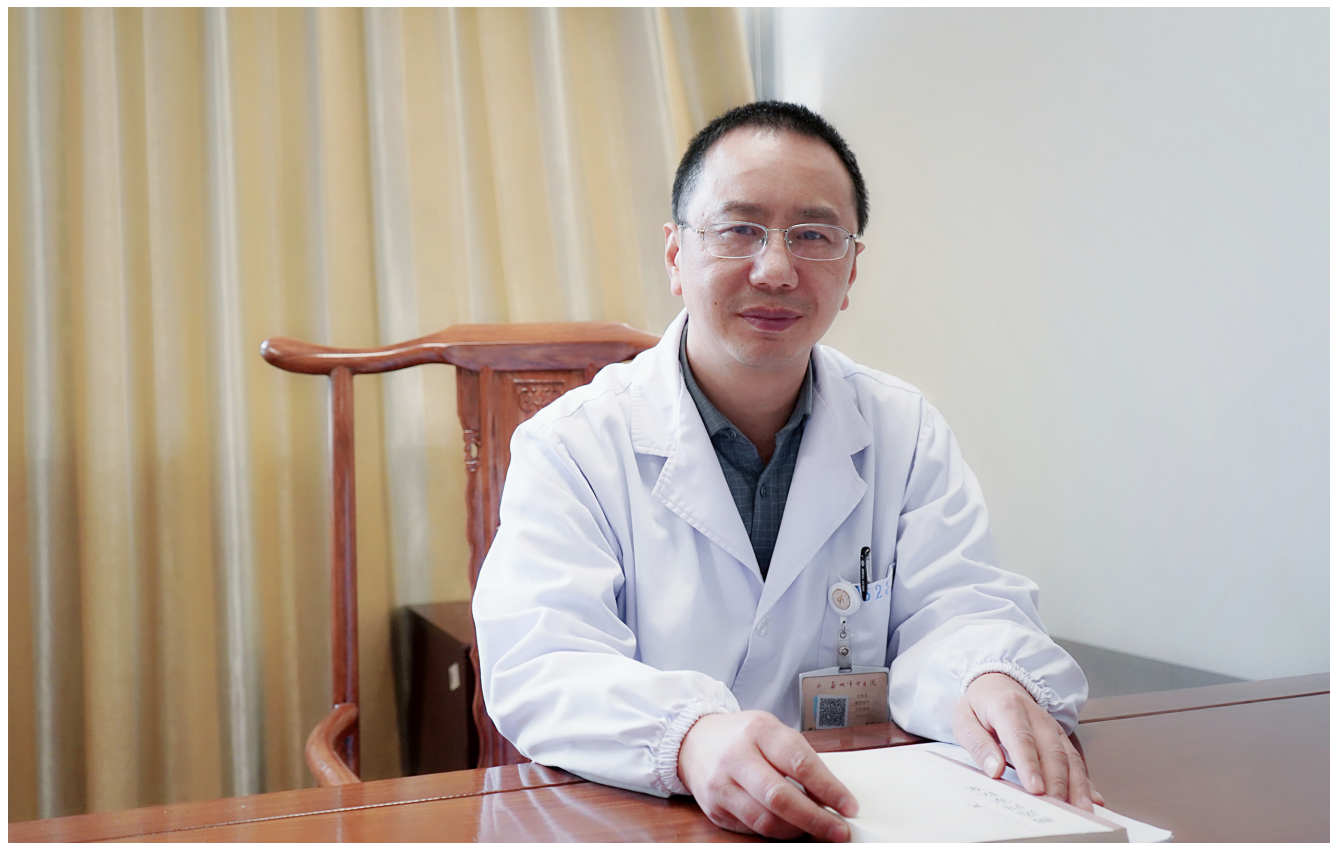


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止血粉治疗急性上消化道出血的研究进展

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Hemostatic powder for acute upper gastrointestinal bleeding: Recent research advances

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Abstract

Acute upper gastrointestinal bleeding (AUGIB) is a clinically common emergency condition. The common causes of AUGIB are peptic ulcer and esophagogastric variceal bleeding. Despite continuous improvements in endoscopic hemostasis techniques, endoscopic treatment is still unsuccessful in 5%-15% of patients. Hemostatic powder, a new drug for endoscopic hemostasis that is sprayed on the bleeding site with the assistance of an air pump, can absorb water to promote clotting substance aggregation and then adhere over the lesion, forming a mechanical barrier and then achieving hemostasis. It is convenient to spray hemostatic powder under endoscopy, where precise positioning is not warranted. The immediate hemostasis rate of hemostatic powder is often high, and it can be used as a remedy after the failure of conventional hemostasis. However, until now, there have been no recommendations in China regarding the use of hemostatic powder for the treatment of AUGIB. This article summarizes the mechanism, clinical applicability, and side effects of five major types of hemostatic powder by reviewing the existing evidence, with an aim to strengthen endoscopists' understanding of this drug.

