

doi: 10.13241/j.cnki.pmb.2019.14.036

鲑鱼降钙素联合糖皮质激素吸入治疗 COPD 合并骨质疏松的疗效 及对血清 PINP、 β -CTX、MMP-9 水平的影响 *

杜娟¹ 管慧² 刘英³ 刘慧红⁴ 林祥晓⁴

(1 凉山州第二人民医院 呼吸内科 四川 凉山 615000; 2 凉山州第二人民医院 内分泌科 四川 凉山 615000;

3 凉山州第二人民医院 呼吸内科肺功能室 四川 凉山 615000; 4 济宁医学院附属医院 呼吸内二科 山东 菏泽 272001)

摘要 目的:研究鲑鱼降钙素联合糖皮质激素吸入治疗慢性阻塞性肺疾病(Chronic obstructive pulmonary disease COPD)合并骨质疏松的疗效及对血清 I 型前胶原氨基端肽 (Amino terminal peptide of procollagen type I PINP)、 β -胶原降解产物(β -Cterminal telopeptide of type I collagen β -CTX)、基质金属蛋白酶(matrix metalloproteinase-9 MMP-9)水平的影响。**方法:**选取 2017 年 3 月至 2018 年 4 月我院收治的 97 例 COPD 合并骨质疏松患者,按照随机数表法分为观察组(47 例)和对照组(50 例),两组均采用常规治疗,对照组在此基础上采用糖皮质激素吸入治疗,观察组在对照组的基础上采用鲑鱼降钙素治疗。观察和比较两组患者的疗效,治疗前后肺功能指标(一秒钟用力呼气量(forced expiratory volume in one second FEV1)、第一秒用力呼气容积占用力肺活量百分比(Forced expiratory volume in the first second is the percentage of forced vital capacity FEV1/FVC)、血清 PINP、 β -CTX、MMP-9 水平、腰椎骨密度、股骨颈骨密度的变化。**结果:**治疗后,观察组总有效率显著高于对照组[91.48%(43/47) vs. 70.00%(35/50)]($P < 0.05$); FEV1、PO2、FEV1/FVC 水平均显著高于对照组[(85.20 $\pm$ 13.72)% vs. (70.62 $\pm$ 11.37)%, (76.30 $\pm$ 8.64)mmHg vs. (62.49 $\pm$ 7.13)mmHg, (68.08 $\pm$ 11.34)% vs. (60.84 $\pm$ 9.75)%]($P < 0.05$); PINP、 β -CTX、MMP-9 水平均显著低于对照组[(17.02 $\pm$ 3.67)mg/L vs. (14.86 $\pm$ 3.13)mg/L, (93.20 $\pm$ 8.01)ng/L vs. (117.39 $\pm$ 11.42)ng/L, (47.24 $\pm$ 3.75)ng/mL vs. (60.26 $\pm$ 4.67)ng/mL]($P < 0.05$); 腰椎骨密度、股骨颈骨密度水平均显著高于对照组[(1.12 $\pm$ 0.25)g/cm² vs. (0.89 $\pm$ 0.23)g/cm², (1.14 $\pm$ 0.23)g/cm² vs. (0.90 $\pm$ 0.21)g/cm²]($P < 0.05$)。结论:鲑鱼降钙素联合糖皮质激素吸入治疗 COPD 合并骨质疏松的疗效显著优于单用糖皮质激素吸入治疗,其能够更有效改善患者肺功能,调节血钙,提高骨密度,缓解骨痛,可能与其降低血清 PINP、 β -CTX、MMP-9 的水平有关。

关键词:鲑鱼降钙素;糖皮质激素;慢性阻塞性肺疾病;骨质疏松

中图分类号:R563 文献标识码:A 文章编号:1673-6273(2019)14-2767-04

Effect of Salmon Calcitonin Combined with Glucocorticoid Inhalation on the COPD Complicated with Osteoporosis and Its Influence on the Serum PINP, Beta-CTX and MMP-9 Levels*

