

应用奥曲肽预防胰十二指肠切除术后胰漏作用的研究

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摘要 目的 预防性使用奥曲肽是否能减少胰十二指肠切除术后胰漏发生率存在着争议。本研究旨在研究奥曲肽在不同胰腺情况下预防胰十二指肠切除术后胰漏发生的作用。方法 本研究将“软胰腺”、“细胰管”作为术后胰漏发生的高危险因素,将 184 例胰十二指肠切除术病例分为 4 组:低危险/非奥曲肽组、低危险/奥曲肽组、高危险/非奥曲肽组、高危险/奥曲肽组。观察术后胰漏等术后并发症情况。结果 共发生术后胰漏 35 例(19%),其中高危险组胰漏发生率是低危险组 2 倍以上(27% versus 10%, $P < 0.01$)。在胰漏发生低危险胰腺情况下,奥曲肽组与非奥曲肽组术后胰漏发生无显著差别;在胰漏发生高危险胰腺情况下,奥曲肽能显著降低术后胰漏发生率。结论 在胰十二指肠切除术围手术期应根据胰腺的具体情况选择性使用奥曲肽既能有效预防术后胰漏的发生,又能避免不必要的浪费。

关键词 胰十二指肠切除术 奥曲肽 胰漏 并发症

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Application of Octreotide in Prevention of Pancreatic Leakage after Pancreaticoduodenectomy

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ABSTRACT Objective: Octreotide has been studied in multiple trials and is thought to prevent postoperative pancreatic fistula (POPF) formation after pancreatic surgery, however, results are controversial. The aim of this study was to evaluate the impact of prophylactic octreotide on POPF in patients with different pancreatic scenarios undergoing pancreaticoduodenectomy. **Methods:** The high-risk glands for POPF were defined as those with soft gland texture and small pancreatic duct size. One hundred eighty-four consecutive patients with pancreaticoduodenectomy were stratified into 4 groups: low risk/no octreotide group ($n=43$), low risk/octreotide group ($n=43$), high risk/no octreotide group ($n=49$) and high risk/octreotide group ($n=49$). In octreotide groups, prophylactic octreotide was administered intraoperatively and continued postoperatively. Outcomes, including complications and survival rates, are reported. **Results:** Overall, POPF were present in 19% of all patients. The incidence of POPF was twice as high among patients with high-risk glands compared with those with low-risk glands. Prophylactic octreotide in low-risk glands was not effective after PD. But in patients with high-risk glands, octreotide prophylaxis was associated with a decreased incidence of POPF (14% versus 39%). **Conclusion:** Soft pancreatic parenchyma and small pancreatic duct size (≤ 3 mm) were correlated with incidence and severity of POPF and octreotide should be administered selectively to patients with high-risk glands.

Key words: Pancreaticoduodenectomy; Octreotide; Pancreatic fistula; Complication

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前言

随着外科手术技巧及围手术期治疗水平的提高,胰十二指肠切除术(pancreaticoduodenectomy, PD)在大的专科中心已是一个相对安全的手术,手术死亡率在 5%以下^[1]。但 PD 术后胰漏(Postoperative pancreatic fistula, POPF)发生率多年来居高不下,据文献报导在 2%-20%^[2,3]。奥曲肽(Octreotide)是生长抑素(somatostatin)长效合成制剂,PD 围手术期使用奥曲肽能否预

防 POPF,目前尚有争论。有研究证实奥曲肽能降低 POPF 发生率^[4,5]。相反,另有一些研究表明奥曲肽并不能降低 POPF 发生率^[6]。

复习近十年来的文献表明,POPF 的发生与病人的年龄、并发病情况、术前黄疸持续时间、术中出血多少、胰腺质地及胰管粗细有直接关系^[7,8]。其中胰管细及胰腺质地软脆是导致 POPF 的最重要因素^[9-11]。本研究根据术中胰体尾胰腺质地及胰管情况所见将病例分成 POPF 发生高危险组和低危险组,研究不同胰腺情况下奥曲肽对 POPF 发生的影响。

1 资料与方法

1.1 病例及手术方法

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本研究包括 2005 年 10 月至 2010 年 10 月我院由 A、B 两医生所做的 184 例 PD 病人。术后病理诊断为：十二指肠癌 60 例、胰头腺癌 58 例、壶腹癌 42 例、胆管下端癌 11 例、胰头部肿块型慢性胰腺炎 8 例、胆囊癌 3 例、胰头神经内分泌癌 1 例、胰头粘液性囊腺瘤 1 例。

