doi: 10.13241/j.cnki.pmb.2015.02.025

盐酸氨基葡萄糖联合塞来昔布治疗不同程度膝关节骨性关节炎的临床研究

唐 进 杨 涛△ 熊小江 关 群 刘王卫

(重庆三峡中心医院骨科 重庆 404000)

摘要 目的:研究盐酸氨基葡萄糖联合塞来昔布治疗不同程度膝关节骨性关节炎的临床价值。**方法:**选取 2011 年 1 月至 2014 年 2 月已被收治的符合标准的病例共 150 例,按照病情轻重分为轻度(64 例)、中度(52 例)及重度(34 例)3 组,各组又随机等分为治疗组和对照组两组,治疗组给盐酸氨基葡萄糖联合塞来昔布治疗,对照组仅给予盐酸氨基葡萄糖治疗,分别于给药第 2、4 、6 周以及停药 8、12 周观察两组患者经两种不同的治疗方案治疗后患者的 Lequesne 评分有无统计学差异。**结果:**轻度:两组停药 12 周后 Lequesne 评分仍低于治疗前,差异有统计学意义(P<0.05),停药 12 周时治疗组低于对照组,差异有统计学意义(P<0.05)。中度:用药 2 周、4 周、6 周及停药 8 周时两组相比差异均有统计学意义 (P<0.05)。重度: 对照组与治疗组在给药 4 周及给药 6 周时其 Lequesne 评分差异有统计学意义(P<0.05),停药后均无统计学意义(P>0.05)。 **结论:**单用盐酸氨基葡萄糖可改善轻度膝关节骨性关节炎的临床症状,对于中度患者联合非类固醇类抗炎药类有较好疗效,对于重度患者两种方式都无明显效果。

关键词:盐酸氨基葡萄糖;塞来昔布;膝关节;骨性关节炎;临床价值

中图分类号:R684.3 **文献标识码:**A **文章编号:**1673-6273(2015)02-294-04

The Clinical Study of Glucosamine Hydrochloride Combined with Celecoxib for Different Degrees of Knee Osteoarthriti

TANG Jin, YANG Tao△, XIONG Xiao-jiang, GUAN Qun, LIU Wang-wei

(Department of orthopedics,Three Gorges Central Hospital of Chongqing, Chongqing, 404000, China)

ABSTRACT Objective: To study the clinical significance of glucosamine hydrochloride combined with celecoxib in the treatment of different degrees of knee osteoarthriti. **Methods:** 150 cases who were in accordance with the standards in our hospital from January 2012 to February 2014 were selected and divided into the mild group, moderate group and severe group according to the severity, and each group was further equally divided into the treatment group and the control group randomly, the treatment group was given glucosamine hydrochloride combined with celecoxib, while the control group was given glucosamine hydrochloride. Lequesne score were recorded at 2, 4, 6 weeks after drug administration and 8 and 12 weeks after drug withdrawal, data were compared between the two groups and among different time points. **Results:** In the mild group, the lequesne score of the two groups at 12 weeks after drug withdrawal were lower than that before the treatment, the difference was statistically significant (P<0.05), the lequesne score in the treatment group was lower than that in the control group in 12 weeks after drug withdrawal, the difference was statistically significant (P<0.05); In moderate group, there were statistically significantly differences in the comparison of the two groups at the time of 2, 4, 6 weeks after drug administration and 8 weeks after drug withdrawal (P<0.05); In severe group, there were statistically significantly differences in comparison of the two groups at 4 and 6 weeks after drug administration (P<0.05), and there were no statistically significant differences after drug withdrawal(P>0.05).**Conclusions:** Using pure glucosamine hydrochloride could improve the clinical symptoms in patients with mild knee osteoarthriti, glucosamine hydrochloride combined with celecoxib has good curative effects for moderate patients, while neither of the two treatment methods has obvious effects on severe patients.

Key words: Glucosamine hydrochloride; Celecoxib; Knee; Osteoarthriti; Clinical significance

Chinese Library Classification(CLC): R684.3 Document code: A

Article ID:1673-6273(2015)02-294-04

前言

膝关节骨性关节炎是骨科的一种常见疾病,主要病理特征为膝关节软骨变性、破坏及骨质增生[1,2]。骨性关节炎的发病机理主要为基质金属蛋白酶和磷脂酶 A2 的激活和炎性因子如白细胞介素、前列腺素 E2 等的产生增加,造成软骨的损伤和引发炎症反应[3,4]。其发病率逐年上升,膝关节骨性关节炎患者的生活量严重受损,亟需研究出有效治疗方案从而改善患者生活质量,减轻社会疾病负担。临床传统治疗方式为手术治疗或者药物治疗。氨基葡萄糖是临床应用最广的特异性药物。但是有学者研究发现氨基葡萄糖治疗骨性关节炎的效果不明显。非类

