

内镜黏膜下剥离术后食管狭窄的防治研究进展*

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随着内窥镜切除技术和设备的发展,大面积食管病变的内镜切除变得越来越普遍。内镜黏膜下剥离术(endoscopic submucosal dissection, ESD)具有创伤小、恢复快、并发症发生率低等优势,目前已成为早期食管癌病变的首选治疗方法,然而ESD术后食管狭窄是常见并发症之一,尤其食管环周病变切除者,术后狭窄发生率几乎达到100%。激素、支架、球囊扩张、组织工程方法、食管黏膜移植等预防方式已被部分证明有助于预防ESD术后狭窄^[1],但是彻底防治ESD术后狭窄仍然是一个尚未解决的问题。为此,本文综述了ESD术后食管狭窄的各种预防方法,以期今后的诊治工作提供帮助。

内镜下球囊扩张术和放射状切开术

预防性内镜下球囊扩张术(endoscopic balloon dilatation, EBD)操作简单,是预防ESD术后食管狭窄的有效方法。Ezoe等^[2]评估了预防性EBD的疗效和安全性,纳入了41例大面积黏膜缺损患者,其中29例EBD组患者经过6个预防性EBD疗程之后,狭窄发生率为59%,而未行EBD的12例患者的狭窄发生率为92% ($P=0.04$),并且EBD组狭窄缓解的时间也明显缩短(29 d vs 78 d, $P=0.04$)。Lian等^[3]在29个ESD术后食管狭窄的患者中进行了117次球囊扩张,平均每人扩张次数是4次,其中28个患者在吞咽困难缓解后随访了3个月,其中2位再次出现吞咽困难,治疗成功率为92.9% (26/28)。近来Li等^[4]研究证实新的自助式EBD设备可让患者在家自行进行食管狭窄预防性扩张治疗。另外一些研究提示单独使用EBD预防ESD术后食管狭窄不足以有效预防狭窄,且患者花费大、不良事件累积风险加大,需寻求替代方法^[5, 6]。

Yano等^[7]采用放射状切开术治疗8例患者,手

术后所有患者的吞咽困难显著改善,但3个月后有效比例降为37.5% (3/8)。Xiang等^[8]在25例反复EBD治疗后的难治性食管狭窄患者中,采用放射状切开术(radial incision and cutting, RIC)和伤口局部注射激素联合治疗后仍有92%出现食管狭窄,但可减轻狭窄的程度和延长EBD治疗的间隔时间。Minamino等^[9]发现尝试了10次EBD后的2例难治性食管狭窄患者利用放射状切开术和切割方法手术后,在随访期间(分别50个月和41个月)未再出现狭窄,提示RIC是一种有效治疗狭窄的方式。但上述研究的病例数量较少,有待高质量研究进一步的阐述。

糖皮质激素治疗

食管ESD术后伤口愈合涉及炎症反应、细胞增殖、重塑和瘢痕形成等过程。糖皮质激素可阻止炎症细胞集聚,减弱炎症反应和抑制成纤维细胞增殖。胶原蛋白是主要的纤维结缔组织蛋白,糖皮质激素不仅可以抑制胶原合成,也可以促进胶原分解,从而多方面减少瘢痕形成^[10, 11],提示糖皮质激素可作为抑制ESD术后伤口瘢痕形成和预防食管狭窄的良好选择。

口服糖皮质激素 糖皮质激素是目前预防食管ESD术后狭窄的重要手段。Yamaguchi等^[12]报道了口服泼尼松可预防食管ESD术后狭窄的形成。他们在ESD后第3天开始口服泼尼松30 mg/d,逐渐减少该剂量(30、30、25、25、20、15、10和5 mg,每种剂量持续7 d),8周后停用。预防性的EBD组在ESD之后的第3天开始扩张,每周2次,持续8周。每当出现吞咽困难时,2组均按需进行额外的EBD。最终结果提示EBD组平均需要的EBD疗程数为15.6次,而口服泼尼松组为1.7次 ($P<0.01$)。Kataoka等^[13]观察了从30 mg开始口服泼尼松的疗效,每周降低10 mg,并在3周后停用泼尼松,结果显示口服泼尼松组的狭窄率为17.6%,远低于对照组

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的68.7% ($P < 0.01$)。但Bartel等^[14]发现对25例患者采用口服布地奈德(3 mg/次, 2次/d, 持续8周)的疗法未能降低食管狭窄率。

研究证实口服泼尼松可能有效,布地奈德可能缺乏疗效,然而全身性类固醇长时间使用可能引起各种不良反应,包括免疫抑制、感染、糖尿病、精神病、骨质疏松、视力损害和消化性溃疡疾病等^[15],减少全身性类固醇的剂量可能会减轻类固醇的不良影响,但也可能降低疗效,需要进一步研究口服类固醇的最佳剂量和服用时间。

