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西比灵联合 NGF 对脑出血患者的 NIHSS、ADL 评分及血肿体积改善效果 *

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摘要 目的：研究西比灵联合神经生长因子(NGF)对脑出血患者的 NIHSS、ADL 评分及血肿体积影响。**方法：**研究对象选取我院 2015 年 9 月到 2016 年 10 月间收治的脑出血 98 例，采用随机数字法分为 2 组，每组各 49 例。对照组接受常规基础性治疗，在此基础上，研究组患者口服西比灵联合肌肉注射 NGF 治疗。比较两组患者的治疗总有效率，同时比较血肿、水肿带体积、神经功能缺损量表(NIHSS)、日常生活能力量表(ADL)评分、神经源性营养因子（BDNF）、单核细胞趋化蛋白 -1（MCP-1）、神经元特异性烯醇化酶（NSE）水平变化情况及不良反应发生情况。**结果：**治疗后，两组总有效率比较差异显著（P<0.05）；治疗前，研究组和对照组血肿体积、水肿带体积比较无显著差异；治疗后，研究组和对照组血肿体积、水肿带体积随着时间的推移而降低，且研究组均低于对照组，差异显著（P<0.05）；治疗前，研究组和对照组 NIHSS、ADL 评分比较无显著差异；治疗后，研究组和对照组 NIHSS 随着时间的推移而降低，且研究组均低于对照组，ADL 评分随着时间的推移而升高，且研究组高于对照组，差异显著（P<0.05）；治疗前，研究组和对照组 BDNF、MCP-1、NSE 比较无显著差异；治疗后，研究组和对照组 MCP-1、NSE 随着时间的推移而降低，且研究组均低于对照组，BDNF 随着时间的推移而升高，且研究组高于对照组，差异显著（P<0.05）；两组不良反应比较无效显著差异（P>0.05）。**结论：**脑出血患者应用西比灵联合 NGF 效果可靠，可明显减少继发性损伤，且治疗安全性较高，值得在临床推广。

关键词：西比灵；NGF；脑出血；NIHSS；ADL；血肿体积

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Sibeline Combined with NGF on NIHSS in Patients with Cerebral Hemorrhage, Hematoma Volume and ADL Score Improvement Effect*

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ABSTRACT Objective: To study the effect of flunarizine combined with nerve growth factor (NGF) on NIHSS in patients with cerebral hemorrhage, ADL score and volume of hematoma. **Methods:** 98 cases of cerebral hemorrhage admitted to our hospital from September 2015 to October 2016 were selected as the study subjects, and divided into 2 groups by random number method, 49 cases in each group. Patients in the control group received conventional basic treatment, and patients in the study group received oral sibiline combined with intramuscular injection of NGF on the basis of this treatment. Compare two groups of patients with total effective rate of treatment, at the same time comparative hematoma, edema zone volume, neural function defect scale (NIHSS) scores, daily life ability scale (ADL) score, neurogenic nutrition factor (BDNF), monocyte chemotactic protein 1 (MCP 1), neuron specific enolization enzyme (NSE) level changes and adverse reactions occur. **Results:** After treatment, the total effective rate between the two groups was significantly different (P<0.05). Before treatment, there were no significant differences in hematoma volume and edema zone volume between the study group and the control group. After treatment, the volume of hematoma and edema zone in the study group and the control group decreased with time, and the difference was significant (P<0.05). Before treatment, there were no significant differences in NIHSS and ADL scores between the study group and the control group. After treatment, the NIHSS of the study group and the control group decreased over time, and the ADL score of the study group was higher than that of the control group, and the difference was significant (P<0.05). Before treatment, there were no significant differences in BDNF, MCP-1 and NSE between the study group and the control group. After treatment, MCP-1 and NSE of the study group and control group decreased with time, and both of the study group were lower than the control group, while BDNF increased with time, and the study group was higher than the control group, the difference was significant(P<0.05). There was no significant difference in ADR between the two groups (P>0.05). **Conclusion:** The effect of sibilin combined with NGF in patients with intracerebral hemorrhage is reliable, which can significantly reduce the secondary injury, and the treatment is safe and wor-

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thy of clinical promotion.

