·基础研究·

早期跑台训练联合超短波治疗对脊髓损伤大鼠功能恢复的影响

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【摘要】 **目的** 观察早期跑台训练联合超短波治疗对大鼠脊髓损伤(SCI)后4周BBB评分、损伤部位水通道蛋白-4(AQP-4)和胶质纤维酸性蛋白(GFAP)表达的影响,探讨两种方法单独应用及联合应用对SCI的疗效及作用机制。**方法** 选取50只雌性SD大鼠,采用改良Allen's法制作大鼠SCI模型,造模成功(40只)后按照随机数字表法将其分为假手术组、对照组、超短波组、跑台组和联合组,每组8只。术后4周,用BBB评分法评价大鼠后肢运动功能的恢复情况。术后4周取材,SCI部位行GFAP和AQP-4免疫组化染色,测定蛋白表达的积分光密度值(IOD),进行比较分析。**结果** 假手术组BBB评分为21分。余4组术后1 d的BBB评分为0~1分,随着时间延长,评分逐渐增加,除假手术组外,余4组术后4周的BBB评分显著增高($P<0.05$)。与对照组同时间点比较,跑台组、联合组大鼠的BBB评分显著较高($P<0.05$)。与超短波组同时间点比较,跑台组术后4周[(12.88±3.04)分],联合组术后2周[(10.12±1.13)分]、3周[(12.38±1.19)分]及4周[(14.50±1.31)分]的BBB评分较高($P<0.05$)。SCI术后4周,超短波组、跑台组及联合组AQP-4 IOD均较对照组低($P<0.05$),联合组AQP-4 IOD较超短波组低($P<0.05$)。SCI后4周,超短波组、跑台组、联合组GFAP IOD均较对照组低($P<0.05$)。与超短波组比较,联合组GFAP IOD较低($P<0.05$)。与跑台组比较,联合组GFAP较低($P<0.05$)。**结论** 跑台训练、超短波治疗均对大鼠SCI后的运动功能恢复有积极作用,其治疗机制可能与减轻损伤部位的AQP-4和GFAP表达有关,且联合应用的疗效更为优异。

【关键词】 脊髓损伤; 跑台训练; 超短波; 水通道蛋白-4; 胶质纤维酸性蛋白
基金项目:国家自然科学基金青年科学基金项目(81101462);辽宁省自然科学基金项目(201602875);辽宁省科学事业公益研究基金项目(2016003001)
DOI:10.3760/cma.j.issn.0254-1424.2019.10.001

The effects of early treadmill training combined with ultrashort wave irradiation on functional recovery from spinal cord injury

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【**Abstract**】 **Objective** To investigate the effect of early-stage training combined with the ultrashort wave therapy on the functional recovery of rats after a spinal cord injury, and to observe the expression of aquaporin protein-4 (AQP-4) and glial fibrillary acidic protein (GFAP). **Methods** Fifty female Sprague-Dawley rats had spinal cord injury (SCI) induced using the modified Allen's method. After successful modeling, 40 were randomly divided into a sham operation group, a control group, an ultrashort wave group, a treadmill group and a combined group, each of 8. Motor function in their hind limbs was evaluated 4 weeks after the operation using BBB scoring. GFAP and AQP-4 immunohistochemical staining were used to determine the integral optical density (IOD) of the protein expression. **Results** The average BBB score of the sham operation group was 21, while the other four groups averages were all less than 1 on the 1st day after the operation. They gradually increased with time, and by 4 weeks the increases were significant. Compared with the control group at the same time point, the average BBB scores of the treadmill and the combined groups were significantly higher. Compared with the ultrashort wave group, the average BBB score of the treadmill group was higher after 4 weeks, and the combined group's average was significantly higher at 2, 3 and 4 weeks after the operation. Four weeks after the SCI modeling, the average AQP-4 IOD and GFAP IOD levels of the ultrashort wave group, the treadmill group and the combined group were lower than that of the control group, while

the average AQP-4 and GFAP IOD levels of the combined group were significantly lower than those of the ultrashort wave group. Compared with the treadmill group, the combined group had a significantly lower average GFAP level. **Conclusions** Both treadmill training and ultrashort wave treatment promote motor function recovery after a spinal cord injury. The mechanism may be related to downregulation of AQP-4 and GFAP expression at the injured site. Combining the two treatments gives better effects.