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Key Words: Acute upper gastrointestinal bleeding; Peptic ulcer; Esophagogastric variceal bleeding; Hemostatic powder

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摘要

急性上消化道出血是临床常见的急危重症之一。最常见的病因是消化性溃疡和食管胃底静脉曲张破裂出血。尽管内镜下止血技术不断改进, 但仍有5%-15%的患者内镜下止血治疗失败。止血粉是内镜下止血的新兴药物, 呈白色粉末状, 在气泵的辅助下喷洒至出血部位, 通过吸收水分以促进凝血物质的聚集和粘附在病变上方形成机械屏障等途径达到止血效果。该技术操作简单、无需精确定位并具有较高的即刻止血率, 可作为常规止血无效的补救措施。然而, 国内尚未推荐止血粉用于治疗急性消化道出血。本文旨在总结现有研究证据, 阐述常见的五种止血粉的作用机制、临床应用及不良事件, 以期加强内镜医生对止血粉的认识。

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关键词: 急性上消化道出血; 消化性溃疡; 食管胃底静脉曲张破裂出血; 止血粉

核心提要: 止血粉是内镜下止血的新兴药物, 白色粉末状, 在气泵的辅助下喷洒至创面, 通过促进凝血物质的聚集和形成机械屏障等途径达到止血效果。该技术操作简单、无需精确定位及高即刻止血率, 可作为常规止血无效的补救措施。

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0 引言

急性上消化道出血(acute upper gastrointestinal bleeding, AUGIB)是指屈氏韧带以上的消化道(食管、胃和十二指肠)出血, 是临床上常见的急危重症之一^[1,2], 据报道, 其发病率为(100-180)/10万^[3], 死亡率为2%-10%^[1]。患者多表现为呕血、黑便等^[1-3]。AUGIB最常见的两种病因是消化性溃疡和食管胃底静脉曲张破裂出血, 其他病因包括食管炎、血管畸形、Dieulafoy病、食管黏膜撕裂症(Mallory-Weiss综合征)、恶性肿瘤、胃窦血管扩张症以及腹主动脉十二指肠瘘等^[4]。内镜在AUGIB的治疗中起着重要作用。AUGIB发生后的24 h内应进行内镜检查^[2], 对于疑似静脉曲张破裂出血者应在12 h内进行内镜检查^[3,5]。尽管内镜下止血技术在不断改进, 如局部药物注射、高频电凝、热探头、氩离子凝固术、机械止血(止血夹、套扎)等^[1,2,6,7], 但仍有5%-15%的患者在内镜下止血失败^[8]。此外, 常规内镜下止血常需要医生具有较高的专业技术,

而这对于基层或急诊的年轻医师来讲有一定难度^[9]。

止血粉为内镜下止血提供了一种新的治疗方式(表1)。止血粉是植物来源的组织黏合剂, 呈白色粉末状, 在气泵辅助下通过输送管将止血粉喷洒至出血部位, 可快速吸收水分以促进局部凝血物质的聚集, 并粘附在管壁上形成机械屏障, 从而达到止血效果^[10-14]。因此, 内镜下止血粉止血操作简单, 无需精确定位, 初级内镜医生在短时间内学习即可掌握; 其也可作为常规止血无效的补救措施(如十二指肠后壁、胃体小弯侧等难以接近的位置或肿瘤相关的消化道出血、食管胃底静脉曲张破裂出血等)^[11,15-19]。目前, 止血粉已被欧美等多个国家的临床实践指南推荐用于AUGIB的内镜下治疗^[2,5,6,20], 而我国指南暂未推荐止血粉^[21]。鉴于此, 本文旨在总结目前常用于AUGIB治疗的止血粉, 并概括它们的作用机制、临床应用证据及不良事件, 从而指导临床应用。