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前言

脑出血是临床常见的急性脑血管疾病,发病率高,病情进展快,其发生率约占所有脑卒中的 20.0%~30.0%,急性期致死率高达 30.0%~40.0%,对患者生命健康构成极大威胁[1-3]。其发病原因较为复杂,可能与脑血管、动脉粥样硬化等因素相关,患者多在情绪激动或剧烈体力活动时突然发病,若得不到及时治疗则会导致患者出现神经功能缺损,出现语言、运动、认知等功能障碍,降低患者的生活质量[4]。临床通常采用降血压等常规方法稳定病情,但效果不理想,因此较多学者提出联合治疗的方式提高治疗效果[5]。西比灵为选择性钙拮抗剂,能改善脑部血流循环,防止细胞内钙负荷过量,抑制脑血管痉挛;NGF 属于神经营养因子,能修复受损的脑细胞,改善新陈代谢能力,保护周围神经生长[6-8]。两种药物所具有促进脑出血患者神经功能恢复效果已得到广泛证实[9],但两种药物联合治疗脑出血的报道较少, 本研究笔者就对西比灵联合 NGF 治疗脑出血的综合疗效展开报道。

1 资料与方法

1.1 一般资料

选取我院 2015 年 9 月到 2016 年 10 月间收治的脑出血 98 例,纳入标准[10]:① 均符合《2015 中国脑出血诊疗指南》标准;② 脑出血量均 <30.0 mL;③ 无合并严重的心肺肝肾等器官组织疾病;④ 本人或家属签署知情同意书且自愿参加。排除标准:① 脑血管畸形、肿瘤等因素出血者;② 脑出血量 >30.0 mL,或已出现脑疝等严重并发症需开颅者;③ 原发性小脑、脑室、脑干等部分出血者;④ 血肿未破入脑室。采用随机数字法分为 2 组,每组 49 例。对照组男 27 例、女 22 例,年龄 47~80 岁,平均年龄为(65.26± 8.23)岁,脑出血量在 16~29 mL,平均出血量为(24.13± 4.57) mL;研究组患者男性 28 例、女性 21 例,年龄范围在 44~83 岁,平均年龄为(66.02± 8.31)岁,脑出血量在 17~29 mL,平均出血量为(23.97± 4.50) mL。两组一般资料比较无显著差异,可比较。

1.2 方法

对照组给予 5.0%葡萄糖与 0.5 mg 胞二磷胆碱混合液,250 mL,1 次 /d,同时静脉滴注 125.0 mL 20.0%甘露醇注射液,3 次 /d,间隔 8 h 给药。在此基础上,研究组患者加口服西比灵(深圳市中联制药有限公司, H44021801, 5 mg) 治疗,10.0 mg/次,于晚餐后至睡前期间服用,同时肌肉注射 NGF(海特生物制药股份有限公司,S20060051, 20 μg)治疗,30.0 μg/ 次,1 次 /d。

1.3 观察指标

① 比较血肿体积和水肿带体积;② 比较两组患者治疗前后的 NIHSS 评分和 ADL 评分。

1.4 疗效标准

疗效评定标准[11],① 显效:精神意识得到明显改善,血肿量吸收 10.0 mL 以上, 血肿四周水肿带面积较治疗前降低 50.0%以上;② 有效:精神意识有所好转,血肿量吸收 5.0 mL,血肿四周水肿带面积较治疗前降低 20.0%~50.0%;③ 无效:经治疗后精神意识状态无改善或加重,血肿量吸收小于 5.0 mL,血肿周围水肿面积降低小于 20.0%或增加。总有效率 =(显效率 + 有效率)× 100.0%。神经功能采用 NIHSS 进行评定,生活质量采用ADL 进行评定,总分为 100 分,分数越高表示患者生活质量越好。

