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A 型肉毒素膀胱内阻滞治疗女性膀胱过度活动症的临床效果观察

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摘要 目的:探讨 A 型肉毒素膀胱内阻滞治疗女性膀胱过度活动症的临床效果。**方法:**选择 2010 年 10 月至 2012 年 10 月,哈尔滨医科大学附属第四医院泌尿外科收治的女性膀胱过度活动症患者 24 例,随机分为治疗组和对照组,治疗组(A 组)选用国产 A 型肉毒素(衡力)100 IU 治疗,用 10 mL 生理盐水稀释后,通过膀胱镜进行壁内注射;对照组(B 组)患者给予口服经典的抗胆碱制剂,酒石酸托特罗定片,每天口服 2 次,每次 2 mg,疗程不少于 6 周。于治疗前,治疗后 1 周和 4 周观察和比较两组患者的 IPSS 评分、初尿意膀胱容量、最大膀胱容量。**结果:**与治疗前比较,A 组治疗后 1 周,IPSS 评分显著下降(P<0.05),初尿意膀胱容量及最大膀胱容量显著上升(P<0.05),治疗后第 2 周和第 4 周均维持在相当水平,残余尿量第 1 周未见明显下降(P>0.05),第 4 周时与基线比较下降明显(P<0.05);B 组于治疗后第 4 周时,以上三项指标与治疗前比较才有统计学差异(P<0.05),残余尿量在第 1 周即有明显下降(P<0.05),并且第 4 周时仍维持第 1 周水平(P>0.05)。此外,治疗后第 1 周两组比较以上指标比较有统计学差异(P<0.05),而治疗后第 4 周无明显差异(P>0.05)。**结论:**经尿道膀胱壁内肉毒素 A 注射和口服酒石酸托特罗定均是治疗女性膀胱过度活动症的有效方法,但 A 型肉毒素膀胱内注射起效更快,同时由于其接触性和直观性,疗效更确切。

关键词:膀胱过度活动症;A 型肉毒毒素;酒石酸托特罗定

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Observation on the Efficacy of Block in the Bladder by Trebotulinum toxin-A in the Treatment of Female Overactive Bladder

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ABSTRACT Objective: To investigate the clinical effect of bladder block relieved by botulinum toxin-A on the female overactive bladder. **Methods:** From Oct 2010 to Oct 2012, 24 female patients with overactive bladder in the Department of Urology, the fourth affiliated of Harbin Medical University were chosen and randomly assigned to trebotulinum toxin-A (Hengli) in their wall of urinary bladder(A group). 100 IU botulinum toxin-A was diluted in 10ml physiologic saline. The control group(B group) was asked to take orally tartaric acid Tolteroine stator twice everyday, 2 mg every time, lasting more than 6 weeks. It was requested to record patients' I-PSS, initial micturition desire bladder capacity, maximum bladder capacity in the pre-therapy and the 1st week, 4th week, 6th week of post-therapy. The data was analyzed with the application of the SPSS12.0 statistic software. **Results:** Compared with the pre-therapy, the IPPS score of A group was decreased significantly (P<0.05), the increment of initial micturition desire bladder capacity (P<0.05)and maximum bladder capacity (P<0.05) were both increased markedly after 1 week treatment, which maintained the equal level in the 2nd weeks and 4th week, no significant difference of residual urine volume was found in the 1st week, which was significantly decreased in the 4th week (P<0.05). In regard to the control group, these 3 indexes showed differences in the 4th week compared with pre-therapy (P<0.05), the residual urine volume was significantly decreased in the 1st week(P<0.05) and maintained the equal level until the 4th week (P>0.05). Moreover, The index mentioned above showed significant difference in the 1st week between 2 groups (P<0.05), but no significant difference was found in the 4th week between 2 groups (P>0.05). **Conclusion:** The results presented that these were effective methods of botulinum toxin-A (Hengli) in their wall of urinary bladder and oral tartaric acid Tolteroine stator in the treatment of female overactive bladder. Further, it is faster in the method of botulinum toxin-A (Hengli) in their wall of urinary bladder. Besides, the method has an advantage of more accurate curative effect due to contact and intuitive features.

