

胆总管结石复发危险因素研究进展

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摘要

胆总管结石是我国的一种常见良性疾病, 可导致患者出现梗阻性黄疸、胆管炎、胰腺炎甚至胆管癌等并发症。目前胆总管结石的治疗方法主要包括内镜逆行胰胆管造影术和腹腔镜胆总管探查术, 虽然结石清除率可高达95%, 但其术后复发率约为4%~24%。本文就手术相关的因素、胆道解剖结构、结石的特质、性别年龄等方面对胆总管结石复发的危险因素进行深入探讨。

关键词

胆总管结石, 复发, 危险因素

Advances in Risk Factors for Recurrence of Choledocholithiasis

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Abstract

Choledocholithiasis is a common benign disease in China, which can lead to complications such as obstructive jaundice, cholangitis, pancreatitis and even cholangiocarcinoma. At present, the treatment of choledocholithiasis mainly includes endoscopic retrograde cholangiopancreatography and laparoscopic or open bile duct exploration. Although the stone clearance rate can be as high as 95%,

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the postoperative recurrence rate is about 4%~24%. This study makes an in-depth discussion on the risk factors of choledocholithiasis recurrence from the aspects of operation-related factors, biliary anatomical structure, characteristics of stones, sex and age, etc.

Keywords

Choledocholithiasis, Recurrence, Risk Factors

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1. 引言

胆结石是世界各地的一种常见病，其患病率在不同的国家有所不同。在美国，胆结石的发病率约为15%，其中10%~15%的患者同时伴有胆总管结石。而中国、日本和韩国等亚洲国家原发性胆总管结石的发病率远高于西方国家[1]。胆总管结石的发病机制目前尚不明确，可能与性别、年龄、胆总管直径、结石大小及手术方式等多种因素相关[2]。现如今，随着医疗水平和仪器设备的快速发展，以及人们生活水平的改善与生活方式的改变，导致胆总管结石的发病率和检出率越来越高，成为了威胁人类健康的一大困扰。经内镜逆行胰胆管造影术(endoscopic retrograde cholangiopancreatography, ERCP)和腹腔镜胆总管探查术(laparoscopic common bile duct exploration, LCBDE)作为目前胆总管结石的一线治疗方案，已经被广泛运用于临床，使得在胆总管结石的治疗过程中可以用最小的创伤取得最大的疗效。但结石的复发仍是难以避免的问题，有报道称ERCP取石术后有约9.2%的复发率，而LCBDE术后胆总管结石复发率为13.5% [3] [4]。同时胆总管结石所导致的化脓性胆管炎、胰腺炎、胆道穿孔等并发症，仍是困扰外科医生的重要的问题[5]。探寻胆总管结石复发的危险因素的重要性由此凸显。

2. 与手术相关的因素

目前，胆总管结石的主要治疗方式包括 ERCP 和 LCBDE。ERCP 为治疗胆总管结石提供了一种侵入性较小的途径，常通过内镜下括约肌切开术(endoscopic sphincterotomy, EST)、内镜下乳头球囊扩张术(endoscopic papillary balloon dilatation, EPBD)等方式治疗胆总管结石。腹腔镜下胆总管探查术的创伤更大，术后恢复期更长，但其避免了 ERCP 在胰腺炎方面的风险。

1) 内镜下治疗胆总管结石 ERCP 具有操作简单、创伤小、并发症少等优点，是目前治疗胆总管结石的首选方法。但一些研究认为首次入院行 ERCP 的次数与结石复发有一定的联系，因为清除结石所需要 ERCP 的次数越多意味着结石数量越多或者取石的难度更大。同时，多次的 ERCP 会对胆道造成更大的损伤，可能增加结石复发的风险[6]。对于核磁共振等检查提示结石较大和困难结石的患者以及首次通过 ERCP 取石失败的患者，更应该考虑行腹腔镜下胆总管探查术，从而避免多次 ERCP 对胆道的损伤造成结石复发及其他并发症。

EST 是通过内镜治疗胆总管结石的标准术式，但乳头切开不仅会导致出血、穿孔等并发症，还可能损伤十二指肠括约肌的功能，从而导致术后出现胰腺炎、胆管炎、乳头狭窄等并发症，引起胆总管结石的复发。在对接受 EST 患者的长期随访中发现，EST 手术本身可能是胆总管结石复发的独立危险因素[5] [7] [8] [9]。一项包括了 1088 例患者的临床研究发现，中切口的 EST 术后结石复发率低于小切口 EST [10]。

