

# ERCP术后胰腺炎防治的进展

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## Prevention and treatment of post-ERCP pancreatitis

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## Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) is widely used in the diagnosis and treatment of cholangiopancreatic diseases, and pancreatitis remains the most common and severe complication. It is therefore important to minimize the incidence and severity of pancreatitis. This paper discusses the recent progress in the prevention and treatment of post-ERCP pancreatitis.

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Key Words: Endoscopic retrograde cholangiopancreatography; Post-Endoscopic retrograde cholangiopancreatography pancreatitis; Prevention

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## 摘要

经内镜逆行胰胆管造影术(endoscopic retrograde cholangiopancreatography, ERCP)是胆胰疾病的重要诊治手段之一,随着内镜技术的不断进步,其应用越来越广泛. ERCP术后常见的并发症有急性胰腺炎、出血、穿孔、感染、心肺意外等,其中胰腺炎是ERCP术后最常见也是最严重的并发症,严重时甚至可致死亡. 因此,降低ERCP术后胰腺炎的发生率、减轻其严重程度至关重要,近年来国内外学者医师对此研究众多,其中临床报道有明确疗效的有术中预防性置入胰管支架和使用非甾体抗炎药(nonsteroidal anti-inflammatory drugs),本文就近年来对ERCP术后胰腺炎的防治进展予以综述.

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关键词: 内镜逆行胰胆管造影术; ERCP术后胰腺炎; 预防

**核心提示:** 内镜预防中预防性置入胰管支架疗效显著,导丝辅助插管、括约肌预切开和电流的选择暂不确定,造影剂方面建议限制性注入,而鼻胆管/胰管引流仍待进一步研究. 药物预防方面,非甾体抗炎药疗效确定,其他如蛋白酶抑制剂、降低Oddi括约肌压力的药物、用于减少胰酶分泌的药物,目前的报道均无统一意见,此外目前也有一些研究使用新的药物来预防经内镜逆行胰胆管造影术(endoscopic retrograde cholangiopancreatography, ERCP)术后胰腺炎(post-ERCP pancreatitis),值得期待.

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## 0 引言

自1968年McCune首次报道经内镜逆行胰胆管造影术(endoscopic retrograde cholangiopancreatography, ERCP)以来,随着内镜技术和的进步,其在

## ■背景资料

内镜逆行胰胆管造影术(endoscopic retrograde cholangiopancreatography, ERCP)是胆胰疾病的重要诊治方法之一,随着内镜技术的进步,其应用也越来越广泛,而作为ERCP术后最常见也是最严重并发症的ERCP术后胰腺炎的预防显得尤为重要.

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## ■ 研发前沿

目前国内外报道有明确疗效的有术中预防性置入胰管支架和使用非甾体抗炎药, 本文就近年来对ERCP术后胰腺炎的防治进展予以综述。

胆胰疾病诊治中的作用愈发举足轻重, 但ERCP相关并发症却制约了其广泛使用。急性胰腺炎是经内镜逆行胰胆管造影术最常见最严重的并发症之一, 文献报道其发生率为1%-10%, 高危患者发病率为30%<sup>[1]</sup>。大多数患者ERCP术后并发急性胰腺炎都为轻到中度, 但仍有小部分患者术后发生重度胰腺炎, 甚至可能出现死亡。因此, 降低ERCP术后胰腺炎(post-ERCP pancreatitis, PEP)发生率和严重程度至关重要, 目前关于内镜技术及药物预防PEP的研究众多, 本文就ERCP术后胰腺炎的防治进展进行简单综述。

## 1 一般措施

严格掌握ERCP指征, 减少不必要的ERCP操作是减少PEP发生的根本方法。术前内镜医师应充分了解患者病情, 结合PEP的高危因素, 全面评估, 当危险因素较多, 不建议行ERCP术。此外, 内镜、附件及操作相关器材材料应该严格消毒, 减少医源性感染的可能性。术后充分补液可改善胰腺灌注及组织氧含量, 并减少胰腺坏死, 有文献报道充分补液可降低PEP的发生率<sup>[2]</sup>。