DU Juan¹, GUAN Hui², LIU Ying³, LIU Hui-hong⁴, LIN Xiang-xiao⁴

(1 Department of Respiratory Medicine, Liangshan second people's Hospital, Liangshan, Sichuan, 615000, China;

2 Department of Endocrinology, Liangshan second people's Hospital, Liangshan, Sichuan, 615000, China;

3 Lung function Room, Department of Respiratory Medicine, Liangshan second people's Hospital, Liangshan, Sichuan, 615000, China;

4 Department of Respiratory Medicine, affiliated Hospital of Jining Medical College, Heze, Shandong, 272001, China)

ABSTRACT Objective: To study the effect of salmon Calcitonin combined with glucocorticoid Inhalation on the Chronic obstructive pulmonary disease (COPD) complicated with osteoporosis and Its Influence on the serum (Amino terminal peptide of procollagen type I PINP), (β -Cterminal telopeptide of type I collagen Beta-CTX) and (matrix metalloproteinase-9 MMP-9). **Methods:** 97 cases of COPD patients with osteoporosis admitted to our hospital from March 2017 to April 2018 were selected as the research objects. According to the random number table, those patients were divided into the observation group (n=47) and the control group (n=50). Both groups were treated with conventional treatment, the control group was additionally treated by glucocorticoid inhalation, while the observation group was treated by salmon-calcitonin on the basis of the control group. The therapeutic efficacy, the indexes of pulmonary function before and after treatment (forced expiratory volume in one second FEV1), (force expiratory volume in the first second is the percentage of forced vital capacity FEV1/FVC), the serum levels of PINP, beta-CTX, MMP-9, Lumbar bone mineral density and femoral neck femoral density were compared between two groups. **Results:** After treatment, the total effective rate of observation group was statistically higher than that in the control group[91.48%(43/47) vs. 70.00%(35/50)]($P < 0.05$); the FEV1, PO2 and FEV1/FVC levels were significantly high-

* 基金项目:四川省卫生厅科研基金资助项目(1002040)

作者简介:杜娟(1971-),女,本科,副主任医师,研究方向:间质性肺部疾病、重症感染、无创呼吸技术,

电话:18113359333, E-mail: pkng456ygz@163.com

(收稿日期:2019-02-23 接受日期:2019-03-18)

er than those in the control group[(85.20± 13.72)% vs. (70.62± 11.37)%, (76.30± 8.64)mmhg vs. (62.49± 7.13)mmhg, (68.08± 11.34)% vs. (60.84± 9.75)%]($P<0.05$); the levels of PINP, beta-CTX and MMP-9 were significantly lower than those of the control group [(17.02± 3.67)mg/L vs. (14.86± 3.13)mg/L, (93.20± 8.01)ng/L vs. (117.39± 11.42)ng/L, (47.24± 3.75)ng/mL vs. (60.26± 4.67)ng/mL]($P<0.05$); the bone mineral density and femoral neck femoral density were significantly higher in the lumbar spine than those in the control group [(1.12± 0.25)g/cm² vs. (0.89± 0.23)g/cm², (1.14± 0.23)g/cm² vs. (0.90± 0.21)g/cm²]($P<0.05$). **Conclusion:** Salmon calcitonin combined with glucocorticoid inhalation is more effective than glucocorticoid inhalation alone in the treatment of COPD complicated with osteoporosis. It can more effectively improve clinical symptoms and lung function, regulate the blood calcium, increase the bone mineral density and relieve the bone pain. It may be related to the reduction of serum PINP, beta-CTX and MMP-9 levels.