【**Key words**】 Spinal cord injury; Treadmill training; Ultrashort wave irradiation; Auaporin protein-4; Glial fibrillary acidic protein

Funding: Youth Foundation of the National Natural Science Foundation of China (No. 81101462); Natural Science Foundation of Liaoning Province (No. 201602875); Liaoning Public Welfare Research Fund for Science Projects (grant 2016003001)

DOI: 10.3760/cma.j.issn.0254-1424.2019.10.001

脊髓损伤(spinal cord injury, SCI)是脊柱外伤最严重的并发症,损伤后神经元细胞的裂解和坏死往往会导致损伤节段以下肢体严重的感觉及功能障碍,产生复杂的生理、心理和社会问题,影响生活质量。由于病理生理过程复杂,SCI 的康复治疗进展缓慢[1]。不仅给患者带来身体和心理的双重伤害,还给社会及家庭带来了巨大的经济负担[2]。目前,普遍认为康复训练是促进 SCI 后运动功能恢复最有效的方法[3-5]。在不完全性 SCI 的动物实验中,跑台训练作为最具代表性且简单易行的训练,对 SCI 后的功能和组织形态恢复非常有效[6-11]。作为物理因子中最具代表性的超短波治疗,因其安全、有效,已被广泛应用于康复科的临床治疗中,且小剂量超短波治疗可以改善血液循环,促进炎症吸收,减轻水肿,增强组织营养,加强局部组织代谢。在前期试验中,小剂量超短波已被证实对 SCI 后的功能恢复有效[12-15]。本研究采用 Allen's 法制备临床最常见的大鼠 SCI 模型,记录 BBB(Basso-Beattie-Bresnahan)运动功能量表评分及损伤部位脊髓的胶质纤维酸性蛋白(glial fibrillary acidic protein, GFAP)和水通道蛋白(aquaporin-4, AQP-4)表达水平,旨在探讨单一跑台训练或超短波治疗及联合治疗的疗效差异、是否存在协同效应及作用机制。

材料与方法

一、实验动物、试剂及仪器

选取 8~10 周龄 Sprague-Dawley 雌性大鼠 50 只,由中国医科大学附属盛京医院中心实验室提供,体重 180~220 g。兔抗大鼠 AQP-4 多克隆抗体(ABCAM 公司),SABC 试剂(北京博奥森生物技术有限公司),山羊抗大鼠 GFAP 多克隆抗体(美国 Santa Cruz 公司),兔抗山羊二抗试剂盒(武汉博士德生物工程公司),DAB 显色剂(福州迈新生物技术开发有限公司),RM2245 石蜡切片机,DMD108 显微图像成像系统(LEICA),BS-60 光学显微镜(OLYMPUS)。五官超短波治疗机(上海医用设备厂、频率 40.68 MHz、最大输出功率 40 W),跑台。

二、模型制备及分组

采用 10% 水合氯醛(0.33 ml/100 g)腹腔麻醉大鼠,无菌条件下在 T_{9-11} 平面打开椎管,暴露 T_{10} 节段脊髓,采用改良 Allen's 法制作 SCI 模型,大鼠立即出现一过性鼠尾摆动和后肢痉挛视为造模成功,苏醒后 BBB 评分为 0~1 分。术后伤口局部青霉素冲洗防止感染,清醒后分笼饲养,自由饮水、进食。术后每日给予大鼠腹腔注射青霉素 8 万 U,每日早晚排尿 2 次,直至建立正常的排尿反射。术后观察大鼠切口愈合情况,保持身体干燥,预防泌尿系感染及压疮等并发症。剔除苏醒后评分过高及死亡大鼠。假手术组仅单纯咬除椎板,脊髓无损伤。将造模成功的 40 只大鼠随机分为假手术组、对照组、超短波组、跑台组和联合组,每组 8 只。

三、干预方法

对照组及假手术组不给予任何治疗。超短波组及联合组损伤后 24 h 进行损伤部位小剂量超短波治疗:大鼠置于特制的塑料固定器内,将直径 4 cm 的圆形电极板对置于大鼠损伤脊髓两侧,电极板与脊髓皮肤间隙 2 cm,调谐后第 1 档输出功率约为 11.58 W,每次 6 min,每日 1 次,每周 5 次,直至取材前 1 d。跑台组及联合组于术前给予 5 min 跑台的适应性训练,于术后 72 h 开始进行跑台训练,起始 2 d 的训练速度为 100 m/h,训练时间 5~10 min。根据大鼠的功能恢复情况逐渐提高跑台速度及时间,每隔 2 d 逐渐上调速度(100 m/h)并增加时间(5 min),直至大鼠可以慢慢移动后肢。训练开始 1 周后,每日跑台训练 20 min,每周 5 次。

