doi: 10.13241/j.cnki.pmb.2017.11.022

胸腺肽 α-1 联合小剂量醋酸泼尼松对高龄重症患者呼吸机肺炎临床疗效及免疫功能的影响 *

孟 锐[1] 王 昱[1] 郁水华[1] 陶 琨[1] 刘 阳[2]

（1 航天中心医院 老年医学科 北京 100049；2 北京大学航天临床医学院 老年医学科 北京 100049）

摘要 目的：探讨胸腺肽 α-1 联合小剂量醋酸泼尼松对高龄重症患者呼吸机肺炎临床疗效及免疫功能影响。**方法：**收集我院就诊的 64 例呼吸机肺炎患者，随机分为实验组和对照组，每组 32 例。两组患者入院后均给予相应的基础治疗，对照组患者给予醋酸泼尼松片治疗，实验组患者在对照组的基础上给予胸腺肽治疗。观察并比较两组患者治疗前后血清 $CD4^+$、$CD8^+$、$CD4^+/CD8^+$ 水平，机械通气时间、ICU 停留时间、临床疗效以及不良反应的发生情况。**结果：**与治疗前相比，两组患者治疗后的 $CD4^+$、$CD4^+/CD8^+$ 水平均升高，$CD8^+$ 水平均下降，差异具有统计学意义(P<0.05)；与对照组相比，实验组患者 $CD4^+$、$CD4^+/CD8^+$ 水平较高，$CD8^+$ 水平较低，差异具有统计学意义(P<0.05)。与对照组相比，实验组患者的机械通气时间以及 ICU 停留时间较短，临床治疗有效率较高，差异具有统计学意义(P<0.05)；两组患者不良反应发生率比较差异无统计学意义(P>0.05)。**结论：**胸腺肽 α-1 联合小剂量激素能够提高高龄重症患者呼吸机肺炎患者的临床疗效和免疫功能。

关键词：胸腺肽 α-1；醋酸泼尼松；呼吸机肺炎；临床疗效

中图分类号：R563 **文献标识码：**A **文章编号：**1673-6273(2017)11-2087-03

Effect of Thymosin α-1 Combined with Small Dose of Prednisone Acetate on the Clinical Efficacy and Immune Function of Senile Patients with Severe Ventilator-associated Pneumonia*

MENG Rui[1], WANG Yu[1], YU Shui-hua[1], TAO Kun[1], LIU Yang[2]

(1 Department of Geriatrics, Space Center Hospital, Beijing, 100049, China;

2 Department of Geriatrics, School of aerospace medicine, Peking University, Beijing, 100049, China)

ABSTRACT Objective: To investigate the effect of thymosin α-1 combined with small dose of prednisone acetate on the clinical efficacy and immune function of senile patients with severe ventilator-associated pneumonia. **Methods:** 64 cases of pneumonia patients were randomly divided into the experimental group and the control group, 32 cases in each group. Basic treatment were given after admission in both groups, the control group was treated with prednisone acetate tablets, patients in the experimental group were given thymosin alpha. The serum $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ levels, the duration of mechanical ventilation, the length of ICU stay, clinical efficacy and incidence of adverse reactions were observed and compared between two groups of patients before and after treatment. **Results:** Compared with before treatment, the serum $CD4^+$, $CD4^+/CD8^+$ levels were significantly increased, $CD8^+$ levels were decreased in both groups of patients after treatment (P<0.05); compared with the control group, the serum $CD4^+$, $CD4^+/CD8^+$ levels were higher and $CD8^+$ level was lower in the experimental group (P<0.05); compared with the control group, the duration of mechanical ventilation and ICU stay, the effective rate of treatment was higher in the experimental group(P<0.05); no significant difference was found in the incidence of adverse reaction rate be- tween two groups of patients (P>0.05). **Conclusion:** Thymosinα-1 combined with small dose of prednisone acetate could more effectively enhance the clinical efficacy and immune function of senile patients with severe ventilator-associated pneumonia than prednisone acetate alone.