EPBD 是内镜下治疗胆总管结石的另一种选择。与 EST 相比, 接受 EPBD 治疗的患者可以在术后短时间内恢复一定的乳头肌功能, 术后并发症也更少出现[11] [12]。研究发现, 接受 EPBD 的患者相比于接受 EST 的患者术后结石复发率明显更低, 远期预后也更好, 这可能和其保留了部分括约肌功能有关[9] [10]。一些学者认为, 小切口的 EST + EPBD 和单独的 EST 相比有相同的疗效, 但其结石复发率更低[5] [13]。内镜大球囊扩张术(Endoscopic papillary large balloon dilation, EPLBD), 拥有和 EST 相似的治疗效果, 适用于较大的胆总管结石, 可减少了手术时间及机械碎石的概率, 降低结石的复发率[14] [15]。但 EPBLD + EST 对胆总管结石复发的影响目前尚有争议, Paspatis 等认为 EPBLD + EST 可能与胆总管结石取石后的低复发率相关, 而胆总管扩张程度越大结石复发的风险也越高[16]。而 Liu 等则认为 EPBLD + EST 与单独的 EST 手术在治疗效果和结石复发方面并没有明显的差异[17], Kim 等的长期随访研究中也发现了与之相同的结果[18]。

当结石较大或者嵌顿, 无法通过 ERCP 取出的时候, 可以行机械碎石术, 但这会增加手术时间, 同时在机械碎石后可能导致结石残留从而增加复发的风险, 一项回顾性研究报告称, 除了结石成分、数量和大小等不可改变的危险因素外, 机械碎石是唯一可改变的危险因素[19]。在碎石术后经胆管盐水冲洗, 可有效清除碎石后残留物, 减少胆道结石复发[20] [21]。

经内镜取石后结石的复发主要与十二指肠乳头功能受损、胆汁淤积、术后胆管炎等并发症、结石残留等因素有关。对此, 胆道引流可能是有效的应对措施, 其包括鼻胆管引流术及胆道支架植入术。鼻胆管引流目前在临床上已取得了广泛的应用, 不仅可以预防术后胆管炎、胰腺炎等并发症, 同时可以排出残留结石减少结石复发[22] [23]。此外, Wang 等的研究表明, 在超声造影引导下经鼻胆管注射造影剂, 有助于术后清晰观察胆总管残留结石, 为预防结石复发提供有利信息[24]。胆道支架置入术是另一种胆道引流的方法, 其可促进胆汁酸排泄、减轻水肿、预防炎症和有助于残石通过, 降低了结石复发率并且减少了并发症的发生。Choi 等认为对于结石较大且多发的患者, 预防性放置胆道支架是安全有效的治疗方法[25]。但 Deng 的研究发现, 支架放入时间过长不仅可能导致胆盐沉积和粘附在支架上, 还会影响胆道动力学导致胆汁淤积、细菌的繁殖, 从而促进结石的复发[26]。并且植入的支架可能出现移位、脱落等意外情况, 故其在临床上的运用相对较少。

2) 内镜后的胆囊切除术目前对于在 ERCP 取石后是否行胆囊切除术这一点仍存在不同的意见, 一些研究表明在 ERCP 后预防性的胆囊切除, 可以降低结石的复发以及并发症, 其原因可能是避免了胆囊结石引起的继发性胆总管结石。而对于继发性胆总管结石的患者, 预防复发最好的办法就是在 EPBD 后接受胆囊切除术[9] [27] [28] [29]。有学者认为在行 EPBD 后只要符合条件者, 都应行预防性的胆囊切除术[28]。一项日本的研究发现, 在内镜治疗下行胆囊切除术的病人中, 青年组的结石复发率明显降低, 但高龄组患者的结石复发率并没有明显的改变[30]。另一项来自韩国的研究也表明, 年龄小于 70 的胆总管结石患者应行胆囊切除术, 以减少结石的复发[29]。而 Kim 等的研究发现, 在内镜下取石后的胆囊切除术对减少结石复发并没有明显作用。所以他们认为胆总管结石未合并胆囊结石的患者, 不建议在内镜取石后择期行胆囊切除术[31]。

