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梗阻性黄疸大鼠胆汁内、外引流术后血浆二胺氧化酶活性变化与肠粘膜屏障变化的相关性研究*

苏璇 罗开发 吴亮 吴丽丽 李闻[△]

(中国人民解放军总医院 消化内科 北京 100853)

摘要 目的:探讨梗阻性黄疸大鼠行胆汁内、外引流术后血浆二胺氧化酶的活性变化与肠粘膜屏障的关系。**方法:**取健康成年雄性SD大鼠60只,随机分为四组:梗阻性黄疸组(OJ)、胆汁外引流组(ED)、胆汁内引流组(ID)及假手术对照组(SH),各组均15只;SH组、OJ组在术后第7天处死大鼠并采集标本,ID组、ED组于引流术后7天处死大鼠并采集标本,检测各组大鼠血浆DAO的活性,光镜下观察末端回肠组织粘膜形态学变化。**结果:**OJ组大鼠肠粘膜损伤明显,粘膜变薄、绒毛稀疏、上皮完整性受到破坏并伴有炎性细胞浸润,ID、ED组大鼠肠粘膜有不同程度的恢复,ID组更接近SH组;OJ组血浆DAO水平显著升高,明显高于SH、ID、ED组(8.183 ± 0.211 vs 3.570 ± 0.280 , 3.978 ± 0.269 , 5.051 ± 0.328 U/L, $P < 0.01$),ID组较ED组下降更明显,二者差异有统计学意义($P < 0.01$),ID组血浆DAO水平略高于SH组,二者差异无统计学意义($P > 0.05$);各组血浆DAO变化与肠粘膜组织病理学变化一致。**结论:**胆汁内、外引流术可降低梗阻性黄疸大鼠血浆DAO水平,内引流术效果优于外引流术;血浆DAO的变化可反映梗

关键词:梗阻性黄疸;胆汁引流;肠粘膜屏障;二胺氧化酶

中图分类号:Q95-2;R575.6 **文献标识码:**A **文章编号:**1673-6273(2014)17-3216-04

The Correlation Study of the Plasma Diamine Oxidase Activities and the Intestinal Barrier Function in Rats with Obstructive Jaundice after Internal and External Biliary Drainages*

SU Xuan, LUO Kai-fa, WU Liang, WU Li-li, LI Wen[△]

(Department of Gastroenterology the Chinese PLA General Hospital Beijing, 100853, China)

ABSTRACT Objective: To investigate the relationship between the plasma diamine oxidase(DAO) activities and the intestinal barrier function in rats with obstructive jaundice after internal and external biliary drainages. **Methods:** Sixty adult healthy male SD rats were randomly divided into four groups :obstructive jaundice group(OJ) external drainage group(ED), internal drainage group(ID) and sham operation group (SH). There were 15 rats in each group. Specimens from the rats of SH and OJ groups were collected one week after the surgery. Different biliary drainages were performed in ID and ED groups, and the specimens were harvested seven days after the operation. The activities of the plasma DAO were determined and the morphological changes of the terminal ileum mucosa were observed under the light microscope. The results were compared between different groups. **Results:** The injuries of the intestinal mucosa were obvious in OJ group with thin mucosa, sparse villous, destruction of the epithelial integrity and inflammation cell infiltration, while the situations of the intestinal mucosa in ED and ID groups recovered, and ID group was more similar to SH group in intestinal mucosal morphology. Compared with the other groups, the levels of the DAO in OJ group increased dramatically(8.183 ± 0.211 vs 3.570 ± 0.280 , 3.978 ± 0.269 , 5.051 ± 0.328 U/L, $P < 0.01$), and the activities of the DAO in ID group, which were similar to the level of SH group($P > 0.05$), decreased more significantly than that in ED group($P < 0.01$). The changes of the plasma DAO activities were significantly correlated with pathological examination of intestinal mucosa. **Conclusions:** These data suggest that both of the internal and external biliary drainages may reduce the plasma DAO activities in rats with obstructive jaundice but the internal biliary drainage is better, and the level of the plasma DAO can reflect the damage of the intestinal barrier function in obstructive jaundice rats.

