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·综述·

A型肉毒素治疗肌源性颞下颌关节紊乱病的研究进展

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【摘要】 肌源性颞下颌关节紊乱病（myogenous temporomandibular disorders，M-TMD）是颞下颌关节紊乱病（temporomandibular disorders，TMD）的主要亚型之一，肌痛为最典型表现，发病率呈逐年上升的趋势。A型肉毒素（botulinum toxin type A，BTX-A）是一种由肉毒杆菌产生的强效神经毒素，可抑制乙酰胆碱从突触前膜释放，从而阻断神经肌肉接头信号传导，使得注射区肌肉麻痹，BTX-A在口腔颌面部非美容性的应用是未来的研究热点。近年来越来越多研究聚焦于BTX-A用于M-TMD的治疗，文献回顾结果显示，在疼痛部位单次注射适宜剂量（单侧10～50 U）的BTX-A可在3～6个月内持续改善肌痛症状，必要时需重复注射。注射后常见不良反应如咀嚼无力、面瘫等均为暂时性，并可通过规范操作规避其发生，但目前临床仍缺少标准化的注射技术指南。

【关键词】 A型肉毒素；　肌源性颞下颌关节病；　颞下颌关节紊乱病；　咀嚼肌；　肌痛；　乙酰胆碱；　副作用；　临床应用
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Research progress on the application of botulinum toxin type A in the treatment of myogenous temporomandibular disorders

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【Abstract】 Myogenous temporomandibular disorder (M-TMD) is one of the main subtypes of temporomandibular disorder (TMD) and typically manifests as masticatory myofascial pain; the incidence of TMD has been increasing annually in recent years. Botulinum toxin type A (BTX-A) is a potent neurotoxin produced by *Clostridium botulinum*. BTX-A inhibits the release of acetylcholine from the presynaptic membrane, thereby blocking neuromuscular junction signaling. The noncosmetic application of BTX-A in the oral and maxillofacial regions is a prominent research topic. In recent years, an increasing number of studies have focused on the application of BTX-A in the treatment of M-TMD. The results of a literature review revealed that an appropriate dose (10-50 U unilaterally) of BTX-A administered in a single injection into the masticatory muscles can effectively treat myalgia over a period of 3-6 months. Common adverse effects, such as masticatory weakness and facial paralysis, are transient and can be avoided by standardized injection techniques. However, there is a lack of standardized guidelines for injection techniques in clinical practice.

【Key words】 botulinum toxin type A;　myogenous temporomandibular disorders;　temporomandibular disorders;

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masticatory muscles;　myalgia;　acetylcholine;　adverse effects;　clinical application
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颞下颌关节紊乱病(temporomandibular disorders,TMD)是包括咀嚼肌紊乱类疾病、颞下颌关节结构紊乱、炎性疾病和骨关节病等一系列临床症状相似的一组疾病的总称[1-3]。TMD在青年人中发病率高,并呈逐年上升的趋势,是导致口腔颌面部慢性疼痛最常见的原因之一[4]。肌源性颞下颌关节紊乱病(myogenous temporomandibular disorders,M-TMD)是TMD的亚型之一,以肌痛为主要表现[1]。A型肉毒杆菌毒素(botulinum toxin type A,BTX-A)是由肉毒杆菌产生的神经毒素,已被广泛应用于整形外科和皮肤科等领域[5]。近年来BTX-A在口腔颌面部非美容性的研究与应用逐渐增多,研究发现将BTX-A注射到咀嚼肌能持续缓解M-TMD患者的肌痛症状,本文旨在对BTX-A治疗肌源性颞下颌关节紊乱病的研究进展进行综述。