Key words: Thymosin α-1; Prednisone; Ventilator-associated pneumonia; Clinical efficacy

Chinese Library Classification(CLC): R563 Document code: A

Article ID: 1673-6273(2017)11-2087-03

前言

近年来，在重症监护病房中，机械通气(Mechanical ventilation，MV)建立人工气道的患者数量不断增加[1]，由此呼吸机相

* 基金项目：北京市自然科学基金项目(5982005)

作者简介：孟锐(1980-)，女，硕士，主治医师，研究方向：老年心血管病，电话：15810039867

(收稿日期：2016-10-16 接受日期：2016-10-30)

关性肺炎(Ventilator associated pneu-monia,VAP)的发生率也不断升高[2]。呼吸机相关性肺炎是指接受呼吸机机械通气治疗 48 小时后发生的肺炎，是应用呼吸机机械通气并发的严重的感染。重症监护的高龄患者均为患有比较严重的基础疾病或处于麻醉复苏阶段,患者免疫力低[3],在应用呼吸机进行机械通气时,在侵入性操作过程中可能造成呼吸道黏膜的损伤,加之无菌操作的不规范，病微生物或误吸入的污染物侵入患者呼吸道,或患者口咽或胃内菌丛吸入到无菌的肺部都有可能导致呼吸机肺炎的发生。在临床工作中,除注意重症监护病房的严格消毒隔离,无菌操作,预防呼吸机肺炎的的发生以外,对于已经发生的呼吸机肺炎要采取积极及时的治疗[4,5]。以往临床多给予患者抗生素治疗,但其发生率以及死亡率并没有得到明显的下降。因此,制订正确而有效的治疗措施对于治疗呼吸机肺炎具有重要意义。既往研究已经证实[6]免疫调节物质在抗感染的治疗过程中的作用较为突出，目前已成为重要的抗感染治疗方法。本实验通过观察高龄重症患者呼吸机肺炎临床疗效及免疫功能的变化,探讨胸腺肽α-1 联合小剂量激素对高龄重症患者呼吸机肺炎的治疗作用,现报道如下。

1 资料与方法

1.1 临床资料

收集 2013 年 3 月 ~2015 年 3 月于我院就诊或住院治疗的 64 例呼吸机肺炎患者,随机分为实验组和对照组,每组 32 例。实验组内患者平均年龄(68.73± 0.84)岁,组内男性 19 例,女性 13 例,呼吸机平均使用时间为(7.64± 2.29)天;对照组内患者平均年龄(67.51± 0.97)岁,组内男性 17 例,女性 15 例,呼吸机平均使用时间为(7.64± 2.29)天。所有患者符合中华医学会制定的《医院获得性肺炎诊断和治疗指南》中关于呼吸机肺炎的的诊断标准,患者呼吸机使用时间在 4~29 天,患者严重的心律失常等心血管疾病;患者无免疫系统疾病;患者无感染性疾病;患者在实验前未使用过实验相关药物,对实验药物无过敏,所有患者签署知情同意均同意进行实验。排除不符合纳入标准的患者,排除年龄在 60 岁以下,85 岁以上的患者;排除发生肺纤维化的患者;排除实验前使用过实验相关药物的患者;排除肝肾功能不全的患者;排除肝肾功能不全的患者;排除有免疫系统疾病的患者;排除对实验药物过敏的患者;排除中途死亡或转院的患者;排除不愿接受实验措施的患者。两组患者一般资料无明显差异(P<0.05)。

1.2 治疗方法

两组患者入院后均给予给予抗感染、平喘等基础治疗,对照组患者给予醋酸泼尼松片(强的松)(国药准字 H33021207 浙江仙琚制药股份有限公司),初始计量为 40 mg/ 次,口服,4 次 /d,待患者临床症状平稳后逐步减为 10 mg/ 次,口服,1 次 /d,实验组患者在对照组的基础上给予胸腺肽α1(迈普新,国药准字 H20103207 成都地奥九泓制药厂)1.6 mg/ 次,皮下注射,1 次 /d。治疗均连续 14 d,治疗期间注意保护患者脏器,及时纠正休克,并给予营养支持。