1.5 统计学方法

所有统计学资料都采用 SPSS21.0 专业统计学软件进行数据分析,计量资料以均数± 标准差表示,进行 t 检验。而所有的计数资料以率(n%)表示,用 x^2 检验,P<0.05 评价为差异具有显著性。

2 结果

2.1 不同治疗方式的临床效果评价

治疗后,两组总有效率比较差异显著(P<0.05),详情见表 1。

表 1 不同治疗方式的临床效果评价[n(%)]

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

Groups	Effective	Valid	Invalid	Total effective rate(%)
Control group(n=49)	12(24.49)	20(40.82)	17(34.69)	65.31
Research group (n=49)	21(42.86)	22(44.90)	6(12.24)	87.76
P		-		0.00
x^2		-		6.87

2.2 不同治疗方式的血肿体积和水肿带体积比较

治疗前,研究组和对照组血肿体积、水肿带体积比较无显著差异;治疗后,研究组和对照组血肿体积、水肿带体积随着时间的推移而降低,且研究组均低于对照组(P<0.05),详情见表2。

2.3 不同治疗方式的 NIHSS 和 ADL 评分比较

治疗前,研究组和对照组 NIHSS、ADL 评分比较无显著差异;治疗后,研究组和对照组 NIHSS 随着时间的推移而降低,且研究组均低于对照组,ADL 评分随着时间的推移而升高,且研究组高于对照组(P<0.05),详情见表 3。

表 2 不同治疗方式的血肿体积和水肿带体积比较($\bar{x}\pm s$)

Table 2 Comparison of hematoma volume and edema volume between the two groups before and after treatment($\bar{x}\pm s$)

Groups	Hematoma volume(cm^3)		Hematoma volume and Edema volume(cm^3)	
	Before treatment	After treatment	Before treatment	After treatment
Control group(n=49)	11.62± 4.27	10.20± 3.65	22.91± 6.83	17.67± 6.38[◎]
Research group (n=49)	11.49± 4.33	7.18± 2.64[◎]	23.12± 6.94	8.44± 2.79[◎]
P	0.88	0.00	0.85	0.00
t	0.15	4.69	0.17	9.28

Note: [◎] compared with before treatment, $P<0.05$.

表 3 不同治疗方式的 NIHSS 和 ADL 评分比较($\bar{x}\pm s$)

Table 3 Comparison of NIHSS and ADL score between the two groups before and after treatment($\bar{x}\pm s$)

Groups	NIHSS scores		ADL scores	
	Before treatment	After treatment	Before treatment	After treatment
Control group(n=49)	19.14± 6.02	14.60± 4.53[◎]	50.67± 7.28	71.90± 6.73[◎]
Research group (n=49)	18.87± 5.98	10.79± 3.58[◎]	51.05± 7.14	83.47± 8.81[◎]
P	0.81	0.00	0.83	0.00
t	0.22	4.62	0.19	7.31

Note: [◎] compared with before treatment, $P<0.05$.

2.4 不同治疗方式的血清学指标比较

治疗前，研究组和对照组 BDNF、MCP-1、NSE 比较无显著差异；治疗后，研究组和对照组 MCP-1、NSE 随着时间的推移而降低，且研究组均低于对照组，BDNF 随着时间的推移而升高，且研究组高于对照组，差异显著（$P<0.05$），详情见表 4。

表 4 不同治疗方式的血清学指标比较($\bar{x}\pm s$)

Table 4 Comparison of serological indexes of different treatment methods($\bar{x}\pm s$)

Groups	BDNF（ng/mL）		MCP-1（pg/mL）		NSE（μSEmL）	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group(n=49)	2.79± 0.56	4.87± 0.06[◎]	8.40± 2.49	5.47± 0.78[◎]	28.44± 3.61	12.33± 1.31[◎]
Research group (n=49)	2.72± 0.52	6.13± 0.05[◎]	8.38± 2.41	3.21± 0.62[◎]	28.49± 3.58	8.60± 1.53[◎]
P	0.52	0.00	0.97	0.00	0.95	0.00
t	0.64	112.93	0.04	15.88	0.07	12.96

Note: [◎] compared with before treatment, $P<0.05$.