四、取材

SCI 术后 4 周,采用 10% 水合氯醛(0.33 ml/100 g)腹腔麻醉大鼠,仰卧位开胸,暴露两肺和心脏,首先以 4 ℃预冷的生理盐水约 80 ml,经心脏-主动脉灌注至肝脏颜色变浅;更换 4 ℃预冷的 4% 多聚甲醛固定液约 40 ml 心脏灌注至大鼠四肢震颤,四肢僵硬,

停止灌流。解剖并暴露脊髓,取以 T_{10} 损伤处为中心向头尾端共 1 cm 的脊髓,置于 4%多聚甲醛 PBS 溶液的标本储存瓶中 4 ℃固定 24 h,石蜡包埋,沿脊髓长轴纵向连续切片,片厚 3 μm。

五、观察指标

1. BBB 评分:术后及 1、2、3、4 周,对所有大鼠进行 BBB 行为学评分,观察时间为 4 min。0 分为全瘫,21 分为正常。

2. 免疫组化染色:制备脊髓组织标本切片若干张(N),将每个脊髓标本纵切若干片(M,且 M>10N),其中第 1 片,N+1 片,2N+1 片…放入切片序号 1 的标本;第 2 片,N+2 片,2N+2 片…放入切片序号 2 的标本;以此类推,每张切片共计 10 片脊髓标本。选取每个脊髓组织序号相同的标本切片,常规脱蜡,高压抗原修复,3%H_2O_2 溶液中孵育,10%胎牛血清封闭,分别滴加山羊抗大鼠 GFAP 多克隆抗体(1∶400,美国 Santa Cruz 公司)、兔抗大鼠 AQP-4 多克隆抗体(1∶800),4 ℃过夜,阴性对照用 PBS 代替一抗;PBS 冲洗,分别滴加 SABC 试剂,具体染色步骤按照试剂盒说明执行。DAB 显色,苏木素复染,透明封片。使用 DMD108 显微图像成像系统对每张切片进行拍照(400×400),每张切片上的每个标本延损伤区域边缘(保证覆盖损伤区)随机选取 4 个视野,每张切片共计 40 个视野。采用 Image-Pro Plus 6.0 软件进行图像处理,行 AQP-4 及 GFAP 的积分光密度(integral optical density,IOD)值测量。

六、统计学分析

采用 Graph Pad Prism 5.0 统计软件进行双因素方差分析,有统计学意义的数据进行 Bonferroni 检验、两两比较,$P<0.05$表示差异有统计学意义。

结　果

一、SCI 造模结果

大鼠麻醉后行 SCI 手术操作,术后约 1~2 h 后苏醒,大鼠双下肢瘫痪,二便障碍,行动迟缓,进食水情况较差,术后 1 d BBB 评分为 0~1 分,说明 SCI 模型造模成功。50 只大鼠中,苏醒后评分过高 2 只,死亡 8 只,剔除后共 40 只。

二、各组大鼠不同时间点的 BBB 评分比较

假手术组 BBB 评分为 21 分。余 4 组术后 1 d 的 BBB 评分为 0~1 分,随着时间延长,评分逐渐增加,除假手术组外,余 4 组术后 4 周的 BBB 评分显著增高($P<0.05$)。与对照组同时间点比较,跑台组、联合组大鼠的 BBB 评分显著较高($P<0.05$)。与超短波组同时间点比较,跑台组术后 4 周,联合组术后 2 周、3 周及 4 周的 BBB 评分较高($P<0.05$)。详见表 1。

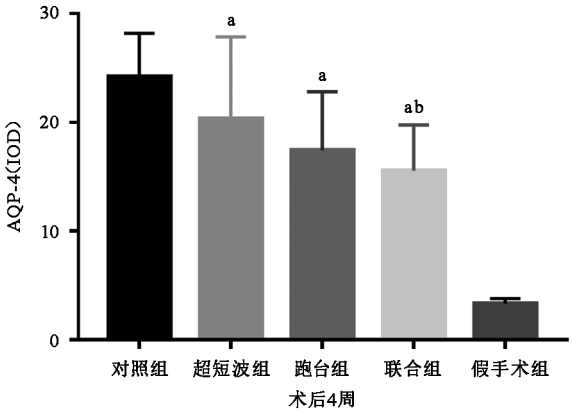
表 1　SCI 后不同时间点各组大鼠的 BBB 评分比较(分,$\bar{x}\pm s$)