Key words: Obstructive jaundice; Biliary drainage; Intestinal barrier; Diamine oxidase

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作者简介:苏璇(1988-),女,硕士研究生,主要研究方向:胆、胰疾病的诊断及治疗,

电话:15001118296, E-mail: pengfeisuxuan@163.com

[△] 通讯作者:李闻, E-mail: liwen2000@yahoo.com

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前言

梗阻性黄疸 (obstructive jaundice, OJ) 是常见的临床综合征,可致机体免疫功能下降,容易发生严重感染,甚至多器官功能障碍综合征。目前认为上述并发症可能与胃肠道细菌移位、巨噬细胞被激活有关,细菌和内毒素刺激巨噬细胞释放过量的炎性介质,后者引起细胞因子的连锁反应,从而引起组织和器官的损伤^[1,2],而肠屏障功能(intestinal barrier function, IBF)受损是内毒素血症和细菌移位形成的主要原因^[3]。肠道作为梗阻性黄疸病情发生发展的重要器官,逐渐成为研究的热点。胆汁内、外引流术是解除黄疸的有效手段,我们的前期系列动物实验采用病理学方法分析显示:胆汁内、外引流术能有效改善肠道机械、免疫屏障,其中又以内引流效果最佳^[4,5]。但在临床工作中,建立更为敏感的无创的方法来判断肠粘膜屏障功能的损伤和修复状况,对深入研究疾病的发生发展及指导疾病的诊断及治疗具有重要意义。本研究就梗阻性黄疸及内、外引流术后肠粘膜屏障功能指标二胺氧化酶(DAO)的变化,探讨其与肠粘膜屏障功能的关系,为指导临床治疗提供实验依据。

1 材料与方法

1.1 动物

选择健康雄性成年 SD 大鼠 60 只,体质量 300~350 g,由军事科学院实验动物中心提供 [批准单位:中国人民解放军总后勤部卫生部]。实验动物均在中国人民解放军总医院 II 级动物实验室分笼单独饲养,常规饲料喂养,自由进食水。保持环境温度在 15~20℃,湿度 40%-70%。

1.2 试剂

大鼠二胺氧化酶酶联免疫(Elisa)试剂盒,购自上海艾来萨生物科技公司。

1.3 造模与分组

大鼠常规喂养一周后,随机分为四组,每组各 15 只,术前禁食 12 h,不禁水。根据我们前期实验研究建立的改良手术方法制备梗黄及内、外引流术模型^[7],分别为假手术组(shame operation, SH 组)、梗阻性黄疸组(obstructive jaundice, OJ 组)、胆汁内引流组(internal biliary drainage, ID 组)、胆汁外引流组(external biliary drainage, ED 组)。

1.4 标本采取及处理

H 组和 OJ 组大鼠在第一次术后 7 天处死并采集标本, ID 组和 ED 组在第二次行引流术后 7 天处死并采集标本。取材前禁食 12 h,不禁水,以 2%戊巴比妥钠 0.25 mL/100 g 腹腔注射麻醉。固定大鼠于手术板,备皮后常规消毒铺巾。于下腔静脉穿刺采血 2 mL, 4℃静置 30 min 后离心, 3 000 r/min×10 min, 收集血清于 -80℃保存,用于检测血浆 DAO 活性。经上腹正中切口逐层开腹,于相同位置处取回肠末端全层标本 5 cm, 用冰 0.9%NaCl 溶液反复冲洗干净后于 10%福尔马林溶液中固定。

1.5 检测指标

1.5.1 体重 SH、OJ 组称取手术前后的体重; ID、ED 组称取二次手术前后的体重,计算前后体重差值。

1.5.2 标本检测 ①以分光光度计法检测血浆 DAO 的活性;②将回肠标本进行石蜡包埋制成蜡块,连续切片,HE 染色,光镜下观察肠黏膜形态学变化。

1.6 统计学处理

计量资料采用均数±标准差($\bar{x} \pm s$)表示,应用 SPSS17.0 统计软件进行统计学分析,两组间比较采用 t 检验,采用单因素方差分析进行多组间比较, $P < 0.05$ 为差异具有统计学意义。