2.5 不同治疗方式的不良反应比较

治疗期间，研究组发生头晕 1 例，恶心 1 例，呕吐 2 例，总发生率为 8.16%（4/49）；对照组发生头晕 1 例，恶心 2 例，总发生率为 6.12%（3/49），比较差异无统计学意义（$P>0.05$）。

3 讨论

脑出血病情凶险，可引起血肿，压迫脑组织供血血管，引起周围脑组织血管微循环障碍、血脑屏障受损，造成脑组织缺血性损伤[12-14]。有研究显示，脑出血可导致机体内环境发生改变，进而影响机体的下丘脑功能，加快细胞凋亡，最终加重神经功能的恶化，危害患者生命[15-17]。随着我国医疗技术的进步，大大降低了脑出血的死亡率，但后期预后仍不理想，部分患者常规治疗后神经功能及生活能力呈恶化趋势，因此治疗应以改善患者的神经功能损伤为主[18,19]。

目前临床治疗脑出血多以联合治疗的方式为主。西比灵是治疗脑出血的常见药物之一，药效作用迅速，可透过脑屏障，阻滞钙离子内流，解除血管痉挛收缩，减轻对细胞的损伤，有研究显示，西比灵能抑制脑细胞钙超载引起的细胞凋亡，保护脑血管内皮，减轻机体的炎症反应，促进神经功能恢复[20-24]。NGF 属于神经细胞生长调节因子，分子中包括 α、β、γ 三种类型蛋白质，能促进神经突起生长，调控神经细胞生长、分化，最初用于颅脑损伤、视神经病变等疾病的治疗中，近年来被用于脑出血的治疗中[25-28]。大量研究已证实[29,30]，西比灵可减轻神经细胞损害和脑水肿，NGF 则可有效促进神经功能和生活质量恢复，但关于两种药物联合治疗脑出血报道较少。本研究结果显示，联合治疗的患者总有效率高于对照组，且治疗期间未发生不良反应，提示，联合治疗脑出血具有较高的安全性，在保证治疗效果的同时不会增加不良反应发生率。

有研究显示,脑出血后出现的血肿、脑水肿是导致患者死亡的重要因素。血肿对脑组织压迫还可激活机体凝血系统,导致大量凝血酶释放,促进白细胞趋化进而诱导多种细胞因子释放,造成血小板的大量聚集,最终破坏患者血脑屏障,加重脑组织血流障碍,导致脑组织缺血损伤和水肿[31]。Meschia J F[32]等研究也显示,脑出血后血肿的发生可改变局部脑循环,导致免疫功能紊乱及神经细胞功能凋亡,加重出血程度。因此,改善脑出血患者血肿情况催提高临床治疗效果具有重要意义,本研究就治疗期间脑出血患者血肿改善情况进行观察,结果显示,西比灵联合 NGF 治疗的患者血肿体积、水肿带体积改善情况明显优于对照组,提示西比灵联合 NGF 能降低脑出血患者血肿体积和水肿带体积。分析其原因可能是因为西比灵能扩张脑部小血管,改善脑出血微循环,提高脑组织血供,促进血肿吸收,进而减轻脑血肿和水肿程度,NGF 能增强过氧化氢酶,抑制氧自由基的释放,有利于清除血管过氧化物自由基,与西比灵实现互补作用,降低血肿和水肿面积。NIHSS 评分是目前国际上广泛应用的神经功能缺损评分,具有良好重测信度和一致性,血清 MCP-1、NSE、BDNF 是临床常用的神经功能指标,在脑出血时其水平明显异常,本研究就治疗期间脑出血患者神经功能改善情况进行观察,结果显示,西比灵联合 NGF 治疗的患者 NIHSS 评分、MCP-1、NSE 低于对照组,ADL 评分及 BDNF 高于对照组,西比灵联合 NGF 治疗促进神经功能恢复的效果更佳。Ordinola A[33]等研究也显示,西比灵联合 NGF 能加快神经功能康复。分析其原因可能是因为西比灵能抑制脑细胞钙超载引起的细胞凋亡,降低细胞损伤;NGF 则可促进新生血管形成,抑制超氧自由基的释放,修复受损的神经,进而促进髓磷脂的修复,从而减缓神经继发性损伤,两种药物联合治疗促进神经功能恢复,改善神经功能损伤情况。