组别	例数	术后 1 周	术后 2 周	术后 3 周	术后 4 周
假手术组	8	21.00±0.00	21.00±0.00	21.00±0.00	21.00±0.00
对照组	8	2.38±0.92	5.75±1.67	7.63±1.40	9.13±1.89^{a}
超短波组	8	4.50±1.20	7.38±1.69	9.00±2.00	10.38±2.13^{a}
跑台组	8	5.88±1.25^{b}	9.00±2.39^{b}	10.75±2.82^{b}	12.88±3.04^{abc}
联合组	8	5.50±1.41^{b}	10.12±1.13^{bc}	12.38±1.19^{bc}	14.50±1.31^{abc}

注:与组内术后 1 周比较,$^{a}P<0.05$;与对照组同时间点比较,$^{b}P<0.05$;与超短波组同时间点比较,$^{c}P<0.05$;与跑台组同时间点比较,$^{d}P<0.05$

三、各组大鼠 SCI 术后 4 周的 AQP-4 表达情况

假手术组 AQP-4 有少量表达。余 4 组 AQP-4 在白质区的神经胶质细胞突起和血管内皮细胞中表达增加。SCI 术后 4 周,假手术组、对照组、超短波组、跑台组、联合组 AQP-4 IOD 值分别为 3.348±0.449、25.404±2.859、20.303±7.534、17.431±5.439、14.822±3.451。超短波组、跑台组及联合组 AQP-4 IOD 均较对照组低($P<0.05$),联合组 AQP-4 IOD 较超短波组低($P<0.05$)。详见图 1、图 2。



注:与对照组比较,$^{a}P<0.05$;与超短波组比较,$^{b}P<0.05$

图 1　SCI 术后 4 周各组大鼠 AQP-4 IOD 比较

四、各组大鼠 SCI 术后 4 周的 GFAP 表达情况

各组大鼠均可在灰质和白质星形胶质细胞中观察到 GFAP 表达,其中假手术组的 GFAP 阳性表达较少,细胞体积小,突起纤细并伸向四周;余 4 组 GFAP 表达以空洞周围显著增多,细胞体积增生且伴有肥大,突起数目增多。SCI 后 4 周,假手术组、对照组、超短波组、跑台组、联合组的 GFAP IOD 值分别为 14.423±7.145、135.029±73.736、78.754±36.980、90.649±26.547、32.434±12.007。超短波组、跑台组、联合组 GFAP IOD 均较对照组低($P<0.05$)。与超短波组比较,联合组 GFAP IOD 较低($P<0.05$)。与跑台组比较,联合组 GFAP IOD 较低($P<0.05$)。详见图 3、图 4。

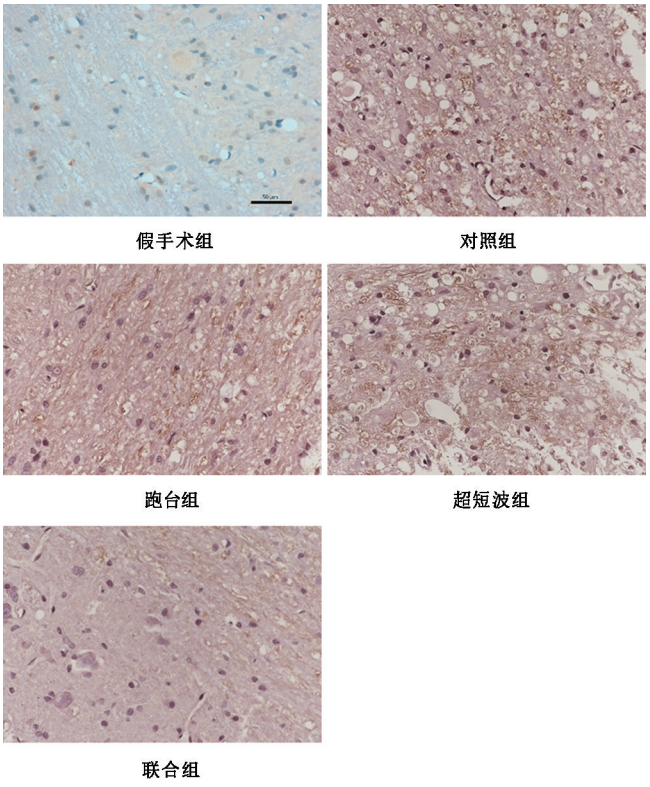


图 2　SCI 术后 4 周各组大鼠 AQP-4 表达(免疫组化染色,400×)