3) 腹腔镜下胆总管探查术 LCBDE 是治疗胆总管结石的另一主要手段, 其对胆总管结石的治疗效果不亚于经内镜取石, 并且大大地减少了胰腺炎的发生, 但其术后胆漏的发生率更高[32] [33]。一些研究表明, LCBDE 治疗结石后的复发率要低于 ERCP, 这可能与 LCBDE 保留了括约肌功能有关[33] [34]。但也有报道称既往有胆道外科手术病史的患者, 在行内镜取石后复发的概率更高, 其原因可能是胆道手术引起局部的粘连导致胆总管倾斜, 从而影响胆道的功能, 最终引起胆汁淤积而增加了复发的概率[35] [36]。在 Peng 等的研究中也证实了这点, 并且他们认为胆总管切开后缝合及手术操作中的损伤可能导致胆管狭窄而引起结石的复发, 同时缝线等异物也可能增加结石复发的风险[2]。

T管引流术是LCBDE后经典的处理方式,其不仅可以缓解胆道压力、减少十二指肠乳头水肿,还有助于残石排出。同时,术后可以通过T管造影观察结石残留及胆道狭窄的情况,为预防结石复发提供了帮助。但在Zhu等最近的一项研究中发现,胆总管探查术后行一期缝合与T管引流术相比在结石残留、胆管狭窄、术后并发症等方面并没有明显差别。他们认为T管作为异物可能引起胆色素和胆盐的沉积。同时,护理不善会成为细菌进入胆道的通道。这些因素会导致结石的复发。相比之下,一期缝合或许可以降低复发率[37]。

3. 与胆道相关的因素

胆道的情况与结石复发有着密不可分的联系,其中胆总管扩张、尖锐的胆总管成角、Oddi括约肌的功能障碍和壶腹周围憩室在一些研究中被认为是结石复发的独立危险因素。而胆囊管汇入胆管的位置也可能和结石复发有一定的联系,但在这一点上仍存在争议。

1) 胆总管直径胆总管扩张目前被认为是结石复发的独立危险因素。这可能与胆管扩张导致的胆汁淤积及胆道感染有关[2] [16] [38]。但目前对胆管的直径和结石复发的具体关系尚有争议,有学者研究发现胆总管直径 $>15\text{ mm}$ 是结石复发的独立危险因素[2] [39]。而Park等则认为,胆总管直径 $>10\text{ mm}$,就已经是胆总管结石复发的危险因素[4]。在Paspatis等对106名患者的长期随访中发现,胆总管直径 $>19\text{ mm}$ 为最准确的阈值,并且认为胆管的直径越大复发的概率也越大[16]。

2) 胆总管成角胆总管成角是指胆总管在下降过程中,会向右倾斜一定的角度然后汇入十二指肠。过于尖锐的胆总管成角同样被认为是胆总管结石复发的独立危险因素,这可能是因为越小的胆总管走行角度越容易导致胆汁淤积,从而引起结石的复发[40]。但在具体的角度上存在不同的看法,一些研究结果表明胆总管角度 $<145^\circ$ 可增加胆总管结石的复发风险[40] [41]。而在国内的一项研究中发现,胆总管成角 $<120^\circ$ 便是结石复发的独立危险因素[2]。

3) 胆囊管汇入位置胆囊管汇入胆管的位置可能和胆总管结石复发有一定的关系,但在这一点上仍没有达成共识。和胆总管扩张及胆总管成角一样,胆囊管汇入的位置过低可能导致胆汁淤积和反流,从而导致结石的复发风险增加。有学者认为,当胆囊管汇入胆管的位置位于肝门与肝胰壶腹之间的胆管远端1/3处时,结石复发的概率会增大,对于这类患者更应该仔细的随访[6]。而Kao等研究结果显示,胆囊管低位汇入患者的壶腹周围憩室发生率更低以及胆汁细菌培养的阳性率更低,这可能与结石复发率更低有关[42]。

4) Oddi括约肌就像一个开关,控制胆汁的排放,同时避免肠内容物反流。如果Oddi括约肌松弛可促进肠内容物反流入胆道,从而导致胆道微生物群落的改变,这可能是其导致结石复发率更高的原因[43]。为降低结石复发,在治疗方式的选择及手术过程中应该尽量重视对Oddi括约肌的保护。但Tsai等却有不同意见,他们的研究发现ERCP术后Oddi括约肌功能丧失者,结石复发的概率更低,这可能是由于保留功能的括约肌会阻碍残留结石的自然通过,从而引发结石的复发[44]。

5) 壶腹周围憩室根据主乳头的位置,定义了三种类型的壶腹周围憩室,分别是:I型,乳头位于憩室深部;II型,乳头位于憩室内缘;III型,乳头位于憩室外。一些研究认为壶腹憩室是结石复发的又一个重要原因[45] [46] [47],这可能是由于憩室干扰了胆汁流动引起胆汁淤积从而导致结石的形成,以及憩室内食物残渣的淤积和其可能影响括约肌的功能,导致菌落的改变、细菌感染胆管,最终造成结石的高复发[2] [47] [48] [49] [50]。其中I型憩室则对结石的复发影响最为重要,这可能与憩室的大小及位置有关。因此,对存在I型憩室的患者更应该引起高度注意。