## 2 内镜技术预防

**2.1 导丝辅助插管** 导丝辅助插管可以分为单导丝法和双导丝法。单导丝法先将导丝置入胆管, 再利用导丝引导导管进入胆管, 多用于困难插管患者。最近的Meta分析显示经导丝引导插管后插管成功率增加, PEP发生率明显降低<sup>[3]</sup>。Cheung等<sup>[4]</sup>建议特别是行预切开和首次插管失败的患者, 单导丝引导插管效果更加明显。双导丝法即置入胰管导丝, 可以通过拉直壶腹部, 帮助避免插管入胰管, 亦多用于困难插管的患者。Hisa等<sup>[5]</sup>曾报道, 使用双腔导管和胰管导丝辅助插管后, 减少了造影剂的用量, PEP的发病率大大降低。但考虑到双导丝法操作难度较大, 建议有相应技术水平的内镜中心采用。

**2.2 括约肌预切开** 曾有报道括约肌预切开可增加PEP的风险, 有学者将其风险归功于困难插管的操作繁杂: 如在Swan等<sup>[6]</sup>的研究中, 73例困难插管的患者, 使用针状刀行括约肌预切开的患者PEP发生率(20.5%)与对照组(17.6%)差异并无统计学意义, 而多变量分析则证明插管次数超过7-8次或插管失败会增加PEP的风险。Cennamo等<sup>[7]</sup>对6项随机对照试验(randomized controlled trials, RCTs)中的966例病例进行统计学分析, 认为经验丰富的内镜医师操作的前提下, 行预切

开后插管成功率与持续尝试插管的成功率相仿, 且预切开能够降低PEP的发生率, 同时并不增加其他的并发症发生率。

**2.3 置入胰管支架** 术中置入临时胰管支架可有效地避免术后十二指肠乳头水肿、Oddis括约肌痉挛导致的胰管引流障碍, 促进胰液的引流。最新的Meta分析综合近年40项RCT, 认为置入胰管支架组PEP患病率明显降低, 其中中重度PEP患者尤其受益<sup>[8]</sup>。Sakai等<sup>[9]</sup>还发现在困难插管患者, 预防性置入胰管支架不仅能够降低PEP和高淀粉酶血症的发生率, 还可以减少腹痛和血清淀粉酶水平。此外, 学者们还探讨了支架的留置时间、支架的性质, 包括支架内径、形状、置放部位等。在Conigliaro等<sup>[10]</sup>的研究中, 所有患者在胰管导丝引导插管后均置入胰管支架(5 F猪尾支架), 术后立即移除支架组的PEP发生率为29%, 而留置支架组PEP发生率为0.0%, 差异有统计学意义。Pahk等<sup>[11]</sup>和Zolotarevsky等<sup>[12]</sup>比较了5 F与4 F及5 F与3 F支架的作用效果, 与5 F支架相比, 3 F降低PEP发生率的疗效较小, 4 F支架更易自行脱落。Tabata等<sup>[13]</sup>则提出棒状支架(stick-type stent)拥有更高的通畅率, PEP发生率较圣诞树支架(branch-type stent)和Y型支架(halfway-type stent)明显降低。另有研究报道, 预防性置入跨胰管括约肌支架可预防PEP, 小口径胰管支架可用于PEP发生后的补救<sup>[14]</sup>。尽管置入胰管支架在降低PEP发生率方面作用突出, 但置入支架的操作难度系数不容忽视, 特别是在乳头口狭窄或胰管迂曲的患者, 置入支架失败同样可能诱发PEP<sup>[15]</sup>。因此, 有学者建议可以给有胰腺炎病史、困难插管、使用胰管导丝辅助选择性插管等高危患者预防性置入胰管支架<sup>[16,17]</sup>。