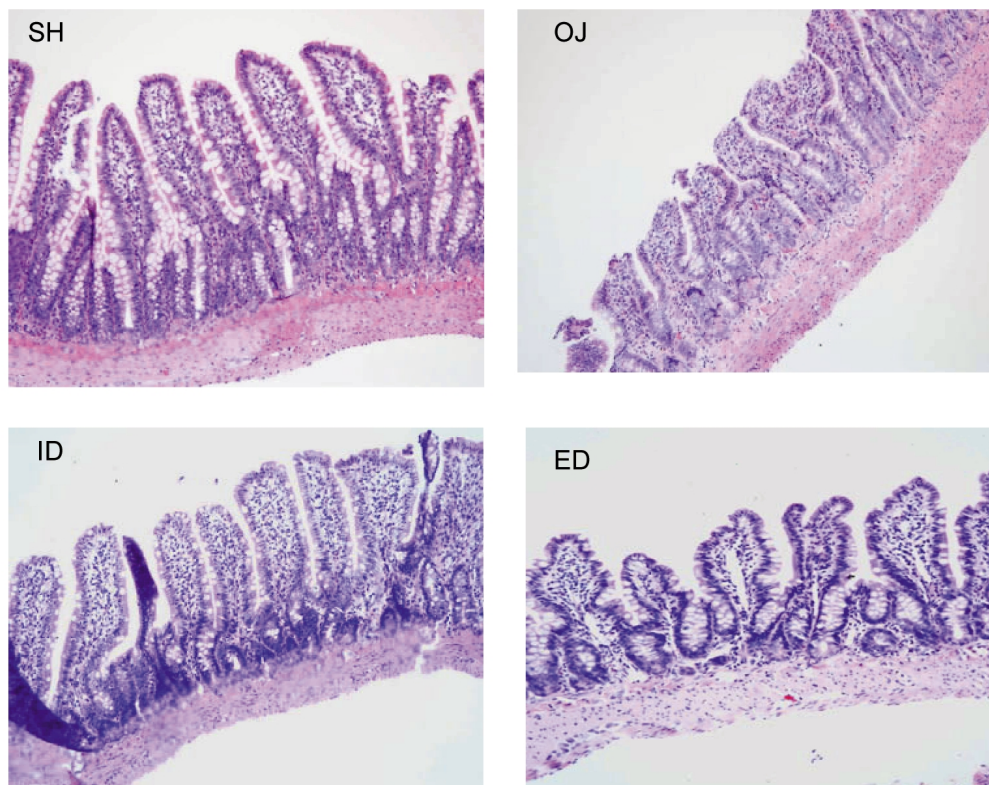


图 1 各组大鼠回肠肠组织 HE 染色结果 (×200)

Fig.1 HE staining of ileal tissue in each group (×200)

表 1 各组大鼠手术前、后体重、二者差值及血浆 DAO 检测结果($\bar{x} \pm s$)Table 1 The weight before and after the surgery, the difference between those and the level of DAO in each group($\bar{x} \pm s$)

Group	n	Weight before surgery (g)	Weight after surgery (g)	Difference (g)	The level of DAO (U/L)
SH	15	309.0 $\pm$ 6.7	328.7 $\pm$ 11.0	19.9 $\pm$ 8.6 [#]	3.570 $\pm$ 0.280 [#]
OJ	15	307.6 $\pm$ 8.7	300.7 $\pm$ 11.6	-6.4 $\pm$ 6.8*	8.183 $\pm$ 0.211*
ED	15	308.0 $\pm$ 8.1	276.9 $\pm$ 11.3	-30.2 $\pm$ 11.2**	5.051 $\pm$ 0.328**
ID	15	310.6 $\pm$ 8.8	336.3 $\pm$ 13.6	24.9 $\pm$ 13.2 [#]	3.978 $\pm$ 0.269 [#]

注:与 SH 组比较,*P<0.01;与 OJ 组比较,#P<0.01。

Note:Compared with SH group,*P<0.01;Compared with OJ group,#P<0.01.