作者简介:唐进(1984-),男,硕士研究生,主治医师,从事骨关节外科方面的研究,E-mail:tangjin1984@126.com

△通讯作者:杨涛(1978-),男,本科,主治医师,从事骨关节科方面的研究

(收稿日期:2014-06-17 接受日期:2014-07-12)

固醇类抗炎药是另一种常用的骨性关节炎治疗药物，但是长期服药易产生肠道等不良反应[5]。本次研究主要对 150 例不同程度膝关节骨性关节炎患者随机给予盐酸氨基葡萄糖联合塞来昔布以及单独给予盐酸氨基葡萄糖治疗，比较两种治疗方案的有效性及安全性，为临床用药给予一定的理论支持。

1 资料与方法

1.1 对象选择

选取 2011 年 1 月至 2014 年 2 月已被我院骨科收治的符合标准的病例共 150 例，其中男 62 例，女 88 例，年龄 55～83 (64.7± 17.7)岁，单膝 106 例，双膝 44 例。入选者严格遵照下列标准[6]：(1)均符合美国风湿病协会 2001 年制定的膝关节骨性关节炎诊断标准；(2)患者知情同意。排除标准为：(1)药物过敏者；(2)依从性差的患者；(3)合并半月板或交叉韧带损伤等的骨性关节炎患者；(4)合并风湿、类风湿或强直性脊柱炎等；(5)肝肾等重要脏器严重疾患或消化道疾患。所选两组病人的男女比例、年龄构成等的差异没有统计学意义，资料具有可比性。

1.2 方法

入选对象根据 Kellgren-Lawrence 分级标准结合 Lequesne 评分分为轻度(64 例)、中度(52 例)及重度(34 例)3 组，各组又随机等分为治疗组和对照组两组，治疗组给盐酸氨基葡萄糖联合塞来昔布治疗，对照组仅给予盐酸氨基葡萄糖治疗，给药方式为：盐酸氨基葡萄糖(香港澳美制药)750 mg/ 粒，1 粒 / 次，2 次 /d，连续 6 周；塞来昔布(美国辉瑞制药)0.2 g/d。分别于给药第 2、4 、6 周以及停药 8、12 周观察两组患者经两种不同的治疗方案治疗后患者的 Lequesne 评分有无统计学差异，并观察两种方案的不良反应发生情况。

1.3 统计学分析

采用 SPSS 18.0 统计软件进行数据录入及统计分析，计量资料以均数± 标准差($\bar{x}$± s)表示；两组资料比较时采用 t 检验、卡方分析及重复测量资料的方差分析等。检验水准 α=0.05。

2 结果

2.1 两种治疗方案对不同程度膝关节骨性关节炎 Lequesne 评分的影响

对于轻度膝关节骨性关节炎患者，对照组于用药 4 周时其 Lequesne 评分开始低于治疗前，停药 12 周后仍低于治疗前，差异有统计学意义(P<0.05)；治疗组用药 2 周时其 Lequesne 评分开始低于治疗前，停药 12 周后仍低于治疗前，差异有统计学意义(P<0.05)，且停药 12 周时治疗组的 Lequesne 评分低于对照组，差异有统计学意义(P<0.05)。

对于中度膝关节骨性关节炎患者，对照组于用药 4 周时其 Lequesne 评分开始低于治疗前，差异有统计学意义(P<0.05)，停药 12 周后与治疗前相比无统计学意义(P>0.05)；治疗组用药 2 周时其 Lequesne 评分开始低于治疗前，差异有统计学意义 (P<0.05)，停药 12 周后与治疗前相比无统计学意义(P>0.05)；且用药 2 周、用药 4 周、用药 6 周及停药 8 周时两组相比差异均有统计学意义(P<0.05)；停药 12 周时两组的 Lequesne 评分差异无统计学意义(P>0.05)。

对于重度膝关节骨性关节炎患者，对照组用药期间及停药期间其 Lequesne 评分与治疗前相比均无统计学意义(P>0.05)，治疗组在给药 4 周及 6 周时其 Lequesne 评分低于治疗前，差异有统计学意义(P<0.05)；停药后其 Lequesne 评分与治疗前相比均无统计学意义(P>0.05)；对照组与治疗组在给药 4 周及给药 6 周时其 Lequesne 评分差异有统计学意义(P<0.05)，停药后均无统计学意义(P>0.05)。详见表 1。