**2.4 内镜下鼻胆管/胰管引流** 采用鼻胆管/胰管引流可以保持ERCP术后胰胆管流出道通畅, 减少造影剂和胰液、胆汁的逆流, 减少胰胆管括约肌损伤和痉挛等诱发的不利因素, 减少PEP和胆管炎的发生。国内对此研究较多, 多数研究认为鼻胆管/胰管引流可明显减少PEP的发生率, 尤其是高危患者, 但Yang等<sup>[18]</sup>的实验中鼻胆管引流组的血清淀粉酶水平及高淀粉酶血症发病率明显降低, 但PEP的发生率没有明显降低。

**2.5 电流的选择** ERCP术中使用电烙术引起的热损伤, 造成乳头口水肿, 阻碍胰液引流, 可能诱发PEP。理论上, 纯切割电流的切割能力较强, 引起更少的水肿, 可用于预防PEP。国外有Meta分

析对此进行了研究, 分析认为纯切割电流与混合电流对PEP的发生无明显影响, 但纯切割电流可能引起出血的风险增大<sup>[19]</sup>. 而Stefanidis等<sup>[20]</sup>的临床试验却证明与混合电流相比, 纯切割电流能够降低血淀粉酶水平和PEP的发生率. 目前对于电流的使用仍无定论, 仍待进一步的大规模研究确定.

**2.6 造影剂的使用** 胰管注入造影剂, 尤其是多次、大量注入是PEP的高危因素之一, 因此有学者提出限制性注入造影剂可预防PEP<sup>[21]</sup>. 此外, Noble等<sup>[22]</sup>针对造影剂的pH值进行了临床试验, 当造影剂pH为7.3时, 患者局部水肿、中性粒细胞浸润以及组织学损伤的程度均较pH为6.9时轻, 由此推测, 如能增加造影剂的pH值, 可能降低PEP的发生率. 除此之外, 国外还有关于低渗非离子型造影剂的报道, 亦未得出确定性结论.

### 3 药物预防

药物预防PEP的机制有: 降低Oddi括约肌压力、减少胰腺炎分泌、抑制胰酶激活、减少全身性炎症反应. 预防PEP的理想药物是能有效地减少PEP的发病率, 且作用时间短, 不良反应小. 关于药物预防PEP的文献报道不胜枚举, 但是大多数药物的疗效仍存在争议.

**3.1 用于降低Oddi括约肌压力的药物** 硝酸甘油(glyceryl trinitrate, GTN)对平滑肌有强大的松弛作用, 15 min内可将Oddi括约肌的压力降至基础水平, 促进胰液引流. 国内外学者对此药研究众多, 如Ding等<sup>[23]</sup>的Meta分析认为, GTN降低PEP的发生率, 尤其是在高危患者, 高淀粉酶血症发生率也明显降低, 分层分析提示皮下给药较经皮给药、局部用药效果更好. 但Bang等<sup>[24]</sup>则注意到, 在降低PEP发生率的铜丝, GTN也增加低血压和头痛的风险.

在乳头喷洒肾上腺素能够减轻局部水肿, 相对降低Oddi括约肌的压力. Xu等<sup>[25]</sup>发现术中在乳头喷洒20 mL 0.02%肾上腺素的患者, PEP的发生率较对照组明显降低. Nakaji等<sup>[26]</sup>的实验也得出相同结论, 并建议尤其是女性患者在胰管插管后, 可在十二指肠乳头喷洒肾上腺素.

肉毒杆菌被广泛应用于治疗平滑肌功能异常, 如食管下括约肌、Oddi括约肌等, 有学者试图将其应用于预防PEP. 但Gorelick等<sup>[27]</sup>发现在胰管括约肌注射肉毒杆菌毒素的患者, 术后发生PEP的数量减少, 但与对照组相比并没有统计学的价值.

乌地那非是一种磷酸二酯酶-5抑制剂, 能够降低Oddi括约肌, 然而临床实验却证实其不能降低PEP发生率和严重程度<sup>[28]</sup>.