综上所述,脑出血患者应用西比灵联合 NGF 效果可靠,可明显减少继发性损伤,且治疗安全性较高,值得在临床推广。

参 考 文 献(References)

[1] Lu K Y, Yuen K F, Luo J Y, et al. Therapeutic effects of acupuncture on sensory ataxia after a cerebral hemorrhage: A case report [J]. Medicine, 2020, 99(29): e21124

[2] Gao Y, Zhang Y, Li Z, et al. Persistent vegetative state after severe cerebral hemorrhage treated with amantadine: A retrospective controlled study[J]. Medicine, 2020, 99(33): e21822

[3] J Wang, Tang Z. Chinese traditional medicine for cerebral hemorrhage:clinical trial update[J]. Brain Hemorrhages, 2020, 1(4): 199

[4] Pasi, Marco, Charidimou, et al. Mixed-location cerebral hemorrhage/microbleeds: Underlying microangiopathy and recurrence risk [J]. Neurology: Official Journal of the American Academy of Neurology, 2018, 90(2): E119-E126

[5] C-Y, Zhang, X-M, et al. Simvastatin alleviates inflammation and oxidative stress in rats with cerebral hemorrhage through Nrf2-ARE signaling pathway[J]. European review for medical and pharmacological sciences, 2019, 23(14): 6321-6329

[6] Simona, Lattanzi, Francesco, et al. Neutrophil-to-Lymphocyte Ratio in Acute Cerebral Hemorrhage: a System Review [J]. Translational stroke research, 2019, 10(2): 137-145

[7] Kitamura M, Tateishi Y, Sato S, et al. Association between serum calcium levels and prognosis, hematoma volume, and onset of cerebral hemorrhage in patients undergoing hemodialysis[J]. BMC Nephrology, 2019, 20(1): 210

[8] Min, Zhang, Yang, et al. Application of Continuing Care in Patients with Mild Cerebral Hemorrhage [J]. Iranian journal of public health, 2019, 48(10): 1930-1932

[9] Qin K, Chen Y, Long H, et al. The biomarkers and potential pathogenesis of lung cancer related cerebral hemorrhage [J]. Medicine, 2019, 98(20): e15693

[10] Epstein M E. Anti-nerve growth factor monoclonal antibody: a prospective new therapy for canine and feline osteoarthritis [J]. The Veterinary record, 2019, 184(1): 20-22

[11] Saloman J L, Singhi A D, Hartman D J, et al. Systemic Depletion of Nerve Growth Factor Inhibits Disease Progression in a Genetically Engineered Model of Pancreatic Ductal Adenocarcinoma [J]. Pancreas, 2018, 47(7): 1

[12] Thompson S M, Jondal D E, Butters K A, et al. Heat Stress and Thermal Ablation Induce Local Expression of Nerve Growth Factor Inducible (VGF) in Hepatocytes and Hepatocellular Carcinoma: Preclinical and Clinical Studies[J]. Gene Expression, 2018, 19(1): 37-47