1 TC-325(Hemospray)

TC-325(Hemospray)是一种无机物粉末, 在内镜下由高压的CO₂推进器将其通过导管在距离出血部位上方约1 cm-2 cm处进行喷洒。当TC-325与胃肠道血液接触时, 会变得具有粘性, 从而粘附并覆盖在出血部位, 形成稳定的机械屏障, 并激活凝血系统, 促进血凝块形成, 进而达到快速止血的目的^[10,12,22-24]。在1 d-3 d内, 粘附层会逐步从管壁脱落并从肠道排出^[10]。

TC-325是目前研究最多的止血粉制剂, 已成功用于多种疾病, 包括消化性溃疡^[10,25,26]、肿瘤相关性上消化道出血^[26-28]、内镜下黏膜切除术及内镜黏膜下剥离术的术中和术后出血^[28,29]、抗凝药相关性出血^[30]、静脉曲张破裂出血^[17,31-33]、门脉高压性胃病^[34,35]及憩室出血^[36]。Sung等^[10]完成的一项前瞻性研究首次探讨了内镜下使用TC-325治疗消化性溃疡的疗效及安全性, 研究共纳入了20例上消化道溃疡伴出血(Forrest分级 I a和 I b)的患者。19例(95%)患者即刻止血; 术后72 h内再次行内镜检查, 均未出现活动性出血; 30 d内随访无严重并发症及死亡事件发生。此后, 多项小型病例系列研究相继表明TC-325在肿瘤相关性上消化道出血^[26-28,37]、静脉曲张破裂出血^[32]、门脉高压性胃病^[34]以及内镜下治疗术中出血^[29]均有着较高的即刻止血率。Ibrahim等^[31]完成的一项随机对照试验表明, 急性食管胃底静脉曲张破裂出血的患者早期(<2 h)使用TC-325可显著减少24 h内的临床再出血, 且TC-325显著提高患者6 wk生存率(7% vs 30%, $P=0.006$)。总体上, TC-325的即刻止血率为95%-100%, 30 d再出血率为8.1%-33.5%^[10,36,38,39]。

TC-325是由高压的CO₂推进器将止血粉喷射在出血部位, 在胃腔中瞬间产生较高的压力, 严重时可能出现

表 1 内镜下止血粉应用总结

	TC-325 (Hemospray)	Endoclot	ABS	UI-EWD	CEGP-003
产地	美国	美国	土耳其	韩国	韩国
作用机制	粘附并覆盖在出血部位, 浓缩血小板和凝血因子	形成凝胶覆盖出血部位, 促进血小板和凝血因子的聚集	形成蛋白质网、促进红细胞聚集	形成粘性凝胶, 在出血部位形成机械屏障	形成粘性凝胶, 促进局部伤口愈合
起效时间	即刻	即刻	即刻	即刻	即刻
维持时效	24 h-72 h	3 h-48 h	不详	48 h	72 h
适用范围	弥漫性出血、肿瘤相关性消化道出血、常规止血无效的补救措施、急诊手术前的桥接、经验不足的内镜医师				
临床应用报道	消化性溃疡、肿瘤相关性上消化道出血、术中出血(内镜下黏膜切除术、内镜黏膜下剥离术等)、抗凝药相关性出血、静脉曲张破裂出血、门脉高压性胃病、憩室出血等	肿瘤相关性上消化道出血、消化性溃疡、静脉曲张破裂出血和术后出血(内镜下黏膜切除术、内镜黏膜下剥离术等)	消化性溃疡、肿瘤相关性消化道出血、括约肌切开后出血、Mallory-Weiss综合征、息肉切除术后出血、静脉曲张破裂出血、消化道出血等	介入术后、吻合口、消化性溃疡、肿瘤相关性消化道出血	消化性溃疡、术后出血(内镜下黏膜切除术、内镜黏膜下剥离术)
不良事件	腹痛、腹胀、穿孔、胆道梗阻、血栓栓塞和内镜孔道堵塞	喷雾导管堵塞	穿孔	喷雾导管堵塞	暂无
禁忌症	疑似胃肠道穿孔或在内镜手术期间有穿孔风险高者; 药物过敏者	暂无	暂无	暂无	暂无

胃肠道穿孔等不良事件^[40]。另外, TC-325仅粘附在活动性出血的病变上, 故再出血风险高, 从而限制了其在非活动性出血和再出血高风险病变中的疗效^[14,17,26,36,41-44]。有学者建议^[1,42,45], 在严重动脉性出血的情况下, TC-325可暂时止血以稳定生命体征, 但仍建议术后24 h内复查内镜。最近发表的欧洲胃肠道内镜学会指南不建议使用TC-325作为急性食管或胃静脉曲张破裂出血的确切性内镜治疗方法; 但当标准内镜治疗无效或不可用时, TC-325可考虑作为确切性治疗的桥接^[46]。综上所述, 疑似胃肠道穿孔或在内镜手术期间穿孔风险高的患者应禁用TC-325, 再出血风险高的患者可联用传统的止血方法。