1.3 $CD4^+$、$CD8^+$、$CD4^+/CD8^+$ 水平检测

所有患者于治疗前后取外周静脉血 3 mL，采用 ELISA 法检测患者 $CD4^+$、$CD8^+$ 水平,并计算其比值。

1.4 机械通气时间以及 ICU 停留时间检测

对所有患者的机械通气时间以及患者在 ICU 的住院时间进行检测。

1.5 临床疗效评价

治疗后,评价患者的临床疗效。患者治疗后体温恢复至正常水平,临床症状明显改善,经 X 线检查,肺部阴影有所吸收为显效;患者治疗后体温接近正常,临床症状有所改善,经 X 线检查,肺部阴影无扩大为有效;患者治疗后持续发热,临床症状加重甚至出现并发症,白细胞数持续升高,经 X 线检查,肺部阴影扩大或出现新的病灶为无效。

1.6 不良反应发生情况

治疗后,对患者头晕、恶心、呕吐、肝功异常、食欲减退等不良反应的发生情况进行观察。

1.7 统计学分析

采用 SPSS 19.0 统计软件进行分析，计量数据以均数± 标准差($\bar{x}\pm s$)表示,采用 t 检验;计数资料以%表示,采用卡方检验。以 P<0.05 认为差异有统计学意义。

2 结果

2.1 两组患者治疗前后 $CD4^+$、$CD8^+$、$CD4^+/CD8^+$ 水平比较

治疗后，两组患者的 $CD4^+$、$CD4^+/CD8^+$ 水平均升高,$CD8^+$ 水平均下降 (P<0.05)；与对照组相比，实验组患者 $CD4^+$、$CD4^+/CD8^+$ 水平较高,$CD8^+$ 水平较低(P<0.05),见表 1。

表 1 两组患者治疗前后 $CD4^+$、$CD8^+$、$CD4^+/CD8^+$ 水平的比较($\bar{x}\pm s$)

Table 1 Comparison of the serum $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ levels between two groups before and after treatment($\bar{x}\pm s$)

		$CD4^+$	$CD8^+$	$CD4^+/CD8^+$
Experimental group	Before treatment	67.21± 11.02	61.28± 10.67	1.09± 0.21
	After treatment	74.14± 9.78*#	51.04± 7.17*#	1.44± 0.32*#
Control group	Before treatment	65.02± 9.78	62.11± 10.27	1.11± 0.19
	After treatment	70.17± 7.17*	55.31± 8.53*	1.27± 0.22*

Note: Compared with Before treatment, *P<0.05; Compared with the control group, #P<0.05.

2.2 两组患者机械通气时间以及 ICU 停留时间比较

与对照组相比，实验组患者的机械通气时间以及 ICU 停留时间较短(P<0.05),见表 2。

2.3 两组患者临床疗效比较

治疗后，实验组的治疗总有效率与对照组相比较高(P<0.05),见表 3。

表 2 两组患者机械通气时间以及 ICU 停留时间比较(d, $\bar{x}\pm$ s)

Table 2 Comparison of the mechanical ventilation time and ICU retention time between two groups(d, $\bar{x}\pm$ s)

	n	Mechanical ventilation time	ICU retention time
Experimental group	32	16.28± 1.19*	11.03± 1.25*
Control group	32	19.36± 1.37	14.29± 1.46

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

表 3 两组患者临床疗效比较(%, $\bar{x}\pm$ s)

Table 3 Comparison of the clinical curative effect between two groups(%, $\bar{x}\pm$ s)

	Excellent	Effective	Invalid	Total effective rate
Experimental group	19(59.38)	12(37.50)	1(3.13)	31(86.88)*
Control group	11(34.38)	12(37.50)	9(28.13)	23(71.88)

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

2.4 两组患者不良反应发生率比较

治疗期间,对照组患者发生头晕 1 例、恶心 1 例、食欲减退 1 例,不良反应发生率为 9.38%,实验组患者头晕 1 例,食欲减退 1 例,不良反应发生率为 6.25%,两组患者不良反应发生率差异无统计学意义(P>0.05),两组患者经及时治疗后不良反应均明显缓解,未对实验造成影响。