[13] Zhai Y, Yao G, Rao F, et al. Excessive nerve growth factor impairs bidirectional communication between the oocyte and cumulus cells resulting in reduced oocyte competence [J]. Reproductive Biology & Endocrinology, 2018, 16(1): 28

[14] Sanchezrodriguez A, Ariasalvarez M, Rebollar P G, et al. 148 Inmunolocalization of β-Nerve Growth Factor (NGF) in Male Reproductive Tract and NGF Levels in Serum and Seminal Plasma at Puberty and Adulthood in Rabbit [J]. Reproduction, Fertility and Development, 2018, 30(1): 214-214

[15] Xue H, Liu H, Xiao K, et al. Silk fibroin improves the release of nerve growth factor from hydroxyapatite particles maintaining its bioactivity[J]. Current Drug Delivery, 2018, 15(6): 879-886

[16] Pan Y, Fang L, Qi X, et al. Nerve Growth Factor Changes and Corneal Nerve Repair after Keratoplasty[J]. Optometry & Vision Science Official Publication of the American Academy of Optometry, 2018, 95(1): 27

[17] Martorana F, D Gaglio, Bianco M R, et al. Differentiation by nerve growth factor (NGF) involves mechanisms of crosstalk between energy homeostasis and mitochondrial remodeling [J]. Cell Death & Disease, 2018, 9(3): 391

[18] Liao S, Zhu Q, Wu Z, et al. Effects of gender and age on protein secretion in saliva of transgenic mice expressing human nerve growth factor[J]. Chinese journal of biotechnology, 2019, 35(6): 1041-1049

[19] Kolli S, Bojic S, Ghareeb A E, et al. The Role of Nerve Growth Factor in Maintaining Proliferative Capacity, Colony-Forming Efficiency, and the Limbal Stem Cell Phenotype [J]. Stem Cells, 2019, 37(1): 139-149

[20] Vines K, Li R, Geetha T, et al. Nerve growth factor receptor TrkA signaling in streptozotocin-induced type 1 diabetes rat brain [J]. Biochemical and Biophysical Research Communications, 2019, 514(3): 1285-1289

[21] Hk A, Mg B, Sf C, et al. Nerve growth factor (NGF) has an anti-tumor effects through perivascular innervation of neovessels in HT1080

fibrosarcoma and HepG2 hepatitis tumor in nude mice [J]. Journal of Pharmacological Sciences, 2019, 140(1): 1-7

[22] Cheppudira B, Trevino A, Alrufaiee O, et al. Role of nerve growth factor/tyrosine kinase receptor a signaling in the plasma of morphine tolerant rat[J]. Journal of Pain, 2018, 19(3): S73

[23] Bonini S, Lambiase A, Rama P, et al. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis [J]. Ophthalmology, 2018, 125(9): 1332-1343

[24] Monteleone, Fabrizia, Nicoletti, et al. Nerve growth factor is elevated in the CSF of patients with multiple sclerosis and central neuropathic pain[J]. Journal of Neuroimmunology, 2018, 314(1): 89-93

[25] 3D bioprinted rat Schwann cell-laden structures with shape flexibility and enhanced nerve growth factor expression[J]. Biotech, 2018, 8(8): 342

[26] Tsai M S, Lee P H, Sun C K, et al. Nerve growth factor upregulates sirtuin 1 expression in cholestasis: a potential therapeutic target [J]. Experimental & Molecular Medicine, 2018, 50(1): e426

[27] Wu J, Chen B, Li W, et al. Effects of Nerve Growth Factor shRNA Inhibition on Asthma Phenotypes in a Mouse Model of Asthma [J]. Iranian Journal of Allergy Asthma & Immunology, 2018, 17(2): 110

[28] Gu B, Ni J S, Yoshimura N. Nerve growth factor-mediated Na+ channel plasticity of bladder afferent neurons in mice with spinal cord injury[J]. European Urology Supplements, 2019, 18(1): e14