手术切除范围按 Whipple 胰十二指肠切除术所述, 对恶性肿瘤病人做相应淋巴结清扫。重建方式按 Child 术式即：胰空肠端侧吻合、肝总管空肠端侧吻合、及结肠前胃空肠端侧吻合, 加做空肠输入输出肠袢侧侧吻合。常规放置腹腔引流管 2 根, 分别放于胰肠及胆肠吻合口处, 分别从右侧腹壁另戳孔引出。行胰肠吻合时注意如下环节：切断胰腺时避免使用电刀, 胰腺断面采用缝扎止血；吻合口胰管内放入支撑管肠管内引流(a transanastomotic stent for internal drainage)；胰肠吻合使用 4-0 Prolene 连续降落伞式吻合 (continuous running and parachuting

suture)^[12]。

1.2 围手术期处理

在奥曲肽使用组中在术中胰肠吻合开始时皮下注射奥曲肽 (Novartis Pharma) 0.1mg, 术后每 8 小时注射 1 次, 共 7 天。术后第 3 天及恢复饮食后第 1 天 (多为术后第 7 天) 常规测定腹腔引流液淀粉酶水平。

1.3 病人分组

本研究将胰头切除后所留胰腺质地软脆或胰管直径 $\leq 3\text{mm}$ 确定为 POPF 发生的高危险因素, 术中根据胰腺情况将 PD 病例分为 POPF 发生低危险组和高危险组, 然后再随机将病例分为如下 4 组：低危险 / 非奥曲肽组、低危险 / 奥曲肽组、高危险 / 非奥曲肽组、高危险 / 奥曲肽组, 分组情况如 Fig.1 所示。

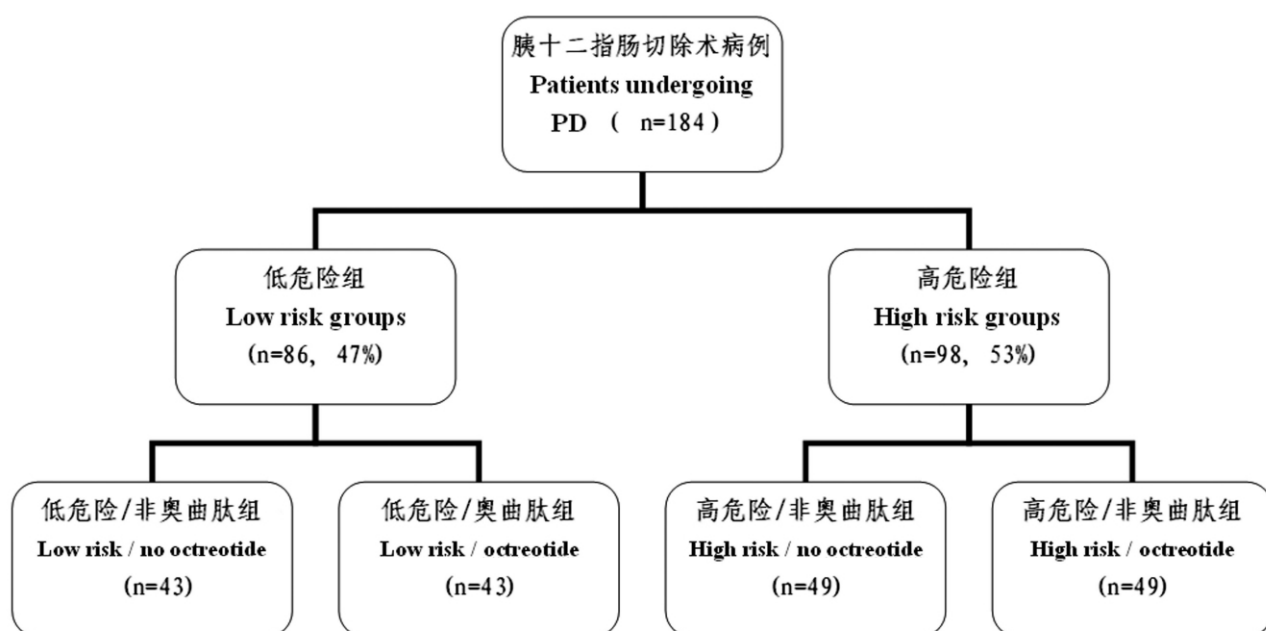


图 1. 病例分组情况 (PD= pancreaticoduodenectomy)

Fig. 1 Classification of patient cohorts based on risk stratification and administration of octreotide prophylaxis.