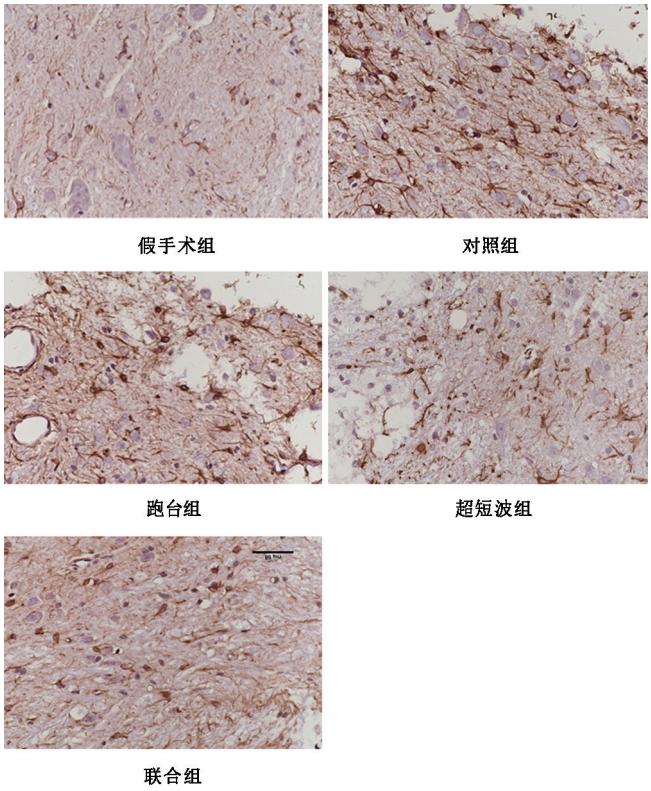
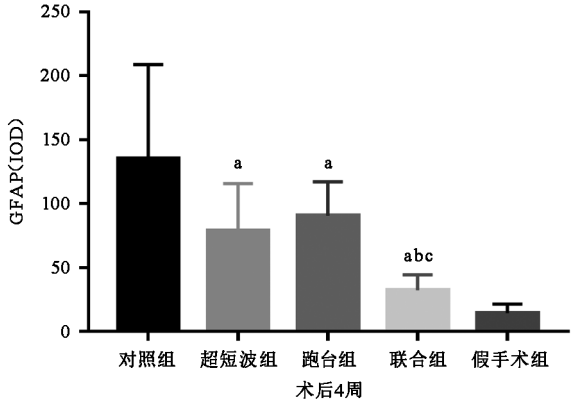


图 4　SCI 术后 4 周各组大鼠 GFAP 表达(免疫组化染色,400×)



注:与对照组比较,[a]$P<0.05$;与超短波组比较,[b]$P<0.05$;与跑台组比较,[c]$P<0.05$

图 3　SCI 术后 4 周各组大鼠 GFAP IOD 比较

讨　论

SCI 是一个严重的全球性难题[16-18]。外伤性 SCI 后大鼠脊髓内压增高[19]以及损伤后出现的瘢痕组织增生,是限制 SCI 大鼠功能恢复的主因。AQP4 是水通道蛋白家族中表达最广泛的亚型,分布在大脑和脊髓组织[20-24]。AQP4 主要功能是调节细胞内外水分子的交换,提供快速和大量的水运动的运输路线,参与体内水的调节,维持体内水平衡[25]。SCI 后脊髓水肿形成和消除与水通道蛋白的表达水平有关[26-27]。GFAP 在 SCI 后第 7 天表达面积显著增加[28]。SCI 后瘢痕形成与 GFAP 表达有关[29]。了解瘢痕形成的机制及如何控制瘢痕形成在一定程度上有益于 SCI 治疗[30]。