2 结果

2.1 大鼠的体重及一般情况

SH 组大鼠饮食、活动量及尿、便正常,体重增加(19.864 $\pm$ 8.559 g);OJ 组大鼠尿色深黄,大便干结、量少,呈现便秘状态,结肠内粪块零星分布,饮食、活动量减低,体重下降(-6.431 $\pm$ 6.825 g);ED 组大鼠尿色恢复正常,呈清亮、透明、无色状,但量较 SH 组略少,大便情况较 OJ 组无改善且略加重,饮食、活动量减少,体重下降(-30.169 $\pm$ 21.127 g),与 ID、SH 组比较,P<0.01,差异有统计学意义;ID 组大鼠饮食、活动量及尿和粪便情况近似于 SH 组,但略呈轻度腹泻状态,体重增加(24.942 $\pm$ 13.153 g),与 SH 组比较,P>0.05,差异无统计学意义(表 1)。

2.2 回肠组织病理学

SH 组:黏膜完整无损,绒毛细长,排列整齐,组织结构完整,无间质水肿及炎性细胞浸润。OJ 组:黏膜萎缩、变薄,绒毛稀疏、凌乱、倒伏,短缩甚至相互融合,间隙增大,腺体稀疏、断裂,杯状细胞减少,上皮的连续性破坏,部分黏膜上皮缺失,尤其是顶端上皮坏死脱落,破溃严重,甚至扩展到黏膜,基底部或上皮完全脱落,炎性细胞浸润明显。ED 组:黏膜完整性略恢复,绒毛稀疏有破坏,上皮的连续性略恢复,仍有炎细胞浸润。ID 组:黏膜完整无损,绒毛稍稀疏,变得细长,排列有序、规则,上皮的连续性好,无炎性细胞浸润,更接近 SH 组(图 1)。

2.3 血浆 DAO 的活性变化

与 SH 组相比较,大鼠梗黄后(OJ 组),血浆 DAO 活性明显升高(8.183 $\pm$ 0.211 vs 3.570 $\pm$ 0.280 U/L,P<0.01);行胆汁内、外引流术解除梗阻后(ID、ED 组),血浆 DAO 活性明显下降,与 OJ 组比较,差异有统计学意义(3.978 $\pm$ 0.269 vs 8.183 $\pm$ 0.211 U/L,P<0.01;5.051 $\pm$ 0.328 vs 8.183 $\pm$ 0.211 U/L,P<0.01),ID、ED 组相比,又以 ID 组下降显著,差异有统计学意义(3.978 $\pm$ 0.269 vs 5.051 $\pm$ 0.328 U/L,P<0.01);ID、ED 组 DAO 活性均高于 SH 组,其中,ED 组与 SH 组比较,差异有统计学意义(5.051 $\pm$ 0.328 vs 3.570 $\pm$ 0.280 U/L,P<0.01),而 ID 组与 SH 组之间差异无统计学意义(3.978 $\pm$ 0.269 vs 3.570 $\pm$ 0.280 U/L,P>0.05)(见表 1)。

3 讨论

3.1 胆汁内、外引流术对梗阻性黄疸大鼠肠黏膜屏障功能的影响

大量研究表明,梗黄患者并发症多的主要原因是肠黏膜屏障损伤,引起细菌和内毒素经门静脉入血循环,导致炎性细胞

因子的“瀑布样”效应,形成所谓的“肠源性脓毒症”。梗阻性黄疸对肠黏膜屏障的破坏机制是多因素、多层次参与、极其复杂的,包括梗黄对肠黏膜机械、化学、免疫及生物屏障的破坏,其中,又以机械和免疫屏障的破坏最为重要。国内外系列动物实验研究^[7-10]证明:梗黄后,肠黏膜萎缩伴有明显的绒毛密度和黏膜厚度减低,与我们的实验结果一致;肠上皮细胞破坏,主要表现为细胞膜和线粒体膜的改变,细胞凋亡数目增加;肠细胞局灶的分离和空泡形成,细胞微绒毛的破坏或丢失、变矮、或不规则,桥粒破坏和水肿间隙形成,炎性细胞浸润;同时,在分子结构上,回肠黏膜紧密连接的两个关键蛋白:闭锁蛋白和 ZO-1 的表达降低,上述改变使肠道通透性增加,肠黏膜机械屏障受损,细菌移位率增高,以回肠末端最为显著。在免疫屏障方面,分泌型 IgA(sIgA)在肠道免疫系统中起核心作用,sIgA 来自于胆汁和肠黏膜固有层内产 IgA 细胞,是肠道分泌物中含量最丰富的免疫球蛋白,是人类黏膜免疫的主要抗体,能中和酶、毒素、病菌和其他生物活性抗原,并刺激肠道黏液的分泌,梗黄后大鼠较正常对照组其小肠黏膜组织及肠液中 sIgA 含量显著降低^[12,13];我们的前期系列实验发现:梗黄后,巨噬细胞过度激活,以肿瘤坏死因子- α (TNF- α)为代表的细胞因子分泌紊乱,致肠黏膜损伤^[4]。