1　肌源性颞下颌关节紊乱病

M-TMD主要表现为开闭口疼痛、张口受限以及咀嚼肌群不适等症状[1]。根据TMD诊断标准(diagnostic criteria for the most common TMD, DC/TMD)可将M-TMD分为四大类:肌痛、肌腱炎、肌炎和咀嚼肌痉挛。肌痛是M-TMD患者的最常见主诉,而肌腱炎、肌炎和咀嚼肌痉挛相对少见[6]。根据触诊表现可将肌痛分为局限性肌痛、播散性肌筋膜痛和牵涉性肌筋膜痛,牵涉性疼痛可伴随偏头痛、牙痛等其他症状出现[7-8]。治疗TMD应循序渐进,先采取保守、可逆、非侵入性的治疗方式,其次才考虑关节外科手术治疗[9]。目前保守治疗方法众多,包括理疗按摩、佩戴颌垫和针刺治疗等[10]。在临床实践中发现咀嚼肌注射BTX-A可有效缓解肌痛、改善张口度,近年来应用逐步广泛。

2　BTX-A作用机制

肉毒杆菌毒素(botulinum toxin,BTX)是由肉毒杆菌产生的神经毒素,根据抗原特性分为A-G和X 8种不同的血清型,BTX-A的作用时间最久,效价是其他血清型的数十倍,已被广泛应用于整形外科和皮肤科等领域[5]。BTX-A由一条轻链和一条重链构成,两者通过二硫键相连,轻链上有催化结构域,是一种锌离子依赖内切酶,不同血清型BTX的内切酶作用于不同蛋白靶点,BTX-A可使可溶性N-乙基马来酰亚胺敏感因子附着蛋白受体(soluble N-ethylmaleimide-sensitive factor attachment protein receptor,SNARE)复合物裂解,后者调控神经递质乙酰胆碱的释放[11]。重链包含一个易位结构域和一个细胞结合结构域,细胞结合结构域根据空间结构分为N和C两个子结构域(图1)[12]。

当BTX-A到达神经肌肉接头,重链的细胞结合结构域与神经元细胞膜的神经节苷脂分子和蛋白质受体结合,BTX-A被胞吞到突触前膜中[13]。胞内体的酸性环境使得易位结构域构象改变,硫氧还蛋白(thioredoxin,Trx)与硫氧还蛋白还原酶(thioredoxin reductase,TrxR)促进二硫键还原,轻链被释放到胞浆中,切割SNARE复合物上的特定位点25 kDa突触相关蛋白(synaptosomal nerve-associated protein of 25 kDa,SNAP-25),导致乙酰胆碱释放阻断[14-15](图2)。若将一定剂量的BTX-A注射于咀嚼肌,即可局部产生持久的抗胆碱能作用,暂时

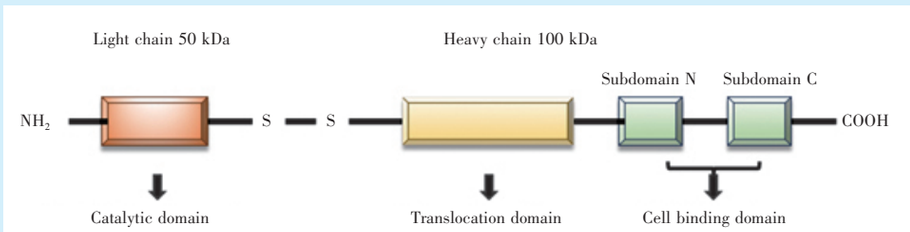
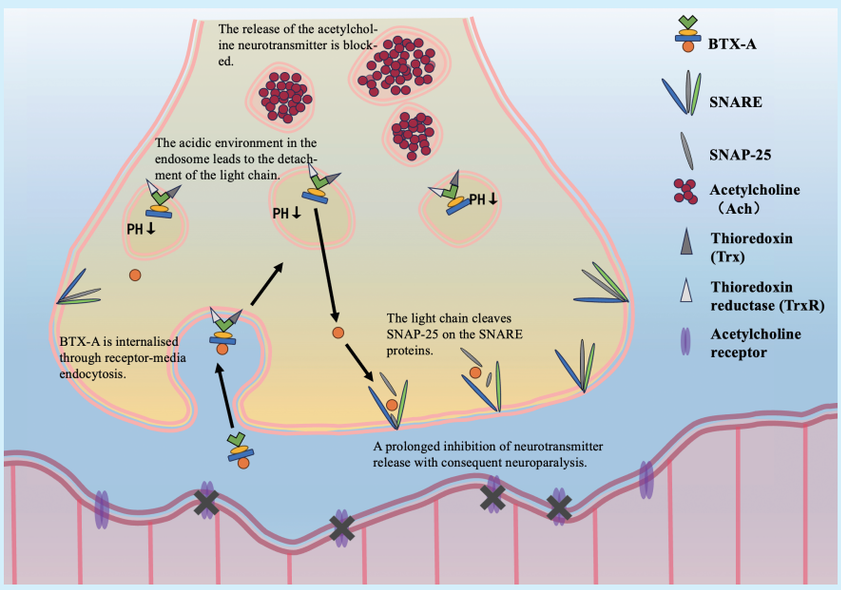