止血粉用量往往不大, 发生不良事件的几率很低, 包括喷洒后立即出现的自限性腹痛和腹胀、穿孔、胆道梗阻、血栓栓塞和内镜孔道堵塞^[15,42]。

2 Endoclot

Endoclot止血装置中的AMP[®]颗粒来源于植物淀粉, 具有快速从血液中吸收水分的作用, 从而在出血部位引起血小板及凝血因子浓缩, 进而加速凝血级联反应, 且AMP[®]颗粒在吸水后形成凝胶, 粘附在出血病变表面, 形成机械屏障, 最终达到快速止血效果^[24,44,47,48]。AMP[®]颗粒在3 h-48 h内可被胃肠道中的淀粉酶和葡萄糖淀粉酶降解, 且易通过盐水冲洗去除, 因此, 若止血效果不理想, 其可被重新使用^[47,49]。

与TC-325止血粉类似, Endoclot已被用于各种AUGIB相关事件^[48-52]。Endoclot的即刻止血率为82%-100%^[47,48], 30 d再出血率为4.8%-16%^[47,52]。一项观察性研究表明^[47], 与其他内镜治疗方法相比, Endoclot有较高的即刻止血率, 而在30 d再出血率及死亡率方面无差异。Vitali等^[40]比较了TC-325与Endoclot治疗AUGIB的疗效的差异, 出血的主要病因包括消化性溃疡、食管胃底静脉曲张破裂出血、肿瘤相关性上消化道出血、反流性食管炎、弥漫性出血; 研究发现, 无论急诊还是挽救性治疗, TC-325与Endoclot在3 d和30 d的止血率及再出血率方面均无差异。与TC-325相比, Endoclot的优势在于粉末的输送方式: TC-325是由高压的CO₂推进器将止血粉喷射在出血部位, 而Endoclot止血装置由恒定压力的压缩机推动止血粉, 过程相对平稳, 腔内压力无明显增加, 进而减少了穿孔的风险。然而, 与TC-325相比, Endoclot对内镜医生的技术要求相对较高^[40,50]。综上, 除表浅的出血性病变外, Endoclot也可用于凹陷性的出血病变。

两项研究报道了喷雾导管堵塞的不良事件^[47,50], 但未观察到其他与手术相关的不良事件。

3 Ankaferd Blood Stopper (ABS)

ABS是土耳其研发的一种新型外用止血剂, 由五种不同植物(百里香、葡萄、光果甘草、良姜、大荨麻)提取组成^[53,54]; 当其与血液接触时, 通过形成蛋白质网、促进红

细胞聚集并激活凝血级联反应等多种途径发挥止血效果, 且对血管再生及细胞增殖有促进作用^[53,55,56]。

内镜下应用ABS成功治疗各种AUGIB的病例已有研究报道^[12,14,53-55,57-60]。Gungor等^[58]报道了内镜下局部喷洒ABS的即刻止血率为73.1%, 再出血率为15.8%。Turhan等^[60]认为ABS可减少消化道肿瘤的血管形成。该研究中, 2例因肿瘤相关性消化道出血患者局部应用ABS, 并测量ABS应用前、后的肿瘤微血管密度; 研究发现, 局部使用ABS可实现即刻止血, 且可显著降低胃肠道肿瘤组织的肿瘤微血管密度。Kurt等^[57]回顾性分析了因肿瘤相关性消化道出血而接受ABS治疗的10例患者; 所有患者均实现即刻止血, 且48 d内均未再出血, 并在无出血期接受手术治疗; 研究表明ABS可作为术前的桥接。因此, ABS对于肿瘤相关性消化道出血具有较好的疗效, 但仍需大样本研究来明确其抗肿瘤血管生成的特性。另外, ABS主要通过激活凝血级联反应来促进止血, 故建议凝血功能障碍或正在服用抗凝药物的患者联用传统止血方法。

有报道^[61], 1例胃十二指肠淀粉样变性患者在局部应用ABS的3 d后发生十二指肠穿孔, 但不排除穿孔与疾病本身有关。

4 UI-EWD

UI-EWD由氧化葡聚糖和琥珀酸修饰的氨基酸组成, 具有生物相容性和可降解性。当UI-EWD与水接触时, 经过席夫碱反应后形成高粘性凝胶, 随后附着在创面表面, 形成机械屏障以实现止血^[62,63]。

