

·综述·

结直肠黏膜病变内镜黏膜下剥离术后电凝综合征的临床研究进展

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【提要】 结直肠癌已成为全球癌症相关死亡的第2常见原因, 结直肠内镜黏膜下剥离术(endoscopic submucosal dissection, ESD)是根治早期结直肠癌变的有效手术方式。与ESD相关不良事件包括出血、穿孔及术后电凝综合征(post-ESD electrocoagulation syndrome, PEECS)等。PEECS以一过性发生发热、白细胞升高、压痛反跳痛等腹膜刺激症状为主要表现, 相较术后出血及穿孔, 通常重视不够。PEECS具体发生机制尚未明确, 针对其高危因素识别和预防尤为重要。

【关键词】 结直肠肿瘤; 电凝术; 综合征; 内镜黏膜下剥离术

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Clinical research progress in electrocoagulation syndrome after endoscopic submucosal dissection for colorectal mucosal lesions

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结直肠癌全球发病率及死亡率持续增加^[1-2], 已成为全球癌症相关死亡的第2常见原因。结肠镜检查是发现早期结直肠癌的关键, 各种微创内镜可用于早期结直肠癌的根治治疗。内镜黏膜切除术(endoscopic mucosal resection, EMR)已成为治疗早期结直肠癌的标准术式之一^[3-5], 具有安全方便的优点, 但当病变长径 ≥ 20 mm时, 病变的完整切除率较低^[6-8]。内镜黏膜下剥离术(endoscopic submucosal dissection, ESD)是在EMR基础上发展而来, 其优势在于对于较大的病变也能实现完整切除, 并提供准确的病理诊断, 避免局部复发^[9-10]。一项荟萃分析显示, 结直肠黏膜病变ESD术后2年随访期内的复发率仅为1%^[11]。与传统的外科手术相比, 结直肠ESD手术具有创面小、恢复快、安全有效的优势。

ESD最初在日本、韩国等东亚国家被广泛应用于食管、胃的早期癌症微创切除^[12-13], 而结直肠ESD则是20世纪90年代首先由Yamamoto等^[14]和Fujishiro等^[15]率先在日本开展, 至今技术已逐步成熟。由于结直肠肠壁血运丰富、肠壁薄、肠身曲度大且有皱褶, 因此结直肠黏膜病变的手术难

度及术后并发症的发生率高, 需引起重视^[16-17]。与EMR相比, 结直肠黏膜病变ESD术后的并发症发生率更高, 主要包括: 出血、穿孔以及术后电凝综合征(post-ESD electrocoagulation syndrome, PEECS)等, 其中术后穿孔和出血概率分别为2%~14%和0.7%~3.1%^[18-20], PEECS发生率为4.8%~40%^[21-26]。

PEECS发生率虽较高, 但相比出血、穿孔其临床症状更为隐匿, 过去未能引起足够的重视。如临床怀疑发生PEECS, 由于其症状隐匿, 通常需要行CT等影像学检查以鉴别诊断, 将延长住院时间并给患者带来不必要的生理、经济甚至精神负担。鉴于对PEECS的认识还比较匮乏, 需引起广泛关注。

一、PEECS的定义

息肉切除术后电凝综合征(post-polypectomy coagulation syndrome, PPCS)一词最初由Waye于1981年提出, 在最初的报道中指的是在没有明显穿孔的情况下, 经内镜治疗息肉切除后出现腹痛、发热、白细胞增多和腹膜炎症, 文献指出PPCS发生率约为1%^[25, 27]。

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PEECS以排除穿孔后一过性发热、白细胞升高、压痛反跳痛等腹膜刺激症状为主要表现^[23]。一般发生于术后数小时至术后7 d^[18,28]。由于PEECS症状与术后穿孔具有一定的相似性,故对其早期识别十分重要,如临床发现可疑症状需立即行腹部X线和(或)计算机断层扫描(CT)以鉴别排除穿孔。

PEECS具体定义为结直肠黏膜ESD术后,一过性出现局部压痛反跳痛,伴发热($\geq 37.8^{\circ}\text{C}$),白细胞增多($\geq 10.8 \times 10^9/\text{L}$)或升高的C反应蛋白(C-reactive protein, CRP)水平($\geq 0.5 \text{ mg/dL}$)^[29]。其中腹痛程度可采用视觉模拟量表(visual analogue scale, VAS)描述^[30],它由一条水平线组成,长度为0~10 cm,代表从无疼痛至最严重的疼痛评分0~10分。当VAS评分超过3分被定义为腹痛^[31-32]。

二、PEECS的临床特征

1、发生率

综合统计国内外现有文献估计PEECS的发生率为4.8%~40%^[21-26],但近5年文献提示,PEECS的发生率显著降低^[29,33],这可能与结直肠ESD手术技术日渐成熟相关。同时随着导致PEECS的危险因素被更加深入地探究,PEECS的概念被更多的术者了解,因此其发生率有所下降。