3 讨论

医院感染是指病人在住院期间在医院内获得的感染,已经成为近年来全球性问题[7]。其中,在重症监护病房内的住院患者常见的医院感染类型以呼吸机肺炎多见,并已经成为威胁机械通气患者生命的主要问题[8]。随着呼吸机在重症监护病房的广泛应用,呼吸机相关肺炎的发生率也不断升高,延长了患者的住院时间、患者的治疗费用也因而增加,推迟了患者的康复,延长了患者的机械通气的时间[9]。由于患者存在较为严重的基础疾病,因此呼吸机肺炎不仅影响疾病预后,还威胁患者生命[10]。据统计[11],呼吸机相关性肺炎的发生率约为 18%~60%之间,其中约一半的患者最后死亡。

胸腺肽 α1 (thymosinα1)已经被证实能够提高患者的免疫功能,对肝炎、免疫缺陷类疾病都取得了较好的治疗效果[12,13]。胸腺肽 α1 能够对淋巴细胞的发育和分化产生积极的调节作用,促进 T 细胞的增殖、分化以及成熟,对 $CD4^+/CD8^+$ 的比值产生良性的调节作用;并能调整患者免疫功能的同时抑制促炎因子水平的升高,减轻炎症介质造成的损伤[14]。老年高龄患者由于体内器官以及患者的生理功能发生减退, 呼吸道免疫能力下降,使重症监护病房的老年患者极易发生感染,且不易被控制,导致机械通气后呼吸机性关性肺炎的发生[15]。有研究证实[16]呼吸机肺炎以革兰阴性菌感染为主, 细菌入侵后内毒素被激活,大量释放炎症介质,导致全身性炎症反应。T 细胞亚群与集体的免疫系统功能关系密切。研究表明[17]$CD4^+$ 为辅助性诱导性 T 细胞的亚群而 $CD8^+$ 代表抑制性和细胞毒性 T 细胞亚群,二者能够反应机体的免疫系统功能。高龄老年患者的 T 细胞水平本身由于年龄的增长而导致其增殖能力以及功能下降,导致体内的疫应答迟缓,患者机体免疫能力下降,表现为 $CD4^+$ 细胞水平的减少以及 $CD8^+$ 细胞数量增高 [19,20], 从而造成免疫系统的失衡。本实验结果显示:治疗后,两组患者的 $CD4^+$、$CD4^+/CD8^+$ 水平均升高,$CD8^+$ 水平均下降, 实验组患者 $CD4^+$、$CD4^+/CD8^+$ 水平较对照组高,$CD8^+$ 水平较低[18],提示应用胸腺肽 α1 促进免疫细胞的分化,升高免疫细胞的数量,提高患者的免疫功能,促进疾病的向愈。

综上,胸腺肽 α-1 联合小剂量激素能够提高高龄重症患者呼吸机肺炎患者的临床疗效和免疫功能。

参 考 文 献(References)

[1] Gunasekera P, Gratrix A. Ventilator-associated pneumonia [J]. BJA Education, 2016, 16(6): 198-202

[2] Matthay M A. Biomarkers to exclude the diagnosis of ventilator-associated pneumonia[J]. Thorax, 2015, 70(1): 5-6

[3] Bouadma L, Sonneville R, Garrouste-Orgeas M, et al. Ventilator-associated events: prevalence, outcome, and relationship with ventilator-associated pneumonia [J]. Critical care medicine, 2015, 43 (9): 1798-1806

[4] Nseir S, Povoa P, Salluh J, et al. Is there a continuum between ventilator-associated tracheobronchitis and ventilator-associated pneumonia? [J]. Intensive care medicine, 2016, 42(7): 1190-1192

[5] Speck K, Rawat N, Weiner N C, et al. A systematic approach for developing a ventilator-associated pneumonia prevention bundle [J]. American journal of infection control, 2016, 44(6): 652-656

[6] Damas P, Frippiat F, Ancion A, et al. Prevention of Ventilator-Associated Pneumonia and Ventilator-Associated Conditions: A Randomized Controlled Trial With Subglottic Secretion Suctioning[J]. Survey of Anesthesiology, 2016, 60(2): 51-53