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膀胱过度活动症(overactive bladder,OAB)是一种以常伴有尿频和夜尿症状,可伴或不伴有急迫性尿失禁,并主要以尿急症状为特征的症候群，逼尿肌过度活动 (detrusor instability,or detrusor overactivity)是其尿动力学的主要表现,也可为其他形式的尿道 - 膀胱功能障碍[1]。近期,日本一项流行病学调查显示,成人尤其是在 40 岁及以上的人群中的 OAB 患者数量达到了 810 万人[2],其作为一种独立疾病越来越受到临床医师的重视。

OAB 既往经典的治疗方法是药物治疗，也有报道提示经典药物治疗联合行为治疗可以起到更好的治疗效果。A 型肉毒毒素(botulinum to xin A,BTX-A)具有降低肌张力、缓解痉挛的作用,在泌尿外科的应用研究也越来越受到重视[3]。本研究通过应用国产 A 型肉毒素 (衡力)100 IU 与酒石酸托特罗定(Tolterodine)，探讨不同治疗方法对女性膀胱过度活动症的疗效及其副作用,以期为临床实践提供参考,现报告如下。

1 资料与方法

1.1 病例资料

选择 2010 年 10 月～2012 年 10 月我院经门诊收治的确诊为女性膀胱过度活动症的患者 24 人，将其随机分为治疗组(A 组)和对照组(B 组),纳入标准:无抗胆碱能药物的禁忌症,无严重的心脑血管疾病及慢性代谢性疾病,无认知及言语言语功能障碍。其中符合要求者 20 例,年龄 30～68 岁,平均 47.34± 12.26 岁,病程 6 月～8 年,平均 2.35± 1.07 年。诊断标准以临床表现为基础,表现为尿急、尿频,诊断时均以排尿次数为参考,日间大于 7 次,夜间大于 4 次。入选患者中,6 例伴会阴部不适和尿痛,伴便秘 3 例,伴不同程度的急迫性尿失禁 11 例。

1.2 干预方法

治疗组(A 组)采用国产 A 型肉毒素(衡力)100 IU,用 10 mL 不含防腐剂的生理盐水稀释后,配置成浓度为 10IU/mL。手术室中,患者取膀胱截石位,常规消毒铺巾后,经闹到外口下乳膀胱镜,大小 i 为 21 F,插入膀胱镜过程中,观察尿道及膀胱颈部，将器质性梗阻惊醒排除。进入膀胱腔后，向膀胱内注入 200-250 mL左右的生理盐水,其主要目的是在膀胱壁内药物注射时使膀胱内膜的黏膜皱褶部分舒展，同时应避免注入过多,因为过度注生理盐水会导致膀胱过度充盈,导致膀胱壁明显变薄,而致注射药物时将膀胱壁穿透。观察膀胱黏膜是否有明显异常,如感染,增生等情况,膀胱镜直视下如无异常则抽取配置好浓度的肉毒毒素,准备行局部阻滞。注射前,专用的旁观内注射用 6F 长针头经膀胱镜置入膀胱腔内，将长针头插入膀胱壁内,直达黏膜下肌层,然后注入配置好的 A 型肉毒素溶液约 1 mL,于粘膜下形成圆形或椭圆形隆起。从膀胱顶开始,并依同样方法再分别于两侧、底部均匀注射,整个膀胱内阻滞点约 10 个,使整个膀胱内壁粘膜均匀隆起。在最后阻滞点结束前,为避免避免针筒内残留药物,向针内注入少量气体。阻滞时注意将双侧输尿管开口、膀胱三角区及膀胱颈部等解剖部位尽量避开,注射后膀胱壁应尽量将药物均匀分布,所有注射深度为黏膜下肌层,避免穿透膀胱壁。常规预防感染选用口服诺氟沙星胶囊 0.2 g,2 次 /d,连续 3d 预防感染[4]。

对照组(B 组)患者采用经典药物治疗,口服酒石酸托特罗定片,2 次 /d,每次 2 mg,疗程连续服用 4 周;根据情况可减至每天口服 2 次,每次 1 mg,以患者耐受程度为准。治疗期间避免使用用其它如巴氯芬,乙哌立松等其他抗痉挛药物。

1.3 观察指标

分别于治疗前、治疗后 1 周、4 周记录患者国际前列腺症状评分问卷表(IPSS)评分、初尿意膀胱容量(primary urinary bladder capacity,PUBC)、最大膀胱容量(maximum bladder capacity,MBC)、残余尿量(residual urine volume,RUV)。由于国际前列腺症状评分问卷表(IPSS)评分包含七项内容,而本研究研究对象为女性患者,故默认为其中的第 5 项,有尿线变细现象和第 6 项感觉排尿费力为 0 分。

1.4 统计学分析

采用统计软件 SPSS13.0 进行分析，计量资料用均数± 标准差($\bar{x}$± s)表示,组内差异性分析采用配对 t 检验;组间差异性分析采用成组设计的 t 检验。以 P<0.05 为差异有统计学意义。