2、发生机制

目前针对于PEECS的发生机制尚不明确,主要存在两种学说:一是认为由于电流延伸至固有肌层及浆膜层引起跨壁烧伤^[34-36],进而引起类似延迟穿孔的一系列临床症状;二是认为ESD术后暴露黏膜缺损,细菌污染创面所导致的炎症反应^[22,37-39]。此外也有文献指出^[23],应用于黏膜注射的导管相关感染也可能是PEECS发生的一种机制^[39-40],该学说认为注射针导管可以在黏膜下注射期间将细菌直接接种到血流中,但此点尚未得到广泛证实。

3、PEECS的危险因素

进入21世纪以来,随着PEECS概念的提出,对导致PEECS危险因素的探究也日渐深入。既往有文献调查了导致PEECS的危险因素,首先是肿瘤的位置。右侧结肠相较于其他位置存在较高发生PEECS的风险^[21-22,27,41]。Arimoto等^[27]的一项纳入106例患者的前瞻性研究中,有15例(14.2%)发生PEECS,其中10例为女性 $[P=0.01, OR=7.74(1.6\sim 36.4)]$,7例为右半结肠及盲肠周围病变 $[P<0.001, OR=20.6(3.7\sim 115.2)]$ 。从解剖结构来说,右半结肠相较左半结肠更薄,因此手术难度更大,在剥离过程中更容易损伤肌层。盲肠的解剖位置在一篇文献中被特殊提及^[26],其推测盲肠肠壁的特殊解剖结构导致其延展性更强,容易被拉伸,电凝后的热量可能更容易延伸到固有肌层,故认为盲肠的解剖形状和免疫功能参与了PEECS的进展过程;直肠发生PEECS概率最低,概因其部分解剖结构位于腹膜折返以下,导致炎症无法传导至腹部,无法出现腹痛等症。

其次,发生PEECS的危险因素是肿瘤的大小^[21-22,27,42]。有文献提示^[21],肿瘤大小 $\geq 3 \text{ cm}$ 及时间较长($\geq 70 \text{ min}$)的手

术是PEECS的独立危险因素。该文献对82例患者进行分析,PEECS风险为40.2%。在PEECS组中,切除标本的平均大小和平均手术时间均大于无PEECS的对照组。在多变量分析中,病变 $>3 \text{ cm}$ 是发生PEECS的独立危险因素($OR=5.0, 95\%CI: 1.2\sim 21.7$)。分析原因可能是肿瘤较大,剥离难度提升,引起手术时间延长,出血风险增加,进而需要更多电凝以局部止血及创面炭化,出现高焦耳热积累,对剥离的黏膜表面造成严重损害,导致PEECS。有文献报道胃肠道壁内的焦耳热累积与PEECS的发生有关,ESD相关的黏膜剥离表面的热损伤可能是PEECS机制的重要组成部分,结直肠ESD手术期间高总焦耳热暴露是PEECS的危险因素,发生PEECS的焦耳热截止值为15 390 J^[43]。

黏膜下纤维化也是PEECS发生的一大影响因素^[26,44]。研究发现结节混合型颗粒侧向发育性肿物严重纤维化的发生率明显高于均匀型侧向发育性肿物^[45-46]。导致黏膜下纤维化的原因还包括:肿物最大长径 $>3 \text{ cm}$,黏膜下的深部浸润等^[24]。黏膜下纤维化的发生,导致剥离的难度增加,间接延长手术时间以及电凝时间,故黏膜下纤维化患者更易发生PEECS。

女性患者似乎是PEECS的一个独立影响因素^[22,26-27]。由于男女对疼痛的感知力不同,女性对疼痛刺激的耐受性和阈值低于男性^[47-49],而用于判断腹痛程序的VAS是一项主观性很强的参考指标。此外,女性通常比男性更容易患上一些与情绪相关的胃肠功能性疾病,如肠易激综合征或功能性腹痛综合征,以及如剖宫产手术等手术史,导致的肠道粘连亦使女性患者腹痛程度增加。

操作的经验水平也是危险因素之一。有研究表明^[43,50-51],正在学习ESD手术的操作者相较独立完成超过50例ESD手术的经验丰富的操作者,发生PEECS的概率更大,概因不娴熟的操作,延长了手术时间。

一些外科相关研究证明,长期小剂量服用泼尼松及免疫抑制剂的患者,更易出现感染等相关疾病^[52]。Yamamoto等^[53]研究显示,因一些疾病需要免疫抑制剂和小剂量泼尼松(约5 mg)作为维持治疗的患者行结直肠ESD时,似乎更容易发生后发热等症状;使用更为敏感有效的16S rRNA聚合酶链反应技术,评估菌血症与发热及PEECS发生的关系,结果ESD术后发热率12.4%,提示PS-ASA和免疫抑制剂等负性免疫反应因子可能会导致ESD术后发热,从而导致PEECS。