**3.2 用于减少胰酶分泌的药物** 生长抑素及其类似物奥曲肽能够抑制胰腺外分泌, 减轻胰腺的自身消化, 同时还有抗炎和细胞保护的作用, 但其用于预防PEP的疗效尚待确定. Wang等<sup>[29]</sup>认为大剂量的生长抑素(0.5 mg/h维持24 h)无论术前术后使用, 对PEP都无明显预防效果. 而Katsinelos报道术后生长抑素静脉维持6 h(0.25 mg/h), 联合术前30-60 min直肠使用双氯芬酸100 mg, 术后PEP发生率明显低于对照组<sup>[30]</sup>. 奥曲肽是长效的生长抑素类似物, 有2项关于奥曲肽的Meta分析, Bai等<sup>[31]</sup>的Meta认为没有足够的证据表明奥曲肽能够预防PEP; 另一项Meta分析着重于奥曲肽的使用剂量, 认为只有足量( $\geq 0.5$  mg)使用奥曲肽才能降低PEP的发生率<sup>[32]</sup>.

另外, 5-羟色胺(5-hydroxytryptamine, 5-HT)参与激活胰酶的分泌, 急性胰腺炎的动物模型中, 应用5-HT拮抗剂利培酮可降低血清白介素-6(interleukin-6, IL-6)、血淀粉酶、脂肪酶水平以及血小板计数, 改善组织学改变. Uchino<sup>[33]</sup>、Tsuji等<sup>[34]</sup>欲将其应用于临床试验, 但结果证明无论是单用还是与乌司他丁连用, 均不能减少PEP的发生.

**3.3 蛋白酶抑制剂** 胰酶的内激活是PEP发生的关键步骤, 因此可以通过抑制胰酶的激活减少PEP的发生并减轻其严重度, 基于此种机制的药物有蔡莫司他、加贝酯、乌司他丁等. 表1总结了近年的Meta分析, 可见蛋白酶抑制剂用于减少PEP发生的疗效并不确定, 且使用剂量、给药途径有待进一步研究.

另外, 肝素能够同时抑制血浆和胰腺组织中的胰酶活性, 并改善胰腺炎模型的胰腺微循环, 曾被建议用于临床, 预防PEP. 但国外已有大规模的临床实验和Meta分析证明普通肝素和低分子肝素对PEP均无预防作用<sup>[35,36]</sup>. 有文献报道了一项使用硫酸镁(镁离子拮抗钙离子的作用, 减少胰酶激活)预防PEP的III期随机双盲空白对照临床试验, 目前尚在进行中<sup>[37]</sup>.

**3.4 抗炎药物** 本组药物包括非甾体抗炎药(non-steroidal anti-inflammatory drugs, NSAIDs)、类固醇、抗氧化剂、抗生素以及免疫调节剂等, 其中NSAID的研究颇有成效, Ding等<sup>[38]</sup>综合分析了近年的10项RCT, 其中包括病例2269例, 涉及的药物有双氯芬酸(100、75、50、25 mg)、

#### ■ 相关报道

由于ERCP的广泛使用, PEP也得到更多的重视, 近年关于预防PEP的临床试验及Meta分析众多, 其中Meta分析多总结了近期的大规模临床试验, 对临床的指导价值更大.



## ■创新盘点

本文有选择的引用大量RCT和Meta分析,并对其结果进行分析,对临床预防PEP有一定参考价值。

表 1 关于蛋白酶抑制剂预防PEP的4项Meta分析

作者	n	涉及药物	结论
Yuhara等 <sup>[50]</sup>	10273(26项RCT)	NSAID、蔡莫司他、加贝酯、乌司他丁	NSAID和蔡莫司他降低PEP的发生率,而加贝酯和乌司他丁不能降低PEP的发生率
Zhang等 <sup>[51]</sup>	5105(12项RCT)	加贝酯、乌司他丁	大剂量加贝酯迅速注入和足量的乌司他丁降低PEP的发生率
Seta等 <sup>[52]</sup>	4966(19项RCT)	蔡莫司他、加贝酯、抑肽酶、乌司他丁	蛋白酶抑制剂不能降低PEP的发生率
Chen等 <sup>[53]</sup>	1039(7项RCT)	乌司他丁	乌司他丁可减少PEP和高淀粉酶血症的发生率,但其术前静脉注射量应不少于150000 U