局部糖皮质激素注射 通过将类固醇直接给药至术后伤口部位相比于全身性类固醇给药方式,其类固醇用量更少,全身性副作用更少,亦可抑制食管ESD后的炎症和纤维化,达到预防食管狭窄的效果^[16]。Takahashi等^[17]报道了一项随机对照研究,将使用25G的3 mm针头将10 mg/mL的0.5 mL曲安奈德注入人造溃疡的基底,间隔10 mm均匀重复注射。曲安奈德组扩张次数低于对照组(6.1次 vs 12.5次, $P = 0.04$),但穿孔率没有显著差异,提示内镜下曲安奈德注射可能是一种安全且有效的方法。Hashimoto等^[18]亦报道局部注射曲安奈德可防止ESD后食管狭窄,显示ESD术后第3、7、10天时接受0.2 mL(2 mg)曲安奈德局部注射的患者的狭窄率为19% (4/21患者),而对照组狭窄率为75%,且该团队在2019年研究再次证实在ESD术后当天和第14天给予曲安奈德药物局部注射,亚环周黏膜缺陷患者的ESD后狭窄率为45.7%,明显低于未行类固醇注射的对照组73.9% ($P = 0.031$)^[19]。近来有研究表明,将食管胃内空气吸尽后,利用曲安奈德填塞的方法亦可有效降低ESD术后食管狭窄^[20, 21]。也有研究证实口服类固醇激素联合局部注射的给药方式可显示出更好的预防食管狭窄的疗效^[16, 22, 23]。

局部激素注射可能导致食管壁坏死、穿孔等并发症^[24]。

聚乙醇酸片

聚乙醇酸(polyglycolic acid, PGA)薄板是一种可生物降解的高分子聚合物,可用于外科手术中加固缝合线、瘘管的修复、防止疤痕挛缩等^[25, 26]。食管ESD术后使用PGA可保护伤口表面不与外源物质接触,并抑制肉芽组织重塑从而实现预防狭窄^[27]。Iizuka等^[27]在ESD术后利用纤维蛋白胶将PGA贴在手术伤口上,结果显示食管黏膜缺损 $\geq 1/2$

的患者中有7.7% (1/13)发生食管狭窄。Sakaguchi等^[28]证实食管黏膜缺损 $\geq 3/4$ 环周的患者中有37.5% (3/8)发生食管狭窄,球囊扩张次数为(0.8 ± 1.2)次,但对于全周切除的患者几乎没有效果。

此外,有研究评估了局部使用曲安奈德注射和PGA片联合治疗对食管ESD术后狭窄预防的疗效^[29],在ESD术后立即将TA注射入溃疡中,然后用PGA片和纤维蛋白胶,结果显示联合治疗可能明显优于单独PGA,但是研究病例数较少,需要大规模病例研究进一步证实。

食管支架

既往研究表明自扩张式金属支架可以有效缓解食管良性疾病的狭窄程度和狭窄症状^[30]。Wen等^[30]为了防止食管ESD术后狭窄的形成,在食管黏膜缺损 $\geq 3/4$ 环周的患者中,在ESD后立即放置支架,并于8周后将其取出,狭窄率为18% (2/11),球囊扩张次数也明显下降(均值0.45次 vs 均值3.9次, $P < 0.05$),而无支架置入组狭窄率为72.7%。Yano等^[31]的研究结果显示ESD术后可生物降解支架的狭窄缓解率在12周和24周分别为66.7% (4/6)和0%,提示其短期效果可,但长期疗效欠佳。Chai等^[32]报告PGA联合支架放置的试验组食管狭窄的发生率为20.5% (7例),低于支架组(46.9%, 15例),提示PGA联合支架放置在预防ESD后食管狭窄性方面更为有效。Lu等^[33]在纳入75例难治性食管良性狭窄患者的一项回顾性研究中显示,支架置入组的狭窄缓解率(35%, 7/20)低于EBD组(70.9%, 39/55),提示支架置入的疗效弱于EBD的疗效。

无论是金属支架或者生物降解支架,其常见的不良事件包括出血、食管穿孔、支架移位、肉芽组织增生、胸痛和狭窄复发等^[31, 34],故支架置入尤其是金属支架在治疗良性食管狭窄方面的应用一直存在争议。考虑到支架置入的复杂性,不良事件发生率高且有其他预防性方法,如类固醇治疗等,未行环周切除术的患者不建议行支架置入。但是使用传统方法(例如局部TA注射、口服类固醇激素或PGA贴片)仍难以防止环周切除后形成狭窄^[35]。因此,在进行环周切除术或治疗难治性狭窄时,放置支架可能是一个不错的选择。