2.2 两种治疗方案的不良反应发生情况比较

两种治疗方案治疗膝关节骨性关节炎时所导致的各种不良反应的差异均没有统计学意义(P<0.05)。详见表 2。

3 讨论

骨关节炎是骨科的常见疾病，其中膝关节骨性关节炎在其中占绝大多数，是膝关节软骨退行性改变而致的软骨丢失破坏并伴有周围骨质增生的一种慢性中老年常见骨科疾病，主要临床表现为膝关节疼痛、僵硬及活动不便等。其发病机制仍不明朗，有学者认为与基质金属蛋白酶和磷脂酶 A 2 激活，白细胞介素等炎性因子产生增加而导致软骨损伤引发炎症有关[7-9]。临床治疗主要为口服药物治疗，旨在缓解患者临床症状如疼痛等进而改善患者生存质量。主要药物有非甾体抗炎药、氨基葡萄糖、软骨保护剂等[10-12]。盐酸氨基酸与非甾体抗炎药是应用最为广泛的治疗骨性关节炎的药物，但是有学者发现这两种药物的疗效与安慰剂无异，因为以往的研究选取的患者病情不一致，不能简单的下结论是否有效[13-15]。本次研究给患者按病情进行分级后再分组，分别给予单独盐酸氨基酸治疗及盐酸氨基酸联合塞来昔布治疗观察这两种治疗方案下患者的 Lequesne 评分情况进而比较两种方案的疗效，为临床治疗给予理论支持[16-18]。

本次研究结果发现，轻度患者对照组于用药 4 周、治疗组 2 周时其 Lequesne 评分开始低于治疗前，两组停药 12 周后仍低于治疗前 (P<0.05)，停药 12 周时治疗组低于对照组(P<0.05)。提示两种治疗方案对于轻度膝关节骨性关节炎均有良好的疗效，且联合用药效果更明显。中度患者对照组于用药 4 周、治疗组 2 周时开始低于治疗前(P<0.05)，停药 12 周后与治疗前相比无统计学意义 (P>0.05)，用药 2 周、4 周、6 周及停药 8 周时两组相比差异均有统计学意义(P<0.05)，停药 12 周时两组差异无统计学意义(P>0.05)。提示对于中度患者联合用药的疗效优于单独用药。重度患者对照组用药期间及停药期间与治疗前相比均无统计学意义(P>0.05)，治疗组在给药 4 周及 6 周时其 Lequesne 评分低于治疗前(P<0.05)，停药后与治疗前相比均无统计学意义(P>0.05)，对照组与治疗组在给药 4 周及给药 6 周时其 Lequesne 评分差异有统计学意义(P<0.05)，停药后均无统计学意义(P>0.05)。提示对于重度患者两种治疗方案均无明显效果，虽然联合组在给药 4 周及 6 周时稍有效果，但是停药后均无效果。而且两种治疗方案所产生的各种不良反应无明显差别，患者均可耐受。因此，在临床治疗时对于轻、中度患者通过给予盐酸氨基葡萄糖联合塞来昔布可有效改善患者临床症状，而对于重度患者应采取关节镜手术或者骨关节置换术等进行治疗，从而改善患者生活质量，延长患者生存时间[19,20]。

参 考 文 献(References)

[1] 朱宁,张斌,李国梅,等.物理疗法结合运动治疗膝关节骨性关节炎的效果观察[J].宁夏医学院学报, 2006, 28(6): 525-527

表 1 两种治疗方案对不同程度膝关节骨性关节炎 Lequesne 评分的影响($\bar{x}\pm s$)

Table 1 Effect of two treatment methods on Lequesne score for different degrees of knee osteoarthritis ($\bar{x}\pm s$)