RCT: 随机对照试验; NSAID: 非甾体抗炎药; PEP: ERCP术后胰腺炎; ERCP: 经内镜逆行胰胆管造影术。

吗啡美辛(100 mg)、伐地考昔(20 mg),给药途径有直肠、口服、静注、肌注、十二指肠,得出结论NSAID降低PEP的发生率和严重程度。Elmunzer等<sup>[39]</sup>采用术后直肠使用吗啡美辛,发现在PEP高危患者中,治疗组发生率(9.2%)较对照组(16.9%)明显降低,且中重度PEP的发病率也明显减少。

类固醇因其不良反应明显,目前很少应用于预防PEP。Zheng等<sup>[40]</sup>和Bai等<sup>[41]</sup>的Meta分析指出类固醇不能降低PEP和高淀粉酶血症的发生率<sup>[40,41]</sup>。但有学者报道泼尼松为肝移植患者发生PEP的保护性因素,这可能与免疫抑制有关,尚需更进一步的临床试验证明<sup>[42]</sup>。

氧化应激和自由基能够增加急慢性胰腺炎患者的十二指肠液和血流量,且抗氧化治疗有助于抑制炎症进程。Gu等<sup>[43]</sup>对11项RCT进行分析,其中涉及的抗氧化剂有亚硒酸盐、β-胡萝卜素、别嘌呤醇、N-乙酰半胱氨酸、己酮可可碱,得出结论抗氧化剂并不能降低PEP的发生率。其中已有Meta分析和多项临床实验证明,别嘌呤醇和N-乙酰半胱氨酸不能减少PEP的发生<sup>[44,45]</sup>。van Westerloo等<sup>[46]</sup>的临床试验提出,ERCP术前1 h使用塞马莫德虽然可以降低血淀粉酶水平和高淀粉酶水平,也不能明显减少PEP的发生。

细胞因子在PEP的发病机制中发挥重要作用,有免疫调节作用的细胞因子因此有望用于预防PEP。如Sherman等<sup>[47]</sup>曾给患者术前使用IL-10,但未能明显降低PEP的发生率;其另一项实验中试图采用血小板活化因子乙酰水解酶减少PEP的发生,然而无论1 mg/kg还是5 mg/kg都没有明显预防PEP的效果<sup>[48]</sup>。

既往曾有学者认为抗生素可以作为重要的预防PEP用药,但抗生素对PEP无预防作用目前已达成共识。

3.5 其他 有实验证实神经源性炎症(感觉神经元的病理激活)在急性胰腺炎发病中的作用,但临床实验中,选择性神经激肽-1(neurokinin-1, NK-1)受体拮抗剂阿瑞吡坦却不能明显降低PEP的发生率<sup>[49]</sup>。此外,尚有报道中药中清胰汤、利胆排石汤、柴胡承气汤、肝胆宁汤剂等也有预防PEP的作用。

## 4 结论

ERCP是一种先进的胆胰系统疾病诊治技术,具有成功率高、创伤小、适用范围广的特点,在胆胰管和十二指肠疾病的诊断和治疗中发挥了重要作用;但作为一项侵入性操作,并发症的发生亦不可避免。可喜的是经过众多学者的共同努力研究,PEP的预防已卓有成效。在PEP的预防中,根据目前的文献报道,疗效确定的有置入预防性临时胰管支架以及预防性使用NSAID类药物,其他预防措施及药物尚待进一步的研究。

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## ■应用要点

本文从一般措施、内镜技术、药物预防三个方面,对近年关于预防PEP的研究进行综述,其中内镜技术中疗效确定的为预防性置入胰管支架,而药物预防方面比较推荐非甾体抗炎药的使用。

# 同行评价

本文就近年来内镜和药物治疗ERCP术后胰腺炎的进展,从一般措施、内镜技术预防、药物预防等方面予以综述。本文所述问题为内镜科临床常见问题,论述清晰,观点明确,论据充分,且引用较多RCT文献,文字流畅,结构合理。

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