胆汁内、外引流术是解除黄疸的有效手段,我们的实验结果表明二者均能有效恢复肠黏膜屏障功能,且内引流较外引流效果更佳,与李秋^[12]实验结果一致。其机制可能与引流术后梗阻解除、高胆红素血症消失、因胆汁淤积导致的受损的肝功能得以恢复、蛋白合成增加、机体免疫功能增强促进小肠黏膜的修复有关。其中,内引流术后,肠道中胆汁复现,生理量的胆汁对肠黏膜有营养作用并能促进肠黏膜上皮细胞增生^[3],且胆汁中的胆固醇的持续提供是肠黏膜细胞生长和损伤修复所必须的^[14];此外,胆汁中的胆盐成分能够抑制致病菌的繁殖,维持肠道菌群平衡,其与内毒素结合能够形成难以吸收的复合物,阻止内毒素吸收入血,从而减少细菌移位及内毒素血症的发生;梗黄后,肝脏 Kupffer 细胞吞噬功能减弱,而在恢复 Kupffer 细胞功能方面,内引流明显优于外引流;国内学者^[12,13]研究发现,内引流术较外引流术更能增加小肠组织及肠液中 sIgA 含量,能更好的恢复肠道免疫屏障。外引流术尽管解除梗阻,缓解了增高的胆盐对机体的损害,但肠道内胆汁的缺乏使得胆汁诸多有利作用无法得以实现,且大量的胆汁丢失,导致脂肪及脂溶性维生素吸收障碍、水电解质及酸碱平衡紊乱、机体抵抗力及免疫力下降,引流管外置增加了感染的风险,这就解释了

内引流优于外引流及外引流术后大鼠体重下降原因。

3.2 梗黄大鼠胆汁内、外引流术后血浆 DAO 活性变化与其肠黏膜屏障变化的关系

DAO 是人类和所有哺乳动物肠黏膜上皮绒毛细胞胞质中具有高度活性的细胞内酶^[5], 95% 以上存在于哺乳动物小肠绒毛上皮细胞中, 极少量分布在胎盘和肾脏中, 在血清中含量极少, 起着控制肠黏膜增殖的作用。当肠黏膜上皮细胞受到损伤后, 胞内释放 DAO 增加, 进入肠细胞间隙、淋巴管和血流, 使血浆 DAO 升高。由于 DAO 在外周血中活性稳定, 通过检测外周血中 DAO 活性变化, 可反映肠黏膜状态。血浆 DAO 增高提示存在肠黏膜屏障的破坏和肠通透性的改变^[16,17]是反映小肠黏膜结构功能的较为理想的指标。近年来, 测定血浆 DAO 水平广泛应用于各类疾病的肠道损伤研究中^[18,20], 以反应肠黏膜损伤和修复情况。杨连祥^[2]对大鼠的胆总管进行结扎造成梗黄模型, 并分别于术后 3、7、14 天采血检测 DAO 活性, 发现梗黄早期既有血浆 DAO 的升高, 且随胆管梗阻时间延长有加重趋势, 表明检测血浆 DAO 水平可评价梗黄后肠黏膜屏障功能损害程度。但关于行胆汁内、外引流术解除梗阻后大鼠血浆 DAO 的变化尚未见报道。在该实验中我们发现, 引流术后血浆 DAO 水平明显下降, 内引流术后血浆 DAO 下降水平较外引流术更明显, 二者差异有统计学意义; 内引流术后梗黄大鼠血浆 DAO 水平略高于假手术组, 但两者比较无统计学差异, 这与我们实验中各组肠黏膜屏障组织学变化相一致, 表明血清 DAO 的水平可评价梗黄不同方式治疗后肠黏膜的修复情况。

综上所述, 梗黄后机体多器官、系统功能紊乱与肠黏膜屏障受损关系密切, 内、外引流术对肠黏膜屏障具有修复作用, 且内引流优于外引流, 而反映肠屏障功能的指标—血浆 DAO 的水平可评价梗黄及内外引流术后肠黏膜的损伤及修复情况。若将该结论推广到临床, 则这一无创生化检查方法可为梗黄及其治疗后肠黏膜功能情况的评估提供理论依据。

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