[7] Zalts R, Neuberger A, Hussein K, et al. Treatment of carbapenem-resistant Acinetobacter baumannii ventilator-associated pneumonia: retrospective comparison between intravenous colistin and intravenous ampicillin-sulbactam [J]. American journal of therapeutics, 2016, 23 (1): e78-e85

[8] Banupriya B, Biswal N, Srinivasaraghavan R, et al. Probiotic prophylaxis to prevent ventilator associated pneumonia (VAP) in children on mechanical ventilation: an open-label randomized controlled trial [J]. Intensive care medicine, 2015, 41(4): 677-685

[9] Branch-Elliman W, Wright S B, Howell M D. Determining the Ideal Strategy for Ventilator-associated Pneumonia Prevention. Cost-Benefit Analysis [J]. American journal of respiratory and critical care medicine, 2015, 192(1): 57-63

[10] Hajiesmaeili M, Moradimoghadam O, Sedaghat A, et al. Evaluation of Ventilator-Associated Pneumonia According to Stress Related Mucosal Disease Prophylaxis Regimen in the Intensive Care Unit [J]. Archives of Anesthesiology and Critical Care, 2015, 1(4): 116-119

(下转第 2067 页)

[3] Liu Bin, Li Gang, Xu Bo, et al. Glucocorticoids-induced osteonecrosis of the femoral head: adipogenic differentiation and treatment progress [J]. Chinese Journal of Tissue Engineering Research, 2014, 18 (29): 4730-4735

[4] Jiang chuan, Shang Jiang-yinzi, Li Zhe, et al. Lanthanum chloride attenuates osteoclast formation and function via the downregulation of rankl-Induced nf-κb and nfatc1 activities[J]. J Cell Physiol, 2016, 231 (1): 142-151

[5] Zheng Hong, He Bing, Zeng Rong, et al. Effect of Recombinant Human Osteoprotegerin on the Polyethylene Particles-Induced Peripheral Serum IL-6 and TNF-α Expression of Patients after Artificial Joint Replacement [J]. Progress in Modern Biomedicine, 2013, 13 (23): 4467-4469

[6] ARCO (Association Research Circulation Osseous). Committee on Terminology and Classification[J]. ARCO News, 1992, 4 (1): 41-46

[7] Mont MA, Hungerford DS. Non-traumatic avascular necrosis of the femoral head [J]. J Bone Joint Surg (Am), 1995, 77(3): 459

[8] Zhao Fu-tao, Han Xing-hai, Guan Jian-long. Ameliorative effect of hip X-ray radiotherapy on the tip involvement in patients with ankylosing spondylitis: 3-year follow-up[J]. Chinese Journal of Clinical Rehabilitation, 2005, 9(34): 88-91

[9] Wang Xing-shan, Zhuang Qian-yu, Weng Xi-sheng, et al. Etiological and clinical analysis of osteonecrosis of the femoral head in Chinese patients[J]. Chin Med J (Engl), 2013, 126(2): 290-295

[10] Wang Jian-zhong, Wu Yong-gang, Dong Hui-zhen. Effects of atorvastatin on the expression levels of tissue inhibitor of metalloproteinases timps / matrix metalloproteinases in bone tissues of femoral head necrosis induced by glucocorticoid [J]. Chinese Journal of Bone and Joint, 2014, 3(11): 865-870

[11] Busillo JM, Cidlowski JA. The five Rs of glucocorticoid action during inflammation: ready, reinforce, repress, resolve, and restore [J]. Trends Endocrinol Metab, 2013, 24(3): 109-119

[12] Ponnapakkam T, Katikaneni R, Sakon J, et al. Treating osteoporosis by targeting parathyroid hormone to bone [J]. Drug discovery today, 2014, 19(3): 204-208

[13] Li Yi-zhou, Wang Yuan, Chen Jun-yu, et al. Correlation between OPG/RANK/RANKL and steroid induced avascular necrosis of the femoral head [J]. Chinese Journal of Bone and Joint Injury, 2015, 30 (8): 892-893