4、PEECS的预防

ESD术后可以从血液中分离出凝固酶阴性葡萄球菌、枯草芽孢杆菌和其他芽孢杆菌^[39]。Lee等^[23]的一篇随机对照试验提示,预防性使用抗生素可有效降低结直肠ESD术后PEECS的发生率。抗生素治疗已被推荐用于胆囊切除术后凝血综合征^[34],而近期来自日本的一项多中心前瞻性研究却有着不同的观点,该研究在21所日本高等院校进行的前瞻性、多中心、随机对照、平行试验^[29],共432例患者被随机纳入抗生素组及非抗生素组,抗生素组192例患者中9例

(4.7%)发生 PEECS,非抗生素组 188 例患者中 14 例(7.5%)发生 PEECS,差异无统计学意义($P=0.29$);非抗生素组 PEECS 发生率仅 7.5%,可能是导致此项研究产生阴性结果的原因。对于 PEECS 的潜在机制,抗生素虽然可以抑制肠道菌群的感染,却无法预防电凝所产生的电流损伤,因此抗生素对于 PEECS 的预防是片面的;对于远端肠腔(如升结肠、横结肠)因滞留的粪水、粪渣更多,相对感染风险更高,可能抗生素的预防能够起到有效的效果,而近端肠腔如直肠,效果可能不明显^[23]。

有研究提示对创面预防性夹闭也可能降低 PEECS 的发生率^[36,54]。有文献介绍了一种线辅助完全夹闭术(line-assisted complete closure, LACC),这是一项治疗结肠直肠 ESD 术后大面积黏膜缺损的新技术^[54]。在该文献中,LACC 组中 PEECS 的发生率、平均住院时间,均明显低于对照组($P<0.05$)。LACC 的一个主要优点是防止大的黏膜缺损接触污染物质,如粪便和细菌。因此,LACC 可降低局部感染的发生率,但这同样不能有效降低电凝所带来的炎症反应风险。在另一篇文献中^[36],作者比较了普通金属夹缝合及进口吻合夹(OTSC)夹闭缝合预防性闭合结肠 ESD 术后大面积黏膜缺损的疗效和安全性。由于 OTSC 能够抓取更多的组织,并施加更大的压缩力,因此它比普通金属夹有着更高的夹闭效率,但二者均可有效地防止局部腹膜炎,缓解结肠 ESD 术后患者的腹部症状。然而,目前的研究并未证明创面夹闭可以减少穿孔和术后出血的发生。有文献指出普通金属夹行创面夹闭似乎并不能预防 PEECS 的发生^[33,55],但创面夹闭对于已经发生穿孔的创面恢复能够起到积极的作用^[56]。有研究将 PEECS 分为 2 种类型:I 型 PEECS,无腔外空气的 PEECS;II 型 PEECS,含腔外气体的 PEECS。相应地,结肠 ESD 术后腹腔内有自由空气可被定义为真正的延迟穿孔;含腔外气体的 PEECS 可能与黏膜下注射相关,未被定义为穿孔^[56]。

不同的圈套器材料也可能会对 PEECS 的发生产生影响。Galloro 等^[57]的一篇文章表明,对息肉切除术中使用的所有 3 种电流模式下的钨和钢圈套进行的比较表明,钨圈套产生的热量不仅分布均匀,而且也很集中,与钢圈套相比,切割的选择性更强。当与切割或混合电流模式结合使用时,会导致较低的热相关并发症发生率。

5. 治疗和预后

PEECS 一般发生于术后 1~7 d,最常见为术后 6~12 h^[35],一般住院时间约为 5.5 d^[58]。术后患者每日需检测体温,如临床发生体温升高,伴腹痛及白细胞、CPR 增高的情况,须立即行腹部 CT 等影像学检查以排除穿孔。经证实未见穿孔者可行保守治疗。针对 PEECS,一般经保守治疗可以得到改善,包括禁食、补液及常规使用抗生素、止疼药等^[55,58]。本病预后良好,一般无须外科手术治疗。

PEECS 是结肠 ESD 术后的常见问题之一,其具体发生机制尚需进一步探究。得益于 PEECS 概念的普及、手术操作水平的提升,近年来文献报道其发生率逐步降低。

PEECS 的早期识别及预防非常重要,其危险因素可能包括:肿瘤位置、较大的肿物、手术操作时间、黏膜下纤维化、女性患者及操作者经验水平等。针对 PEECS 的预防,预防性使用抗生素及预防性的创面夹闭效果尚存争议。临床如发生疑似 PEECS,需立即行影像学检查,如未见穿孔情况,行保守治疗,预后良好。

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