Key words: Salmon Calcitonin; Glucocorticoid; Chronic obstructive pulmonary disease; Osteoporosis

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

Article ID: 1673-6273(2019)14-2767-04

前言

慢性阻塞性肺疾病是一种全身长期慢性缺氧性疾病,以持续气流受限并进行性发展为特征,临床表现为咳嗽、咳痰、气短、呼吸困难、胸闷、疲乏等,患病率及病死率均较高^[1]。目前,临床上对于慢性阻塞性肺疾病的发病机制还尚不完全明确,但基础研究表明^[2]环境、个体、吸烟、化学物质、粉尘、呼吸道感染等均为其诱发因素。若未及时得到有效的治疗,慢性阻塞性肺疾病可发展为肺动脉高压、呼吸衰竭,给患者的日常生活和生命健康带来了严重的威胁^[3]。骨质疏松是一种全身性骨骼疾病,以骨微细结构退化、骨量减少、骨强度降低为特征,可增加患者的骨脆性和骨折危险性^[4]。近年来研究显示^[5]COPD与骨质疏松疾病之间存在密切的关系,发病率极高。

糖皮质激素是机体内极为重要的一类调节分子,能够改善患者的肺功能和减少慢性阻塞性肺疾病加重次数。鲑鱼降钙素被认为是目前临床上缓解骨质疏松患者骨痛的首选药物之一,能够抑制骨吸收、改善骨密度^[6]。有学者研究表明^[7,8]I型前胶原氨基端肽(Amino terminal peptide of procollagen type I PINP)、β-胶原降解产物(β-Cterminal telopeptide of type I collagen β-CTX)、基质金属蛋白酶(matrix metalloproteinase-9 MMP-9)在COPD合并骨质疏松疾病的发生、发展中发挥了重要作用。本研究旨在探讨鲑鱼降钙素联合糖皮质激素吸入治疗COPD合并骨质疏松的疗效及其可能的作用机制,结果报道如下。

1 资料与方法

1.1 一般资料

收集2017年3月至2018年4月我院收治的97例COPD合并骨质疏松患者,均符合慢性阻塞性肺疾病诊疗规范诊断标准、世界卫生组织(WHO)骨质疏松诊断标准^[9]。纳入标准:年龄<80岁;无其他严重疾病;无需机械通气治疗;心肝肾重要器官正常者;无其他代谢性骨病;配合研究者;对本次治疗药物不过敏者;排除标准:患有精神疾病;患有糖尿病;过敏体质;腰部或髋部骨密度均不符合OP诊断;妊娠期或哺乳期者;同时参与其他研究者。按照随机数表法分为观察组($n=47$)和对照组($n=52$),观察组男28例,女19例,年龄45~75岁,平均(63.19± 3.58)岁,病程5~15年,平均(6.30± 2.48)年;对照组男30例,女20例,年龄46~75岁,平均(62.87± 3.60)岁,病程6~15年,平均(5.96± 2.51)年。两组患者在性别、年龄、病程等一般资料上无差

异($P>0.05$),具有可比性。

1.2 治疗方法

两组患者入院后均给予常规治疗,包括解痉平喘、COPD对症治疗、补钙,对照组在基础治疗上,采用糖皮质激素吸入治疗,雾化吸入布地奈德混悬液(生产厂家:澳大利亚阿斯利康有限公司)1~2 mg,每天2次,治疗疗程为7~10天。观察组在对照组的基础上,采用鲑鱼降钙素(生产厂家:银谷制药有限责任公司)治疗,每次100 μg,以皮下注射方式治疗。两组治疗疗程为2个月。

1.3 观察指标

观察和比较两组患者的疗效,治疗前后肺功能指标((一秒用力呼气量(forced expiratory volume in one second FEV₁)/第一秒用力呼气容积占用力肺活量百分比(Forced expiratory volume in the first second is the percentage of forced vital capacity FEV₁/FVC))、血清PINP、β-CTX、MMP-9水平、腰椎骨密度、股骨颈股密度的变化。

1.3.1 指标检测 分别于两组患者治疗前后采集静脉血,离心分离血清后等待检测,采用双抗体夹心法检测PINP、β-CTX水平,试剂盒来自武汉博士德生物工程有限公司;采用酶联免疫吸附法检测MMP-9水平,试剂盒来自上海天呈科技有限公司。采用Challenger双能X线骨密度仪(生产厂家:法国DMS公司)检测患者的腰椎骨密度、股骨颈股密度。