1.4 POPF 定义

POPF 的确定及其严重程度分级按国际胰瘘研究组 (International Study Group on Pancreatic Fistula, ISGPF) 2005 年公布的标准^[13]。根据 ISGPF 标准 POPF 定义为术后第 3 天以后腹腔积液或腹腔引流液淀粉酶水平高于血清淀粉酶正常值上限 3 倍以上。ISGPF 将 POPF 按严重程度分为 3 级：A 级为一过性腹腔引流液中淀粉酶增高, 病人无临床表现, 影像学无明显变化, 无需特殊处理, 术后住院时间无明显延长；B 级病人有临床表现：腹痛、发热、呕吐等, 影像学检查提示胰周积液, 需做干预处理；C 级可出现腹腔内出血、腹腔内脓肿, 多脏器功能衰竭, 术后引流时间超过三周, 常需再次手术治疗。

1.5 统计学处理

使用 SPSS10.0 软件包进行统计。计数资料用 Chi-square 检验, 计量资料以 $\bar{X} \pm S$ 表示, 用 t 检验。P<0.05 为有统计学意义。

2 结果

2.1 4 组患者一般临床资料

四组患者年龄、性别、合并其他疾病情况、术前血清总胆红素水平、手术时间及术中出血情况比较差异无统计学意义 (P>0.05), 具有可比性 (表 1)。

2.2 高危险组与低危险组 POPF 发生率比较

184 例 PD 病例, 共发生 POPF 35 例 (19%), 高危险组 POPF 发生率是低危险组 2 倍以上 (27% versus 10%, P<0.01)。其中高危险组发生 B/C 级胰瘘的几率更是高于低危险组 (18% versus 3%, P<0.01) (表 2)。

2.3 在低危胰腺组内使用奥曲肽与未使用奥曲肽 POPF 发生率比较

将 POPF 发生低危险组分成非奥曲肽组和奥曲肽组, 从表 3 可见两组之间 POPF、术后出血、术后腹腔内脓肿等并发症无显著差异。

2.4 在高危胰腺组内使用奥曲肽与未使用奥曲肽 POPF 发生率比较

表 1 四组患者一般临床资料的比较

Table 1 Patients characteristics, preoperative factors and intraoperative parameters of the four groups undergoing pancreaticoduodenectomy

	Low-risk glands		High-risk glands		p Value
	No octreotide (n =43)	Octreotide (n =43)	No octreotide (n =49)	Octreotide (n =49)	
Age (years)	59.9± 2.0	58.8± 2.0	58.3± 2.1	62.1± 1.90	NS
Gender (male)	30	28	33	32	NS
Diabetes	10	9	11	12	NS
CHD	16	17	20	18	NS
CPD	21	20	23	24	NS
STB(μmol/L)	85.6± 9.6	78.3± 7.5	76.6± 7.6	82.9± 8.1	NS
Operative time (min)	308± 16	312± 14	311± 13	320± 15	NS
Blood loss (ml)	528± 47	539± 36	592± 51	519± 73	NS
RBC transfusion (units, [range])	0.3± 0.1	0.3± 0.1	0.3± 0.2	0.3± 0.1	NS

CHD= Chronic heart disease; CPD=Chronic pulmonary disease ;STB= Pre-operative serum total bilirubin level; RBC=Red blood cell; NS=nonsignificant.

表 2 高危险组与低危险组 POPF 及其他术后并发症情况

Table 2 POPF and other postoperative complications for patients with low- and high-risk glands after PD

Outcomes	Low-risk glands	High-risk glands	P Value
n (%)	86(47)	98(53)	
POPF, n (%)	9(10)	26(27)	0.0056
Grade A	6(7)	8(8)	NS
Grade B/C	3(3)	18(18)	0.0015
PPH, n (%)	0	8(8)	0.0189
IAA, n (%)	1(1)	11(11)	0.0058
Reoperation, n (%)	0	4(4)	NS
30-d hospital mortality, n (%)	0	2(2)	NS

POPF = postoperative pancreatic fistula; PD = pancreaticoduodenectomy; PPH= postpancreatectomy hemorrhage; IAA= intra-abdominal abscess; NS=nonsignificant

表 3 低危险组内使用与未使用奥曲肽时 POPF 等术后并发症情况

Table 3 Impact of prophylactic octreotide on postoperative outcomes for patients with low-risk glands