Figure 1　Simplified structure of botulinum toxin type A
图1　A型肉毒杆菌毒素的简化分子结构



BTX-A: botulinum toxin type A; SNARE: soluble N-ethylmaleimide-sensitive factor attachment protein receptor; SNAP-25: synaptosomal nerve-associated protein of 25 kDa

Figure 2　Mechanism by which botulinum toxin type A enters and paralyzes nerve terminals

图2　A型肉毒素进入神经末梢及神经末梢瘫痪的机制

性降低注射区肌肉兴奋传导，改善咀嚼肌酸痛与痉挛等症状，肌肉功能将在3～6个月内随着新的神经肌肉接头和轴突连接建立而逐渐恢复[12, 14]。

BTX-A在缓解肌肉紧张的同时还可能间接抑制炎症过程[16]。研究表明将BTX-A注射到大鼠颞下颌关节腔中可显著抑制P物质、谷氨酸和降钙素基因相关肽等疼痛介质的释放[15]；体外研究观察到在原代大鼠小胶质细胞中，BTX-A可抑制多种白细胞介素和一氧化氮合酶-2的表达，抑制p38、ERK1/2和NF-κB介导的多个细胞内信号通路，降低了炎症趋化性[17-18]。此外，BTX-A还能干扰细胞膜的痛觉敏感受体，包括瞬时受体电位阳离子通道香草素亚家族成员1、ATP门控P2X受体阳离子通道家族3等多个受体[15, 19]。痛觉信号以脉冲放电的方式在钠离子通道内传导，BTX-A可抑制钠离子通道使痛觉信号无法传递到中枢神经系统[20]。上述机制都可能有助于BTX-A的抗伤害作用。

3　咀嚼肌注射BTX-A治疗肌源性颞下颌关节紊乱病

Freund等[21]在1999年首次报道了咀嚼肌内注射BTX-A能改善TMD患者的临床症状和体征，如缓解疼痛、改善开口度和咀嚼功能等。Oksanen等[22]让63例M-TMD患者接受了BTX-A肌肉注射治疗，结果显示87%的患者疼痛症状改善，并且女性患者疗效更好。De la Torre Canales等[23]开展的随机对照临床研究（randomized controlled trial，RCT）将BTX-A注射到M-TMD患者的双侧咬肌和颞肌前份，在治疗后28 d和180 d咬肌和颞肌触诊疼痛均得到有效缓解，并且各项下颌运动指标，包括无痛张口度、最大自由张口度和被动张口度、下颌侧方运动等在治疗后180 d均有显著改善。BTX-A通过降低肌肉疼痛敏感性，可能促进咀嚼肌功能平衡的重建，从而改善下颌运动范围[23]。此外，多项研究表明BTX-A在改善疼痛与下颌运动方面，低剂量与中剂量和高剂量同等有效，表明其镇痛作用并无剂量依赖性[23-24]。为进一步探究BTX-A注射后对咀嚼肌厚度的长期影响，研究者对接受了单次注射治疗的患者的随访结果表明注射部位咀嚼肌厚度在治疗后6个月有所降低，但6年后基本恢复正常[25]。