1.3.2 肺功能指标 采用肺功能检测仪MasterScope(德国耶格公司)检测患者的肺功能指标(FEV₁、PO₂、FEV₁/FVC)^[10]。

1.4 疗效评定标准

临床症状完全消失、患者疼痛缓解≥2级为显效;临床症状明显改善、患者疼痛缓解1级为有效^[11];临床症状、患者疼痛无变化为无效。总有效率=显效+有效。

1.5 统计学分析

使用SPSS18.0统计软件进行t检验,数据均符合正态分布,计量资料以($\bar{x} \pm s$)表示,采用t检验,计数资料以[(例)%]表示,用 χ^2 检验比较,采用 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组患者治疗疗效对比

治疗后,观察组治疗总有效率为91.48%,显著高于对照组(70%, $P<0.05$),见表1。

表 1 两组患者治疗疗效的对比[例(%)]

Table 1 Comparison of therapeutic effects between two groups of patients[n(%)]

Groups	n	Effective	Effective	Invalid	Total efficiency
Observation group	47	37(78.72)	6(12.76)	4(8.51)	43(91.48)
Control group	50	27(54.00)	8(16.00)	15(30.00)	35(70.00)

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

2.2 两组患者治疗前后肺功能对比

两组患者治疗前 FEV1、PO₂、FEV1/FVC 水平比较差异无统计学意义($P<0.05$)。治疗后,两组患者 FEV1、PO₂、FEV1/FVC

水平均较治疗前显著升高($P<0.05$),且观察组以上指标均显著高于对照组($P<0.05$),见表 2。

表 2 两组患者治疗前后肺功能指标的对比($\bar{x}\pm s$)Table 2 Comparison of the lung function between two groups before and after treatment($\bar{x}\pm s$)

Groups	n	FEV1(%)		PO ₂ (mmhg)		FEV1/FVC(%)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	47	46.02± 10.37	85.20± 13.72**	55.29± 6.37	76.30± 8.64**	57.40± 9.27	68.08± 11.34**
Control group	50	46.10± 10.03	70.62± 11.37 [#]	56.01± 6.10	62.49± 7.13 [#]	56.93± 9.20	60.84± 9.75 [#]

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

2.3 两组患者治疗前后血清 PINP、β-CTX、MMP-9 水平对比

两组患者治疗前血清 PINP、β-CTX、MMP-9 水平比较差异无统计学意义($P<0.05$)。治疗后,两组患者血清 PINP、β-CTX、

MMP-9 水平均较治疗前显著降低($P<0.05$),观察组以上指标均明显低于对照组($P<0.05$),见表 3。

表 3 两组患者治疗前后血清 PINP、β-CTX、MMP-9 水平对比($\bar{x}\pm s$)Table 3 Comparison of the serum PINP, beta -CTX and MMP-9 levels between two groups before and after treatment($\bar{x}\pm s$)

Groups	n	PINP(mg/L)		β-CTX(ng/L)		MMP-9(ng/mL)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	47	11.47± 2.94	17.02± 3.67**	145.56± 15.29	93.20± 8.01**	83.40± 6.29	47.24± 3.75**
Control group	50	12.01± 2.90	14.86± 3.13 [#]	146.02± 14.97	117.39± 11.42 [#]	84.01± 6.38	60.26± 4.67 [#]

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

2.4 两组患者治疗前后腰椎骨密度、股骨颈股密度的对比

两组患者治疗前腰椎骨密度、股骨颈股密度比较差异无统计学意义($P<0.05$)。治疗后,两组患者腰椎骨密度、股骨颈股密

度水平均较治疗前显著升高($P<0.05$),观察组以上指标均显著高于对照组($P<0.05$),见表 4。

表 4 两组患者治疗前后腰椎骨密度、股骨颈股密度情况对比($\bar{x}\pm s$, g/cm²)Table 4 Comparison of the lumbar bone mineral density and femoral neck femoral density between two groups before and after treatment($\bar{x}\pm s$, g/cm²)