[14] Xiong Qi, Zhang Li-cheng, Zhang Li-hai, et al. Effects of recombinant human osteoprotegerin and recombinant RANK protein on the differentiation of osteoclast precursors [J]. China J Orthop Trauma, 2013, 26(4): 324-327

[15] Kadri A, Ea HK, Bazille C, et al. Osteoprotegerin inhibits cartilage degradation through an effect on trabecular bone in murine experimental osteoarthritis [J]. Arthritis Rheum, 2008, 58(8): 2379-2386

[16] Zhong Wen-yi, Wu Qi-shan, Gao Li, et al. Effect of recombinant human osteoprotegerin on RANKL, OPG protein expression in alveolar bone tissue of rat with periodontitis [J]. Chongqing Medicine, 2015, 44 (14): 1879-1881

[17] Daugaard H, Elmengaard B, Andreassen T T, et al. Systemic intermittent parathyroid hormone treatment improves osseointegration of press-fit inserted implants in cancellous bone: A canine study [J]. Acta orthopaedica, 2012, 83(4): 411-419

[18] Gao Fei, Zhang Yu, Wang Hong-wei, et al. Correlations of osteoporotic vertebral deformation to bone mineral density and bone metabolic levels [J]. Chin Orthop J Clin Basic Res, 2015, 7 (3): 133-140

[19] Zhang Meng-meng. Bone metabolism indexes in bone remodeling[J]. Chin J Osteoporos, 2013, 19(8): 866-873

[20] Yao Li, Zhao Jing, Zhou Qiang, et al. The Effect of Qutanhuayulishi Decoction on Synocial IL-1β, MMP-1 and Serum IL-1β, MMP-1, COMP and CTX-Ⅱ in Rats with Knee Osteoarthritis [J]. Chinese J Trad Med Traum & Orthop, 2015, 23(11): 5-8, 14

（上接第 2089 页）

[11] Ego A, Preiser J C, Vincent J L. Impact of diagnostic criteria on the incidence of ventilator-associated pneumonia [J]. CHEST Journal, 2015, 147(2): 347-355

[12] Valachis A, Samonis G, Kofteridis D P. The role of aerosolized colistin in the treatment of ventilator-associated pneumonia: a systematic review and metaanalysis [J]. Critical care medicine, 2015, 43 (3): 527-533

[13] Nair G B, Niederman M S. Ventilator-associated pneumonia: present understanding and ongoing debates[J]. Intensive care medicine, 2015, 41(1): 34-48

[14] Damas P, Frippiat F, Ancion A, et al. Prevention of ventilator-associated pneumonia and ventilator-associated conditions: a randomized controlled trial with subglottic secretion suctioning [J]. Critical care medicine, 2015, 43(1): 22-30

[15] El-Rabbany M, Zaghlol N, Bhandari M, et al. Prophylactic oral health procedures to prevent hospital-acquired and ventilator-associated pneumonia: A systematic review [J]. International journal of nursing studies, 2015, 52(1): 452-464

[16] Younan D, Lin E, Griffin R, et al. Early trauma-induced coagulopathy is associated with increased ventilator-associated pneumonia in spinal cord injury patients[J]. Shock, 2016, 45(5): 502-505

[17] Leonard K L, Borst G M, Davies S W, et al. Ventilator-Associated Pneumonia in Trauma Patients: Different Criteria, Different Rates[J]. Surgical infections, 2016, 17(3): 363-368

[18] Dimopoulos G, Matthaiou D K. Duration of therapy of ventilator-associated pneumonia [J]. Current opinion in infectious diseases, 2016, 29(2): 218-222

[19] Chastre J. Ventilator-associated pneumonia and ventilator-associated conditions: apples are not oranges (mix only in a salade de fruits!)[J]. Critical care medicine, 2015, 43(1): 227-229

[20] Lutmer J E, Brilli R J. Unanswered Questions and Consternation: The Ventilator-Associated Pneumonia Diagnostic Challenge Continues[J]. Pediatric Critical Care Medicine, 2016, 17(2): 175-176