异，也显示出该方式在 ALI/ARDS 患儿中也具有较好的应用安全性。在 Veneroni C 等[38]研究中显示，HFOV 在减少病死率方面较 CMV 相比更明显，更有助于改善患儿预后。但本研究中两组患儿的病死率分别为 2.50%he 5.00%，使用 HFOV 联合 PS 治疗的患儿略低，但两组在统计学比较上差异无统计学意义，HFOV 模式并未体现出明显的优势，考虑是由于本研究的样本量过少相关，今后也将进行更大样本量的研究来进一步验证此部分内容，且本研究时间过短，对于该方式对患儿更远期的预后方面也将进行持续探讨。

综上所述，HFOV 联合 PS 治疗新生儿 ALI/ARDS 疗效明显，可有效改善患儿肺动态顺应性，促进血气分析指标恢复，且可降低炎症因子的表达，值得推广应用。

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