4. 与结石相关的因素

结石本身的性质同样也影响着结石复发的风险,原发结石的数量被认为是结石复发的独立危险因素,

而结石的成分及结石的大小也可能和结石复发有一定的关联。

1) 结石的数量多发结石被认为是胆总管结石复发的独立危险因素,这可能由于多发的结石对十二指肠括约肌的机械压迫,导致其功能障碍而引起肠道内容物反流及菌群的变化,最终造成结石的复发[2]。目前的研究认为结石数量 ≥ 2 是术后结石复发的独立危险因素[2] [4]。

2) 结石的成分胆结石主要有胆固醇结石和胆色素结石组成。胆固醇结石的形成与肝脏中胆固醇的合成及代谢的限速酶有关。在 Yoo 等研究发现,一些患者的肝脏中胆固醇降解为胆汁酸的限速酶 7 α -羟化酶的浓度降低,所以他们认为胆固醇结石是结石复发的独立危险因素之一[40]。胆总管内的胆色素结石主要为棕色色素结石,其通常被认为和细菌感染有关。有报道称,无论是复发组还是非复发组,棕色色素结石都比胆固醇结石多,是结石复发的危险因素[39] [51]。

3) 结石的大小通常情况下,较大的结石会导致更大的胆管扩张及损伤胆管功能,容易引起胆汁淤积和细菌感染,从而导致结石的复发,同时较大的结石通常需要碎石,这可能会增加结石术后复发的风险。有研究发现,结石直径 ≥ 10 mm 是复发的危险因素[13] [26] [40] [52]。但仍存在一定的争议, Peng 等认为直径 ≥ 10 mm 的结石并不会增加结石复发的风险[2]。

5. 其他

现有的研究显示,年龄大于 65 岁是胆总管结石复发的独立危险因素。其原因可能与老年人缺乏体力活动和油腻饮食、十二指肠乳头括约肌功能随年龄增长而下降、胆管壁张力和胆管动力不足、胆汁引流不良有关[2] [26]。然而, Keizman 等认为年龄不是结石的独立危险因素,但老年患者胆管扩张、壶腹周围憩室和既往手术史等危险因素发生的概率更大,所以随着年龄增长,结石复发的风险也就越大[53]。女性比男性更容易发生胆结石,特别是年龄大于 40 岁、肥胖、多次生产的女性。一项涉及 457 名患者的回顾性分析发现,男性是胆总管结石复发的保护因素[3]。

肝硬化是胆囊结石形成的重要危险因素, Tsai 等的研究结果表明,肝硬化同时也是胆总管结石复发的一个重要因素,但其机制目前尚不明确,需要进一步探索[54]。

6. 胆总管结石复发的预防

为了预防胆总管结石的复发,除了上述提到的通过选择合理的手术方式、胆道引流、胆道冲洗等方式外,还应该尽量避免损伤胆道及括约肌的功能。同时对可能存在胆汁淤积、胆道感染等危险因素的患者予以消炎利胆的药物也可以预防结石的复发。有研究称,熊去氧胆酸可以增加胆汁排泄、改善胆汁淤积及促进胆固醇结石的溶解,在治疗肝脏、胆道和消化系统的各种疾病方面具有有效性和安全性,是预防结石复发的一种策略[55] [56]。在国内的一些研究中还发现,阿拉坦五味丸、柴芍四金汤等消炎利胆的中成药及中药不仅对预防胆总管结石的复发有一定作用,还能改善腹胀、腹痛等临床症状及各项生化指标[57] [58]。

7. 总结

胆总管结石治疗后复发率较高,且复发机制尚未明确,目前的研究表明其复发可能和手术的方式、术中情况、胆总管直径及成角、Oddi 括约肌的功能、壶腹周围憩室、结石数量和大小、结石的成分以及患者自身的情况等多种因素相关。但在这些危险因素中仍有很多因素存在极大的争议,还需要更多的临床研究去探讨。且目前的研究大多是回顾性研究,没有研究者的预先干预,研究结果难免存在偏倚。

明确胆总管结石复发的危险因素可以让临床医生在面对胆总管结石的患者时选择合理的治疗方案。并且对有胆总管结石复发危险因素的患者,可以通过预防性治疗、定期监测、早期诊治、早干预来降低

结石的复发及减少并发症的发生。

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