Groups	n	Lumbar spine bone mineral density		Femoral neck femoral density	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	47	0.70± 0.23	1.12± 0.25**	0.69± 0.21	1.14± 0.23**
Control group	50	0.69± 0.22	0.89± 0.23 [#]	0.71± 0.20	0.90± 0.21 [#]

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

3 讨论

慢性阻塞性肺疾病(COPD)是可治可防的呼吸系统疾病,但具有病情反复、死亡率高的特点^[12]。研究表明^[13,14]COPD 的发病机制主要在于炎症反应,机体需要不断的产生代偿低氧状态产生保护性反应,从而促使骨代谢指标出现代偿性增高^[15]。骨质疏松是 COPD 的常见并发症,与缺氧和运动功能下降存在密切的关系^[16]。以往有研究表明^[17],COPD 患者骨质疏松的发生率

显著高于正常人,患者骨质疏松后又易增加 COPD 患者脊柱压缩性骨折的发生率。

糖皮质激素是人体重要的调节剂,能够抑制巨噬细胞、免疫细胞、B 细胞之间相互传递,可有效抑制免疫反应,减少对细胞的损伤,改善 COPD 患者的肺功能,减少发病次数^[18,19]。本研究显示两组患者采用糖皮质激素吸入治疗后,临床症状及肺功能指标均较治疗前明显改善,说明糖皮质激素在改善 COPD 疾病上具有一定的疗效^[20]。但有研究表明^[21,22]单独使用糖皮质激

素治疗可增加发生骨质疏松的风险,可能是由于长期的高激素影响导致骨吸收增加及骨细胞凋亡。因此,在使用激素治疗 COPD 的时候应严格控制使用剂量^[23]。

鲑鱼降钙素是抑制甲状旁腺的激素之一,具有调节钙代谢的作用,能够抑制溶骨、降低骨钙丢失、抑制破骨细胞活性,延缓破骨细胞生长速度,刺激骨细胞的活性和形成,具有降低血钙作用^[24]。降钙素水平会随着年龄的增长而降低,女性更为显著,导致降钙素出现分泌障碍^[25]。本研究显示采用联合鲑鱼降钙素治疗的患者治疗疗效、肺功能及腰椎骨密度、股骨颈股密度均较单独采用糖皮质激素吸入治疗的患者效果更好,提示两种药物联合治疗能够有效的提高治疗效果,改善临床症状、肺功能^[26]。

临床上对于骨质疏松的诊断多根据骨密度检测和临床症状判断,但其敏感度较低,PINP、 β -CTX 由成骨细胞分泌,稳定性和骨密度的特异性均较高,通过观察 PINP、 β -CTX 水平变化能够评估骨质疏松患者的病情,为临床提供治疗依据^[27]。基究表明^[28]MMP-9 在 COPD 发展的不同阶段所表达的水平是非常明显的不同,MMP-9 水平显著高于正常人。由于 MMP-s 是一种较为重要的调节因素,可有效降解细胞外基质所有成分^[29]。MMP-9 在破骨细胞中呈现特异性表达,对骨质疏松起促进作用,若 MMP-9 的表达显著升高,则表明破骨细胞的骨吸收能力也不断加强^[30]。本研究结果显示采用联合鲑鱼降钙素治疗的患者 PINP、 β -CTX、MMP-9 水平显著低于单独采用糖皮质激素吸入治疗的患者,提示两种药物联合治疗能够进一步的降低 PINP、 β -CTX、MMP-9 水平,提高治疗疗效。

综上所述,鲑鱼降钙素联合糖皮质激素吸入治疗 COPD 合并骨质疏松的疗效显著优于单用糖皮质激素吸入治疗,其能够更有效改善患者肺功能,调节血钙,提高骨密度,缓解骨痛,可能与其降低血清 PINP、 β -CTX、MMP-9 的水平有关。

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