程度分级 Degree classification	时间点 Time point	对照组 Control group	治疗组 Treatment group	t	P
轻度(n=64) Mild group(n=64)	治疗前 Before treatment	3.45± 0.54	3.47± 0.49	0.155	0.877
	给药 2 周 2 weeks after drug administration	3.12± 0.52	2.12± 0.41[1)]	8.543	<0.001
	给药 4 周 4 weeks after drug administration	2.10± 0.31[1)]	1.07± 0.27[1)]	14.173	<0.001
	给药 6 周 6 weeks after drug administration	0.87± 0.21[1)]	0.81± 0.26[1)]	1.016	0.314
	停药 8 周 8 weeks after drug withdrawal	1.75± 0.34[1)]	1.54± 0.331)	2.507	0.015
	停药 12 周 12 weeks after drug withdrawal	2.47± 0.35[1)]	2.14± 0.31[1)]	3.993	<0.001
中度(n=52) Moderate group(n=52)	治疗前 Before treatment	8.47± 2.76	8.58± 2.52	0.150	0.881
	给药 2 周 2 weeks after drug administration	7.89± 2.84	5.96± 2.15[1)]	2.763	0.008
	给药 4 周 4 weeks after drug administration	5.54± 1.42[1)]	4.16± 1.42[1)]	3.504	0.001
	给药 6 周 6 weeks after drug administration	3.50± 1.221)	2.24± 1.181)	3.785	<0.001
	停药 8 周 8 weeks after drug withdrawal	5.31± 1.52[1)]	4.14± 1.35[1)]	2.935	0.005
	停药 12 周 12 weeks after drug withdrawal	7.82± 2.22	7.62± 2.41	0.311	0.757
重度(n=34) Severe group(n=34)	治疗前 Prior treatment	14.17± 3.26	14.54± 3.51	0.318	0.752
	给药 2 周 2 weeks after drug administration	14.39± 3.81	14.40± 3.15	0.008	0.993
	给药 4 周 4 weeks after drug administration	14.05± 3.42	10.62± 3.04[1)]	3.091	0.004
	给药 6 周 6 weeks after drug administration	13.05± 2.21	9.42± 2.15[1)]	4.854	<0.001
	停药 8 周 8 weeks after drug withdrawal	14.32± 2.55	14.46± 3.35	0.137	0.892
	停药 12 周 12 weeks after drug withdrawal	15.83± 3.21	14.65± 2.44	1.207	0.236

注:1)治疗前比较,P<0.05。

Note:1)compared with prior treatment, P<0.05.

表 2 两种治疗方案的不良反应发生情况比较

Table 2 Comparison of adverse reactions of two treatment methods

指标 Indexes	对照组(n=75) Control group(n=75)	治疗组(n=75) Treatment goup(n=75)	X^2	P
胃肠道反应 Gastrointestinal reaction	9	5	1.261	0.262
头痛 Headache	0	1	1.007	0.316
皮疹等过敏反应 Skin rash and other allergic reactions	2	0	2.027	0.155

Zhu Ning, Zhang Bin, Li Guo-mei, et al. Effect observation of physical therapy and exercise in the treatment of arthritis of knee joint [J]. Journal of Ningxia Medical University, 2006, 28(6): 525-527

[2] Update on current care guidelines:knee and hip osteoarthriti [J]. Duodecim, 2012, 128 (20): 2114-2115

[3] Bertin P, Taieb C. NSAID-sparing effect of glucosamine hydrochloride in patients with knee osteoarthritis:an analysis of data from a French database[J]. Curr Med Res Opin, 2014, 30(2): 271-277

[4] Trudeau J, Van Inwegen R, Eaton T, et al. Assessment of Pain and Activity Using an Electronic Pain Diary and Actigraphy Device in a Randomized, Placebo-Controlled Crossover Trial of Celecoxib in Osteoarthritis of the Knee[J]. Pain Pract, 2014[Epub aheadof print]

[5] Yoo W H, Yoo H G, Park S H, et al. Efficacy and safety of PG201 (Layla) and celecoxib in the treatment of symptomatic knee osteoarthritis: a double-blinded, randomized, multi-center, active drug comparative, parallel-group, non-inferiority, phase III study [J]. Rheumatol Int, 2014, 34(10): 1369-1378

[6] Chopra A, Saluja M, Tillu G, et al. Ayurvedic medicine offers a good alternative to glucosamine and celecoxib in the treatment of symptomatic knee osteoarthritis:a randomized, double-blind, controlled equivalence drug trial [J]. Rheumatology (Oxford), 2013, 52(8): 1408-1417

[7] 黄式环,韦宏文,覃水梅,等.人工膝关节置换术围术期镇痛下的康复训练[J]. 广西医学, 2011, 33(4): 511-512
Huang Shi-huan, Wei Hong-wen, Qin Shui-mei, et al. The artificial knee joint replacement rehabilitation training under theoperative analgesia[J]. Guangxi Medical Journal, 2011, 33(4): 511-512

[8] Gong L, Dong J Y, Li Z R. Effects of combined application of muscle relaxants and celecoxib administration after total knee arthroplasty (TKA) on early recovery: a randomized,double-blind, controlled study[J]. J Arthroplasty, 2013, 28(8): 1301-1305

[9] Gonzalez E B. ACP Journal Club. Review: Glucosamine (sulfate or hydrochloride) does not reduce pain in knee or hip osteoarthritis[J]. Ann Intern Med, 2013, 159(12): C8