针刺治疗常被用于治疗全身各个部位的肌痛，虽然针刺治疗可在短期内改善M-TMD的肌痛症状，但也有研究表明其短期内的效果可能是一种安慰剂效应[26-27]。一项RCT研究表明在缓解肌痛方面BTX-A与针刺治疗效果接近，但BTX-A治疗后患者的压痛阈值（pressure pain threshold，PPT）显著高于针刺疗法，同时治疗后BTX-A注射部位的咀嚼肌肌电图活性显著降低[28-29]。PPT是评价内源性疼痛机制变化的最敏感手段，PPT值的提高表明BTX-A比针刺治疗更具优越性，但也应重视其带来的咀嚼肌肌电活动降低等不良影响。

翼外肌紊乱与关节盘前移位的发生密切相关，但由于BTX-A翼外肌注射操作风险相对较大，临床较少选择该部位注射，可供参考的研究结论

有限[30]。Rady等[31]对比了BTX-A和低水平激光治疗(low level laser therapy,LLLT)及前导型咬合板三种治疗方式对可复性关节盘前移位的疗效,通过对比治疗前及治疗后3个月的核磁共振及患者体征改善情况,发现3种治疗方式均可有效改善疼痛、关节弹响等症状,并且BTX-A和LLLT组的关节盘-髁突关系也有所改善。但此研究随访时间较短,仅为3个月,需要更多的患者和更长的随访时间来评价BTX-A对关节盘-髁突关系的影响。

也有研究表明BTX-A效果有限。Rezazadeh等[32]对38例同时患有单侧颞下颌关节疼痛、弹响和翼外肌触痛的患者进行了一项RCT研究,将15 U的BTX-A注射到单侧翼外肌,在注射后1周、1个月、3个月分别评估了Helkimo指数、疼痛视觉模拟评分法(visual analogue scale,VAS)评分和下颌运动,结果显示BTX-A组的3项评估指标与安慰剂组差异并无统计学意义。但该研究首次采用了Helkimo指数评估BTX-A注射效果,该指标用于排除心理因素的影响,考虑到注射安慰剂同样可能在短期内改善患者症状,将Helkimo指数纳入疗效评估是值得借鉴的[28]。

一项针对M-TMD的不同保守治疗方案的系统综述与Meta分析指出,在缓解肌痛方面,短期内(≤5个月)手法治疗效果最好,而从中远期(≥6个月)疗效来看,BTX-A注射疗法是最佳治疗方式[33]。此外,研究表明BTX-A注射后在降低咀嚼肌力的同时夜磨牙患者的磨牙频率也有所降低,因此对于伴有夜磨牙的M-TMD患者,BTX-A注射治疗相较于其他保守治疗手段可能更具优势[14, 34]。

目前大部分研究都存在受试者数量过少的问题,部分研究缺乏安慰剂组用于空白对照[35]。未来需更大样本量的RCT研究来验证BTX-A用于M-TMD的临床疗效。操作人员注射技术的差异也可能是导致BTX-A疗效不同的原因之一。DC/TMD是目前TMD最常用的诊断标准,部分研究采用了其他诊断标准,使研究结论间的比较难以进行[7]。患者既往接受过的各类治疗也不容忽视,因为这些患者的社会心理状态和颞下颌关节的病理生理状态更具复杂性,所以有必要对既往未接受过治疗的M-TMD患者进行研究,以进一步探索BTX-A的疗效(表1)。

4　咀嚼肌局部BTX-A给药的注射技术

咬肌和颞肌位置相对表浅,注射技术简单,为

表1　A型肉毒素治疗肌源性颞下颌关节紊乱病的疗效

Table 1　Efficacy of botulinum toxin type A in the treatment of myogenous temporomandibular disorders