组织工程学方法

组织工程的概念,即移植的材料可以替代受损

的组织并保持生理功能并促进无疤的伤口愈合。预防食管狭窄的组织工程方法分为两类:基于细胞的治疗和基于支架的治疗。

基于细胞的工程学方法 移植细胞释放细胞因子和生长因子等并与其它宿主细胞相互作用,继而 对宿主产生一定营养作用^[36]。在犬动物模型中,研究者将采集的口腔黏膜上皮细胞粘附在溃疡底层的肌肉层上可缓解食管狭窄^[37]。在猪模型中,研究者利用人羊膜(human amniotic membrane)或人角质细胞片证实了其对ESD术后伤口的抗纤维作用和减轻食管狭窄^[38, 39]。Ohki等^[40]评估了黏膜缺损 $\geq 1/2$ 的9名患者使用自体口腔黏膜上皮细胞片的情况。他们采用离体技术制作了上皮细胞片,并在内镜下将其直接移植到溃疡表面,完全再上皮化发生的中位时间为3.5周,仅1名接受全周切除的患者出现狭窄。但直接将原代细胞注射到宿主器官中有两个主要缺点:低生存力和移植后从宿主部位快速扩散。为了克服这种局限性,Perrod等^[41]将脂肪组织来源的基质细胞片移植到切除部位,在猪模型中显示出ESD后实验组的狭窄率为17%,而对照组为100%。上述结果显示自体细胞移植在预防食管狭窄方面有着较好的应用前景。

基于支架的工程学方法 细胞外基质(ECM)支架可以支持上皮细胞的生长并促进伤口恢复,无细胞真皮基质(acellular dermal matrix, ADM)是一种ECM由去除细胞过程产生的支架,它去除了潜在的免疫原性物质,同时保留了生物学特性^[42]。Han等^[42]利用猪模型,在半环周食管ESD术后立即将ADM贴片移植应用于手术伤口处,ADM组中没有动物出现临床上显著的食管狭窄,而ESD对照组中有42.8%(3/7)出现狭窄。而Oumrani等^[43]在猪模型中证实环周食管ESD术后利用自组装肽基质可以使狭窄率降低67%。Hoppo等^[44]在内镜下环周切除后应用了ECM支架,3例患者均避免了狭窄。相反,Schomisch等^[45]报道了使用3种ECM支架(小肠黏膜下层、ADM和膀胱基质)预防狭窄失败,ECM支架的疗效仍存在争议。另外,由于ECM对于癌细胞和细菌的植入是有利的环境,因此担心支架材料可能导致更高的局部复发或局部感染的风险^[44, 46]。因此,在广泛应用于临床实践之前,ECM需要更多的研究。

食管黏膜移植

Liao等^[47]描述了食管黏膜移植防止环周ESD

后狭窄的形成,通过内镜黏膜切除术(endoscopic mucosal resection, EMR)从正常食管切下几块自体食管黏膜组织,并将其附着在手术伤口表面,用覆膜支架固定,手术后7d将支架移除,9名患者中有8名出现狭窄,但EBD的平均次数为2.7次,比既往报告明显减少。Hochberger等^[48]报道,将胃黏膜移植到部分食管伤口处后,5个月未出现狭窄,而未移植胃黏膜的食管伤口出现了狭窄。He等^[49]在3例患者中证明了自体食管黏膜移植的有效性,其中1例随访1年,可正常饮食,另外2例吞咽困难明显缓解。这种治疗结果令人鼓舞,然而,该技术是侵入性的,需要切除多块正常黏膜并进行了支架置入的辅助,过程较为复杂。

其他使用常规药物或材料的方法

A型肉毒杆菌毒素(BTX-A)是一种神经毒素,可抑制胶原纤维的沉积并改善肥厚性瘢痕。为了研究预防食管ESD后狭窄形成的方法,Wen等^[50]进行了一项包含67例患者的随机研究,纳入了ESD后黏膜缺损 \geq 食管环周1/2的患者,BTX-A组(11%)发生ESD后狭窄的百分比显著低于未注射的对照组(38%, $P < 0.05$),且没有发生与BTX-A注射相关的严重不良事件。但是在这项随机研究中,大多数入选患者的黏膜缺损小于食管环周的3/4,只有6名患者的黏膜缺损 \geq 环周3/4,且缺损非环周的。因此,需要对这种治疗方法进行更大样本且在黏膜缺损 \geq 食管环周3/4的患者进一步研究。

另外,还有其他一些抑制炎症和胶原合成的药物被尝试用于预防狭窄,例如抗肿瘤药丝裂霉素C^[51]、5-氟尿嘧啶^[52]、胸腺素 thymosin $\beta 4$ (T $\beta 4$)^[53]、广谱抗球虫药卤夫酮(halofuginone)局部注射^[54]和Hemospray止血粉^[55]等,但研究例数较少。近来Sato等^[56]证实,靶向作用于糖基转移酶15的小干扰RNA(small interfering RNA, siRNA)黏膜下注射可减少食管狭窄的发生。

食管大面积病变ESD术后狭窄这一临床问题目前尚未有十分有效的预防方案,尤其是涉及近环周或环周食管病变的ESD患者,狭窄发展的风险极高,而本综述中所述的预防策略的疗效有限,激素及其它药物、以及相关技术和材料等已经在实验和/或临床研究中进行了不同程度的尝试,但相关临床研究样本量较少,仍没有高质量证据的结果获得普遍认可,有待于未来进一步探索。

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