[10] 刘守正,乙军,朱宝林,等. 牛膝联合塞来昔布治疗早期膝关节骨性关节炎的疗效观察[J].中国医药导刊, 2012, 14(2): 277-278
Liu Shou-zheng, Yi Jun, Zhu Bao-lin, et al. The Clinical Observation for Treatmentof Eaply Knee Osteoarthritis with Bibentatae and Celecoxid[J]. Chinese Journal of Medical Guide,2012,14(2): 277-278

[11] Essex M N, Bhadra P, Sands G H. Efficacy and tolerability of celecoxib versus naproxen in patients with osteoarthritis of the knee:a randomized,double-blind,double-dummy trial[J]. J Int Med Res,2012, 40(4): 1357-1370

[12] Kanzaki N, Saito K, Maeda A, et al. Effect of a dietary supplement containing glucosamine hydrochloride, chondroitin sulfate and quercetin glycosides on symptomatic knee osteoarthritis: a randomized, double-blind, placebo-controlled study [J]. J Sci Food Agric, 2012, 92(4): 862-869

[13] 雷祯斌,杨家福,张恒,等. 关节松动术治疗老年性膝关节骨性关节炎[J].按摩与康复医学(下旬刊), 2011, 02(7): 19-20
Lei Zhen-bin,Yang Jia-fu, Zhang Heng, et al. Joint mobilization in the treatment of senile knee osteoarthritis [J].Chinese Manipulation & Rehabilitation Medicine, 2011, 02(7): 19-20

[14] Hochberg M C, Fort J G, Svensson O, et al. Fixed-dose combination of enteric-coated naproxen and immediate-release esomeprazole has comparable efficacy to celecoxib for knee osteoarthritis:two randomized trials[J]. Curr Med Res Opin, 2011, 27(6): 1243-1253

[15] Kazerooni R, Bounthavong M, Tran J N, et al. Retrospective evaluation of inpatient celecoxib use after total hip and knee arthroplasty at a Veterans Affairs Medical Center [J]. J Arthroplasty, 2012, 27(6): 1033-1040

[16] Cheng G, Cheng W, Jiang YG.Controlled observation of clinical efficacy on knee osteoarthritis treated with auricular electroacupuncture and the isolated moxibustion with Lingxian herbal paste[J]. Chinese Acupuncture & Moxibustion, 2014, 34(3): 230-234

[17] Goodin BR, Bulls HW, Herbert MS, et al. Temporal summation of pain as a prospective predictor of clinical pain severity in adults aged 45 years and older with knee osteoarthritis: ethnic differences [J]. Psychosom Med, 2014, 76(4): 302-310

[18] Katz JN, Brownlee SA, Jones MH. The role of arthroscopy in the management of knee osteoarthritis[J]. Best Pract Res Clin Rheumatol, 2014, 28(1): 143-156

[19] 李明辉,刘洋,王彩民,等.盐酸氨基葡萄糖联合塞来昔布治疗膝骨性关节炎的随机对照[J].中国组织工程研究, 2013, (43): 7654-7660
Li Ming-hui, Liu Yang, Wang Cai-min, et al. Glucosamine hydrochloride combined with celecoxib for the treatment of knee osteoarthritis:Randomized controlled trials [J]. Journal of Clinical Rehabilitative Tissue Engineering Research, 2013, (43): 7654-7660

[20] Barker T, Rogers VE, Henriksen VT, et al. Serum cytokines are increased and circulating micronutrients are not altered in subjects with early compared to advanced knee osteoarthritis [J]. Cytokine, 2014 , 68(2): 133-136

（上接第 327 页）

[17] 刘恩梅,黄英罗.无痛纤维支气管镜检术在小儿肺部疾病诊断和治疗中的应用[J].重庆医科大学学报,2006,3(02):281-283
Liu En-mei, Huang Ying-luo. Application of painless fiberoptic bronchoscopy in the diagnosis and treatment of pediatric pulmonary disease [J]. Journal of Medical University of Chongqing, 2006, 3(02): 281-283

[18] 白浪,蔡一榕.小儿支气管异物取出术中采用保留自主通气和控制通气麻醉方式的比较[J].第二军医大学学报,2008,29:455-457
Bai Lang, Cai Yi-rong. The Cai Yirong children, bronchial foreign body removal in spontaneous ventilation and control ventilation mode [J]. Journal of Second Military Medical University, 2008, 29: 455-457

[19] Murgu SD, Pecson J, Colt HG. Bronchoscopy during noninvasive ventilation:indications and technique[J]. Respir Care, 2010, 55(5):595-600

[20] Abraham GE 3rd, Sumrall BH, Bowling MR. The air apparent: a rare complication during flexible bronchoscopy [J]. Am J Med Sci, 2011, 34(3): 243-245