2 结果

与治疗前比较,治疗组(A 组),治疗后 1 周,IPSS 评分显著下降(P <0.05),初尿意膀胱容量(P <0.05)及最大膀胱容量显著上升(P <0.05),治疗后并第 2 周,和第 4 周均维持在相当水平,残余尿量第 1 周未见明显下降(P>0.05),第 4 周时与基线比较下降明显(P<0.05);对照组(B 组)于治疗后第 4 周时,以上三项指标与治疗前比较才出现有统计学差异(P <0.05),残余尿量在第 1 周即有明显下降(P<0.05),并且第 4 周时仍维持第 1 周水平(P>0.05)。同时此外,组间比较治疗后第 1 周两组比较以上指标比较有统计学差异(P <0.05),而治疗后第 4 周无明显差异(P >0.05),见表 1。

3 讨论

目前，国内外尚无明确的评估女性排尿障碍的主观问卷,IPSS 问卷表是当前国际上一种通行的对前列腺症状发生频率和对目前症状的耐受程度的定量评分系统,不完全客观,但仍不失为比较症状进展情况和治疗前后疗效对比的量化评价方法。在本研究中,由于研究对象是女性患者,所以默认了其中的第五项和第六项为 0 分,而其余 5 项在女性膀胱过度活动症的患者中均可出现,故尽管这种应用没有经过严格的信度和效度的检验,但是作为症状的主观评估可以借鉴,因此本研究借用了该评估量表。

治疗 OAB 的经典一线药物目前依然是抗胆碱能药物,较为常见的药物包括托特罗定 (Tolterodine)、曲司氯胺(Trospium)、奥昔布宁(Oxybutynin)、索利那新(Solifenacin)等。其主要作用机制:① 毒蕈碱受体是产生膀胱平滑肌兴奋收缩的主

表 1 两组治疗前及治疗后 1 周和 4 周各项观察指标的比较

Table 1 Comparison of the indexes between two groups pre-therapy and 1st and 4th week post-therapy

Group	IPSS	PUBC(mL)	MBC(mL)	RUV(mL)
Base-line				
A	17.32± 5.34	65.14± 11.22	377.19± 37.28	21.23± 7.79
B	17.72± 6.18b	67.29± 12.71	385.57± 42.91	19.56± 6.77
1st week				
A	12.41± 4.73 a	133.97± 23.34	653.55± 57.73	19.88± 7.75
B	16.77± 5.55	117.72± 19.58	627.81± 60.36	16.65± 8.71
4th week				
A	13.27± 7.32a	139.26± 20.39 a	600.11± 53.25 a	16.44± 7.99 a
B	14.112± 3.34bc	113.11± 16.53bc	609.30± 51.29bc	17.31± 8.53bc

要受体,通过抑制使逼尿肌收缩的毒蕈碱受体(M 受体),提高膀胱感觉功能的阈值, 同时通过该机制抑制逼尿肌不稳定收缩;② 对膀胱逼尿肌的高选择性,利用这一特性使此类药物在保证了疗效的基础上,最大限度减少副作,该特性是抗胆碱能药物作为经典药物治疗的主要依据。托特罗定(Tolterodine)是一种高选择性的强效毒蕈碱受体(M 受体)拮抗剂,对 M 受体具有高亲和性和高专一性,许多研究[5-7]显示,该药物能够明显缓解 OAB 的尿频、尿急和急迫性尿失禁的临床症状,疗效良好。

A 型肉毒毒素(BTX-A)是梭状芽孢杆菌产生的一种嗜神经毒素,作用机制为:(1)作用于运动终板(神经 - 肌接头)处,抑制运动终板前膜兴奋性神经介质乙酰 γ 胆碱的量子释放,从而降低终板电位的绝对值,明显抑制运动电位的产生;(2)降低肌肉的位相性牵张反射的敏感性, 降低传入感受器的兴奋性;(3)抑制所作用的副交感和胆碱能节后交感神经元乙酰胆碱释放。BTX-A 应用于临床治疗肌肉痉挛和强直是基于以上三点机制所引起肌肉松弛性麻痹作用而实现的[8]。近年,BTX-A 在泌尿外科的应用日益得到重视[9],特别是用于膀胱过得活动症的治疗日益增多[10]。

本研究对膀胱壁内 A 型肉毒毒素阻滞术与口服托特罗定进行对比分析,发现二者均是治疗女性膀胱过度活动症后的有效方法,口服托特罗定后,患者的近期效果好,并且无创、方便,患者易接受,虽然有些副作用,仍是治疗女性膀胱过度活动症的经典一线用药;BTX-A 逼尿肌注射也是是治疗 OAB 的有效方法[1],并且由于是局部给药,具有临床疗效确切,副作用小,疗效持续时间长的特点, 是一种很有前途的治疗方法。随着对 BTX-A 临床研究的不断深入[11-20],相信其在治疗 OAB 方面必然会取得进一步的进展。

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