超短波操作简单、费用合理、治疗效果显著。在一项采用骨髓间充质干细胞移植联合超短波治疗 SCI 的研究中,证实了超短波具有减少瘢痕形成、抑制炎性细胞因子、减轻炎症、促进功能恢复等作用[13-14,31-32]。运动训练对改善患者的运动功能有积极作用。有研究报道,在 SCI 后早期给予适宜强度的运动训练,可以改善损伤后脊髓局部的血液循环、促进营养因子的分泌、减少胶质瘢痕的形成,最终对运动功能的恢复产生显著效果[33]。张立新等[34]研究证实,早期运动训练可以促进 SCI 大鼠后肢运动功能恢复,其机制可能与跑台训练减轻 SCI 后水肿、减小损伤面积、减少细胞凋亡和炎症反应有关。

本研究中,与对照组同时间点比较,跑台组、联合组大鼠的 BBB 评分显著较高($P<0.05$)。与超短波组同时间点比较,跑台组术后 4 周,联合组术后 2 周、3 周及 4 周的 BBB 评分较高($P<0.05$)。提示跑台训练及联合治疗均可以改善 SCI 大鼠的运动功能,且跑台训练与超短波联合应用的治疗效果显著优于单一的超短波治疗。SCI 术后 4 周,超短波组、跑台组及联合组 AQP-4 IOD 均较对照组低($P<0.05$),联合组 AQP-4 IOD 较超短波组低($P<0.05$)。SCI 后 4 周,超短波组、

跑台组、联合组 GFAP IOD 均较对照组低($P<0.05$)。与超短波组比较,联合组 GFAP IOD 较低($P<0.05$)。与跑台组比较,联合组 GFAP 较低($P<0.05$)。提示超短波治疗及跑台训练在改善 SCI 后水肿及瘢痕增生性反应方面的效果显著,且联合治疗效果更为优异。超短波、跑台训练的治疗原理不同,跑台训练可以促进营养因子分泌及轴突再生,超短波治疗可以消除脊髓水肿、抑制炎症反应、促进血液循环。二者联合治疗时,其治疗效果被叠加、放大,进而表现出更好的治疗作用。

综上所述,跑台训练和超短波治疗对大鼠 SCI 后的治疗均有一定效果,二者联合应用的效果更好,可以减少瘢痕形成、抑制细胞水肿,进而促进功能恢复。但其深层的治疗机制及临床应用仍有待后续的实验来进一步探究,以期早日取得进展,为广大 SCI 患者提供更多的帮助。

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(修回日期:2019-08-23)
(本文编辑:凌 琛)

·外刊撷英·

Transvaginal trigger point injections improve pain scores in women with pelvic floor hypertonicity and pelvic pain conditions

OBJECTIVES Chronic pelvic pain in women often requires multimodal treatment regimens. We describe our method of transvaginal trigger point injections (TPIs) and report outcomes using change in pain scores.

METHODS This was a retrospective review of women treated with in-office pelvic floor muscle injections from January 2012 to August 2015. Lidocaine 1% and 2%, bupivacaine 0.5%, or ropivacaine 0.5% with or without the addition of triamcinolone 40 mg was used for the injections. Pain was reported on a 0- to 10-point numerical rating scale before and after injection. Differences in pretreatment and posttreatment pain scores were analyzed after the first injection and after subsequent injections. Repeated-measures analysis was used to determine if any variable affected treatment response.

RESULTS One hundred one women with a mean age of 44 years had a total of 257 separate visits for pelvic floor muscle injections. Triamcinolone was used at 90.2% (230/255) of the TPI visits. After the initial TPI visit, there was significant decrease in total levator numerical rating scale score (maximum score, 20; mean, −6.21±4.7; $P<0.0001$), and 77% (70/91) of patients had improved. These significant improvements were noted at all visits 1 through 4 and whether bilateral or unilateral injections were done. Only the total amount of local anesthestic used had a significant effect on the change in total levator pain scores ($P=0.002$). Minor adverse effects including leg numbness, dizziness, nausea, bleeding, and headache occurred at 10% of visits.

CONCLUSIONS Pelvic floor muscle injections decrease pain levels in women with pelvic floor dysfunction.

【摘自:Bartley J, Han E, Gupta P, et al.Transvaginal trigger point injections improve pain scores in women with pelvic floorhypertonicity and pelvic pain conditions. Phys Ther, 2019,9,2,pii: pzz124. DOI: 10.1093/ptj/pzz124.】