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·综 述·

早期关闭预防性末端回肠造瘘口的研究进展

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[摘 要] 随着人们生活水平的提高,结直肠癌的发病率逐年上升,目前其主要治疗方式为手术。为了减少低位直肠癌高危患者吻合口漏的发生,常在手术切除的同时行预防性末端回肠造瘘,但造瘘口长时间存在会给患者的生活质量带来较大的负面影响。目前多数患者造瘘口还纳的时间仍为造瘘术后3个月甚至更久,国内外对能否提前早期关闭造瘘口以减少长期保留造瘘口带来的生理及心理负担仍然存在较大争议。因此,探讨早期关闭预防性末端回肠造瘘口的时机对临床具有重要意义。

[关键词] 结直肠癌;手术治疗;预防行造瘘;早期闭瘘

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Advances in early closure of prophylactic terminal ileostomy

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Abstract: With the improvement of people's living standard, the incidence rate of colorectal cancer has increased year by year, and its main treatment is surgery. In order to reduce the incidence of anastomotic leakage in high-risk patients with low rectal cancer, preventive terminal ileostomy is often performed at the same time of surgical resection, however, the existence of stoma for a long time may negatively affect the quality of life of patients. At present, the time for most patients to closethe stoma is still 3 months after the operation or even longer. There is still a great controversy at home and abroad on whether to close the stoma early and reduce the physiological and psychological burden caused by long-term retention of the stoma. Therefore, it is of great significance to investigate the timing of early closure of prophylactic terminal ileostomy.

Keywords: colorectal cancer; surgical treatment; prophylactic ileostomy; early closure of stoma

结直肠癌是全球第三大常见恶性肿瘤,而直肠癌约占结直肠癌的60%,并且以中低位直肠癌为主[1-2]。对于肿瘤位置较低、有发生吻合口漏高危因素的直肠癌患者,术中通常同期行预防性转流,以减少吻合口C级漏发生,减轻吻合口漏造成的不良后果,如非计划二次手术等[3-5]。通常造瘘可选择的肠段有末端回肠、横结肠及乙状结肠,多数医师会选择行末端回肠造瘘术,因为其更易于构建和还纳,并且不会造成结肠周围血管损伤[6]。造瘘口还纳的时间多为术后3个月左右,这期间大约50%的患者会发生回肠造瘘口相关并发症(如皮炎、回肠副肿瘤感染、电解质紊乱、造瘘口狭窄、回肠收缩、回肠坏死、回肠脱垂等),从而导致患者再次入院就诊[7-9];同时,这些并发症引起的身体结构改变、不受控制的排便排气等还会导致患者出现心理障碍,严重影响其生活质量[10]。此外,由于需要等待术后辅助治疗(放化疗)的完成,造瘘口还纳的时间也有可能延迟[11]。虽然一些研究报告了早期(术后2周内)造瘘口还纳的可行性与安全性,但多数患者造瘘口还纳时间依然在术后3个月左右[12-15]。目前关于造瘘口还纳时机的文献较多,但对于造瘘口还纳最佳时机的选择仍然没有共识和统一的指南。故本研究针对直肠癌低位前切除术后预防性末端回肠造瘘早期还纳的可行性及安全性作一综述。

1 直肠癌术中行预防性造瘘的原因

随着直肠癌全系膜切除术及腹腔镜技术的快速发展与应用,越来越多的直肠癌患者获得了低位吻合保肛的机会。低位吻合是指吻合位置在距离齿状线上方5 cm以内,但直肠癌低位吻合手术后常出现吻合口漏,其发生率为2% ~19%[5,16]。而一旦发生吻合口漏,将带来一系列严重并发症,其中C级漏对患者的影响极大,可能导致弥漫性腹膜炎、脓毒血症,甚至危及患者生命。有研究表明,预防性造瘘口可有效降低吻合口漏的发生率及与吻合口漏相关的再手术率[5,17]。因此在直肠癌低位吻合保肛手术中,行预防性造瘘成为了一种常规选择。