Outcomes	Low-risk glands		P Value
	No Octreotide	Octreotide	
n (%)	43(50)	43(50)	
POPF, n (%)	5(12)	4(9)	NS
Grade A	3(7)	3(7)	NS
Grade B/C	2(11)	1(12)	NS
PPH, n (%)	0	0	NS
IAA, n (%)	1(2)	0	NS
Reoperation, n (%)	0	0	NS
30-d hospital mortality, n (%)	0	0	NS

POPF = postoperative pancreatic fistula ; PD = pancreaticoduodenectomy ;PPH= postpancreatectomy hemorrhage; IAA= intra-abdominal abscess; NS=nonsignificant

将 POPF 发生高危险组分成非奥曲肽组和奥曲肽组 ,从表 4 可见预防性使用奥曲肽可显著降低 POPF、术后出血、术后腹

表 4 POPF 发生高危组内使用与未使用奥曲肽时 POPF 等术后并发症情况
Table 4 Impact of prophylactic octreotide on postoperative outcomes for patients with high-risk glands

Outcomes	High-risk glands		P Value
	No Octreotide	Octreotide	
n (%)	49(50)	49(50)	
POPF, n (%)	19(39)	7(14)	0.0060
Grade A	6(12)	2(4)	NS
Grade B/C	13(27)	5(10)	0.0367
PPH, n (%)	7(14)	1(2)	0.0267
IAA, n (%)	9(18)	2(4)	0.0250
Reoperation, n (%)	4(8)	0	NS
30-d hospital mortality, n (%)	2(4)	0	NS

POPF = postoperative pancreatic fistula ; PD = pancreaticoduodenectomy ;PPH= postpancreatectomy hemorrhage;
IAA= intra-abdominal abscess; NS=nonsignificant

腔内脓肿等并发症。

3 讨论

近 30 年来由于手术技巧、重症监护治疗及外科营养支持的提高 ,PD 术后死亡率显著降低 ,但 PODF 发生率仍居高不下 ,PODF 可引起术后腹腔内脓肿、腹腔内出血 ,甚至可引起脓毒症、呼吸功能不全、休克等。所以如何预防 PODF 的发生是多年来外科医生绞尽脑汁、反复研究的课题。

胰液分泌量与 POPF 发生有直接关系^[14]。早在上世纪 70 年代 Klempa^[15]等就提出使用生长抑素来减少术后 PODF 的发生率 ,生长抑素的上述作用被很多文献所肯定^[16]。但是后来又有研究否定了生长抑素预防 POPF 发生的作用^[17]。奥曲肽(Octreotide)是合成的生长抑素(somatostatin)的八肽类似物 ,它较生长抑素作用更强、半衰期更长 ,适合临床应用^[18,19]。本研究是根据术中所留胰体尾情况将 PD 分为 POPF 发生高危组和低危险组 ,采用最新有关 POPF 定义及分级的 ISGPF 标准探讨不同情况下奥曲肽预防 POPF 的作用

本研究表明如果胰腺质地硬或胰管直径 >3mm 时 ,奥曲肽没有预防 PD 术后 POPF 的作用 ,而且两组之间术后 POPF 严重程度及术后出血、腹腔内脓肿等并发症发生率亦无显著差别。如果胰腺质地软或胰管直径≤ 3mm 时 ,即如果有 POPF 发生的高危因素时 ,预防性使用奥曲肽能显著降低 POPF 的发生率及 POPF 的严重程度 ,术后出血及腹腔内脓肿发生率也显著降低。

胰腺质地偏硬 ,或有纤维化 ,常见于合并有慢性胰腺炎时 ,这样的胰腺情况有利于做胰肠吻合。相反胰腺质地软脆 ,常见壶腹周围癌时的胰腺 ,不利于做胰肠吻合。

当然本研究有其局限性 ,如怎样判断“软胰腺”还是“硬胰腺” ,缺乏量化的标准 ,主要是凭外科医生术中感觉。不过已有文献报导使用“硬度测定仪”在 PD 术中测定胰腺硬度^[20] ,为术中判断胰腺软硬带来了量化的方法。

总之 ,本研究再一次证实了胰腺质软及胰管直径≤ 3mm 是 PD 术后 POPF 发生的高危险因素。本研究揭示在 PD 手术中对胰腺的质地及胰管情况不加区别 ,盲目使用奥曲肽 ,不会

起到预防 POPF 的作用。如果胰腺质地软或胰管直径≤ 3mm 时 ,即如果有 POPF 发生的高危因素时 ,预防性使用奥曲肽能显著降低 POPF 的发生率及 POPF 的严重程度 ,术后出血及腹腔内脓肿发生率也显著降低。本研究对 PD 术后合理使用奥曲肽及控制住院医疗费用有重要意义。

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