[29] Wood R L, Karlinsey K S, Thompson A D, et al. Baseline effects of lysophosphatidylcholine and nerve growth factor in a rat model of sciatic nerve regeneration after crush injury[J]. Neural Regeneration Research, 2018, 13(05): 846

[30] Xue H, Liu H, Xiao K, et al. Silk fibroin improves the release of nerve growth factor from hydroxyapatite particles maintaining its bioactivity[J]. Current Drug Delivery, 2018, 15(6): 879-886

[31] Pollins A C, Boyer R B, Nussenbaum M, et al. Comparing Processed Nerve Allografts and Assessing Their Capacity to Retain and Release Nerve Growth Factor[J]. Annals of Plastic Surgery, 2018, 81(2): 1

[32] Meschia J F. Predicting Who Will Experience Cerebral Hemorrhage When Anticoagulated [J]. Mayo Clinic Proceedings, 2020, 95(10): 2057-2059

[33] Ordinola A, Osmar S S, Marussi V, et al. Cerebral hemorrhage during the active phase of SARS-CoV-2 infection in a patient with amyloid angiopathy: case report [J]. Revista Brasileira de Terapia Intensiva, 2020, 32(4): 603-605

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[20] Zhang C, Jia Y, Jia Y, et al. Prognostic and predictive value of plasma D-dimer levels in patients with small-cell lung cancer [J]. Int J Clin Oncol, 2018, 23(6): 1070-1075

[21] Toumpanakis D, Vassilakopoulou V, Mizi E, et al. p38 Inhibition Ameliorates Inspiratory Resistive Breathing-Induced PulmonaryInflammation[J]. Inflammation, 2018, 41(5): 1873-1887

[22] Sato H, Nakamura K, Baba Y, et al. Low tidal volume ventilation with low PEEP during surgery may induce lunginflammation [J]. BMC Anesthesiol, 2016, 16(1): 47

[23] 王智利, 罗斯颖, 易茜, 等. CPAP 在先天性心脏病合并重症肺炎心功能不全患儿中的应用[J]. 临床儿科杂志, 2020, 38(1): 10-15

[24] Qi YY, Jiang GL, Wang LB, et al. Lung Function in Wheezing Infants after Acute Lower Respiratory Tract Infection and Its Association with Respiratory Outcome[J]. Chin Med J (Engl), 2017, 130(1): 4-10

[25] Gama de Abreu M, Güldner A, Pelosi P. Spontaneous breathing activity in acute lung injury and acute respiratory distress syndrome[J]. Curr Opin Anaesthesiol, 2012, 25(2): 148-155

[26] Lippi G, Favaloro EJ. D-dimer is Associated with Severity of Coronavirus Disease 2019: A Pooled Analysis [J]. Thromb Haemost, 2020, 120(5): 876-878

[27] 刘芳君, 龚财惠, 秦江蛟, 等. 肺炎支原体肺炎婴幼儿肺功能的变化[J]. 中国当代儿科杂志, 2020, 22(2): 118-123

[28] Enshaei H, Molina BG, Del Valle LJ, et al. Scaffolds for Sustained Release of Ambroxol Hydrochloride, a Pharmacological Chaperone That Increases the Activity of Misfolded β-Glucocerebrosidase [J]. Macromol Biosci, 2019, 19(8): e1900130

[29] Xiaorong D, Li M, Xuefeng L, et al. Effects of dexamethasone combined with ambroxol hydrochloride on T-Cell subsets and hearing in patients with secretory otitis media [J]. Pak J Pharm Sci, 2019, 32(3 Special): 1437-1440

[30] Xiang J, Wang P. Efficacy of pulmonary surfactant combined with high-dose ambroxolhydrochloride in the treatment of neonatal respiratory distress syndrome[J]. Exp Ther Med, 2019, 18(1): 654-658