Park等^[64]回顾性分析了因急性非静脉曲张性上消化道出血而接受UI-EWD单药治疗的56例患者, 出血的主要病因是介入术后、吻合口、消化性溃疡及肿瘤相关性消化道出血。在所有病例中, UI-EWD均成功用于出血部位, 即刻止血率为96.4%, 30 d再出血率为3.7%; 术后3 d复查内镜显示39%的患者创面附着的凝胶未脱落, 这表明创面保护的时间更长^[64]。而对于Forrest分级1a的病変, 只有50%的患者达到了即刻止血^[63]; 对肿瘤相关性消化道出血的患者, 即刻止血率为97.5%, 7 d再出血率为7.5%, 28 d再出血率为22.5%^[65]。由于UI-EWD无需形成血凝块来实现止血, 因此它具有预防出血的作用, 可用于非活动性出血的病変中^[62]。

一项研究报道了喷雾导管堵塞的不良事件^[64], 但未观察到与手术相关的不良反应。

5 CEGP-003

CEGP-003粉末是由羧乙基纤维素和表皮生长因子组成。当CEGP-003接触潮湿的粘膜时, 会变成一种粘性凝胶,

从而保护伤口免受胃内高酸性环境的影响; 此外, 表皮生长因子可与表皮生长因子受体结合, 诱导透明质酸和水通道蛋白3的合成, 进而促进创面愈合, 减少再出血^[15,66]。在3 d内, 凝胶从管壁脱落并经肠道排出^[66]。

一项随机对照研究比较了CEGP-003与肾上腺素注射治疗AUGIB的疗效的差异, 共纳入72例患者, 出血原因包括消化性溃疡、内镜下黏膜切除术和内镜黏膜下剥离术后出血; 研究发现, CEGP-003组比肾上腺素组的即刻止血率更高, 且无手术相关的不良事件发生; 研究表明^[66], CEGP-003治疗AUGIB是安全且有效的。据报道^[66], CEGP-003的即刻止血率为100%, 术后3 d的再出血率为8.6%。因此, CEGP-003可用于消化性溃疡及内镜下治疗术后出血, 但仍需更多随机对照研究来评估其用于其他AUGIB事件的疗效。

由于相关研究少, 尚无与CEGP-003相关不良事件的病例报告。

6 结论

综上, 止血粉作为内镜下止血的新型手段, 具有较多优势。首先, 该技术操作简单, 学习曲线短; 其次, 无需精确定位即可实现快速止血, 可作为AUGIB的主要治疗方法或作为常规止血无效后的补救措施; 此外, 对于肿瘤相关性消化道出血的患者, 可作为术前的桥接以暂时止血, 从而避免急诊手术。然而, 动脉性出血需谨慎使用止血粉, 因其再出血率较高, 故术后24 h内需重复内镜检查。未来需要更多的前瞻性研究来评估止血粉是否可作为肿瘤相关性消化道出血及消化性溃疡尤其是Forrest分级为Ib的内镜下止血的首选药物以及其联合传统止血方法治疗AUGIB的疗效; 另外, 传统常规止血方法相对价廉, 因此还应进行止血粉治疗急性上消化道出血的成本-效益分析; 此外, 应进一步明确止血粉的适应症和禁忌症。

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• 消息 •

书 讯



本刊讯 由池肇春教授等主编的《代谢相关脂肪性肝病肝外并发症》已由天津科学技术出版社出版发行。

本书的出版为国内首创, 填补了国内有关这方面的空白, 拓宽了对《代谢相关脂肪性肝病》认识的高度和深度。《代谢相关脂肪性肝病肝外并发症》分总论和各论两部分。1-4章为总论, 分别介绍代谢相关脂肪性肝病肝外并发症研究现状与进展, 包括发病风险、发病机制和治疗近展; 脂肪代谢生物化学和分子生物学; 代谢相关脂肪性肝病肝外并发症免疫学; 肠道微生物生态失衡与代谢相关脂肪性肝病肝外并发症。5-18章为各论, 分别介绍代谢相关脂肪性肝病肝外并发症与机体各系统疾病的相关性。可为消化科、肝病科、内分泌代谢科、普外科、肿瘤科、影像科、其他相关科临床医师和从事MAFLD研究的人员学习和参考。

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