Population	Symptoms	Administration site	Number of injections	Outcomes	Side effects	Reference
60(The BTX-A group n =20)	Masticatory myofascial pain syndrome.	Bilateral masseter(24-30 U), temporal(24 U), andlateral pterygoid muscles(8 U).	1	A significant reduction in pain and improvement of mandibular movements was found after 6 months.	Not found.	[36]
63(All patients received injections)	Masticatory muscle pain and disorders.	Bilateral masseter and temporalis muscles. Averaged 105 U.	Averaged 3.9 (Females); 1.8(Males)	8 patients (13%) not beneficial, 15 (24%) beneficial, 40(63%) highly beneficial. Female reported betterresponses than males.	Difficulty speaking or eating occurred in 8(3%). (The total number of injectionwas 249).	[22]
80(The BTX-A group *n* = 20)	Persistent myofascial pain.	Bilateral masseter(50 U) and temporalis muscles(20 U).	1	The mandibular movements significantly improved after 6 months.	Not found.	[23]
27(The BTX-A group *n* = 9)	Temporomandibular joint disc displacement with reduction (DDwR) with Pain and clicking.	The lateral pterygoid muscles(30 U).	1	BTX-A reduced joint pain, clicking, and improved disc position after 3 months.	Diminished contra-lateral mandibular movements.	[31]
52 (The BTX-A group *n* = 26)	Localized masticatory myalgia.	Bilateral masseter(36 U) and temporalis muscles(36 U) and lateral pterygoid muscles(36 U).	1	BTX-A reduced pain and improved muscle function after 3 months.	Not found.	[37]
15(The BTX-A group *n* = 7)	Clinical diagnosis of myalgia.	Bilateral masseter (50 U)and temporalis muscles(50 U).	1	Significant improvements in the myalgia scores were observed at the six-month follow-up.	Not found.	[38]

临床首选注射部位，翼外肌注射BTX-A的报道相对较少，因为翼外肌与上颌动脉及翼静脉丛关系密切，注射过程中发生并发症的可能性更高[39]。咀嚼肌注射用BTX-A的剂量目前缺乏统一标准，有文献资料建议BTX-A浓度为25～50 U/mL，单侧咀嚼肌初始剂量分别为：颞肌10～25 U；咬肌25～50 U；翼外肌7.5～15 U[16, 23, 35, 37, 40]。为保证药物充分作用于肌肉，应用低浓度药物在同一肌肉的多个部位给药，咬肌3～5个进针点，颞肌2～3个进针点。但为避免并发症的发生，有专家建议翼外肌仅进针一次，并严格控制剂量[16, 35-36]。

咬肌：根据触诊确定咬肌范围，沿肌肉长轴至少在3个部位间隔1 cm分别进针，回抽无血后注入药物[37, 39]。

颞肌：根据触诊确定颞肌范围，至少在两个部位间隔1 cm进针，为防止注射器针头破损，进针不需抵达骨面，或轻轻抵达骨面后再退针少许，回抽无血后注入药物[37, 39, 41]。

翼外肌：分为口外法和口内法。①口外法：嘱患者做下颌运动，通过触诊确认髁突位置。进针点在乙状切迹区皮肤，颧弓中央下1 cm，髁突前0.5～1 cm处以45°角向前内进针，回抽无血后注入药物[42]。②口内法：进针点为上颌第二磨牙远中根部的颊黏膜，与咬合平面成30°角，与中线成20°角，向上后外方向进针2～3 cm达翼外肌下头，回抽无血后注入药物[37, 41]。临床上更推荐口内法，因其类似常规牙科治疗口腔内局部麻醉，可减少患者害怕心理，其次可减少上颌动脉损伤或刺入静脉丛造成血肿的可能性，也避免了口外法注射时因患者下颌运动导致注射针折断等风险[43]。Yoshida等[44]在数字化导板引导下将BTX-A精准注射到M-TMD患者的翼外肌下头，数字化导板可将注射不当引起的并发症降到最低，并且已有团队发布了数字化导板引导下的翼外肌注射BTX-A技术指南[45]。

5　咀嚼肌注射BTX-A的并发症及预防

一项BTX-A用于面部美容治疗安全性的系统综述表明，局部注射BTX-A引起的不良反应大多为轻度和自限性的，表现为局部疼痛和表情肌瘫痪[46-47]。咀嚼肌注射BTX-A的剂量相对较低，不良反应少见，可表现为咀嚼无力、注射区组织损伤、药物扩散至非治疗区域等。其他轻微的不良反应如局部肿胀、感觉异常、吞咽困难等偶有报道，全身反应少见[41]。BTX-A在注射后可形成中和抗体诱发超敏反应，轻者表现为荨麻疹、眼睑水肿并伴有四肢肌肉无力，严重全身过敏反应非常罕见[47-48]。治疗前应详细询问患者过敏史，一旦过敏反应发生，应立即停止操作，行抗过敏治疗，必要时采取相应急救措施。

咀嚼肌注射不当可能会导致血管损伤引起出血。如翼外肌注射时可能损伤上颌动脉和翼静脉丛，造成出血或血肿，因此不建议将翼外肌作为首选注射部位，有条件的机构应在肌电图仪或超声等影像技术引导下操作[49]。此外，每次注射前应确保回抽无血。

注射器进针位置偏斜或注射剂量过多可能导致药物扩散到非治疗部位，引发相应症状。颞肌注射时进针太靠近眼眶，或注射剂量过多，药物可能会扩散到邻近区域导致眉下垂、上睑下垂甚至复视[46]。咬肌注射时进针太靠近颧大肌，可能会导致嘴角歪斜，如果药物扩散到腮腺，可能会导致唾液分泌减少，但这些症状都是可逆的，会在注射后3个月逐渐恢复正常[16, 39]。肌电图仪显示BTX-A可在注射点直径3 cm范围内扩散，因此精准进针和严格控制剂量能有效防止上述并发症的发生[46]。在肌肉边缘可降低药物浓度并减少剂量，进针点距离邻近重要结构1.5 cm以上，并嘱患者注射后3～4 h内减少下颌运动，有助于降低药物扩散风险[50]。

咀嚼肌接受过多剂量的BTX-A可能对肌肉和骨密度带来不良影响。BTX-A进入肌肉后约在注射后第7天开始起效，在第2～3周达到最大效应，并持续约3个月后才逐渐减弱[41]。3～6个月后需酌情考虑重复注射，以获得稳定疗效。在常规剂量和频率下注射BTX-A是安全的，Pingel等[51]的临床研究表明咀嚼肌注射常规剂量的BTX-A不会有显著的下颌骨密度相关改变。但有研究表明过高浓度或过高剂量的BTX-A会导致严重的肌肉萎缩和肌肉附着区域的骨密度下降[24, 51]。一项研究报道了一名女性每季度在单侧咀嚼肌注射高达140 U的BTX-A，一年后影像学检查发现注射侧关节发生了严重的髁突退行性变[52]。因此，对于需重复接受BTX-A治疗的患者，临床医师有必要进行骨密度监测。

6　BTX-A作为M-TMD保守治疗的优缺点

相较于佩戴颌垫等保守治疗方式，注射操作对患者依从性依赖较低，疗效更加可预见；对合并骨质疏松症、高血糖症、糖尿病等皮质类固醇应用禁忌证的M-TMD患者，BTX-A可作为皮质类固醇的替代药物[32]；若患者伴有咬肌肥大，咬肌给药后可使肌肉缓慢萎缩，可能带来潜在的美学收益[53]；但BTX-A在临床应用中仍存在一些问题，如BTX-A用于咀嚼肌的注射剂量、注射技术均缺乏统一标准[54]；不同厂商的药品规格存在差异，计算等效剂量存在困难[16]；BTX-A价格昂贵，重复注射费用较高[22]。此外，还应关注多次注射可能对骨密度及咀嚼肌带来的不良影响[51]。

7　小　结

咀嚼肌注射BTX-A可有效缓解肌痛和肌肉紧张，且不良反应少见、轻微、可逆，是治疗M-TMD的一种有效方法。对于经其他保守治疗效果不佳或希望通过单次诊疗获得较长时间疼痛缓解的M-TMD患者，咀嚼肌注射BTX-A可作为一种良好的治疗方案。但是需要临床医生充分了解BTX-A的作用机制、注射技术、局部和全身的不良反应，并谨慎选择适应证，才能在安全的情况下取得满意的治疗效果。

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