在造瘘口部位的选择中,与结肠相比,末端回肠血供丰富、肠腔清洁、活动度好、无需过多游离即可良好显露、操作容易、发生血运障碍概率小;同时,再手术时可利用原造瘘口将回肠拖出腹腔外进行吻合,操作简单可靠,可大大减少再手术的时间,避免再次开腹给患

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者带来的损伤[6,18]。因此,直肠癌低位前切除术后预防性造瘘常选择行末端回肠造瘘,即预防性末端回肠造瘘。

2 临床上常用的造瘘口还纳时机

行预防性造瘘术后,不同的研究机构关闭回肠造瘘口的时间有所不同,但是大多数患者的造瘘口会保留2~3个月[19-21]。结肠吻合口愈合的胶原纤维合成在术后3 h开始增加,术后4 d胶原纤维合成达到最大刺激的6倍,术后4周恢复到术前水平[22]。在行闭瘘术前,外科医生必须确保吻合口愈合良好,无吻合口漏发生的迹象。吻合口漏有许多危险因素,如高龄、男性、营养不良或过度肥胖、饮酒、吸烟、美国麻醉师协会(American Society of Anesthesiologists,ASA)评分≥3分、术前辅助性化疗、使用激素、糖尿病病史及腹部手术史;同时,手术相关因素也会影响吻合口漏的发生,如手术时间、出血量、网膜包裹情况、肿瘤与肛门距离、吻合方式及技术、手术方式、预防性造瘘口、肠系膜下动脉结扎水平、术前肠道准备及盆腔引流情况[23-24]。考虑到这些影响因素,确定患者吻合口愈合良好及造瘘口还纳的确切时间具有一定的挑战性。如上所述,如果没有其他问题,吻合口愈合所需的时间至少为4 d。然而,当患者具有影响吻合口漏发生的因素时,预测吻合口完全愈合的时间更加困难,通常认为需要2~3个月才能确保吻合口的完全愈合,因此,大多数回肠造瘘口通常在术后2~3个月行闭瘘术[19-21]。

然而,在造瘘口保留期间,有10%~50%的患者会出现造瘘口相关并发症[7-9,12,14,25-28];除上述并发症外,造瘘口相关的其他问题,如性欲低下、自身形象问题(着装困难、感觉缺乏吸引力)和与造瘘口本身有关的实际问题(需要找特定地方清空造瘘口袋、解决造瘘口袋泄漏等),都会对患者整体生活质量产生负面影响[29]。有研究表明,造瘘口保留时间越长,产生的相关并发症越多,对患者生活质量的影响也就越大[30-31]。有研究指出,造瘘口对结直肠癌患者生活质量的影响主要存在于术前及术后3个月内,3个月后常会趋于稳定[32]。因此,为了缩短造瘘口保留的时间,减少造瘘相关并发症的发生,有学者提出早期闭瘘的观点,即在术后14 d对无吻合口漏及其他并发症的患者进行闭瘘。

3 早期闭瘘的可行性

Li等[11]进行了一项对照研究,其结果显示在常规时间之前(<3个月)闭瘘是安全可行的,不会增加手术并发症,且对于减少造瘘口相关并发症有利。Menegaux等[33]于2002年通过一项非随机前瞻性研究证明,一期肿瘤切除术后10 d即可关闭回肠造瘘口。Bakx等[34]的一项非随机前瞻性研究也表明术后1~3周关闭回肠造瘘口是可行的,且并发症发生率低,无死亡病例发生。此外,Alves等[35]的随机临床试验证明,在肿瘤根治术后8 d对特定的患者行回肠造瘘口关闭是可行的,且可缩短患者住院时间,减少术后并发症。基于以上研究结果,一些外科医生断言,术后14 d内关闭回肠造瘘口是安全可行的。Lee等[27]在最近的一项前瞻性研究中选择了30例行直肠癌根治术+预防性末端回肠造瘘的患者,在术后1周内均无明显并发症;行肠镜检查发现其中6例出现了吻合口瘘,其余24例吻合口愈合完全,无明显肠梗阻或瘘的迹象;这24例患者在肿瘤分期、身体情况等方面均具有可比性,且均无明显术后并发症,经评估均能承受二次闭瘘手术,直肠癌根治性手术和造瘘口关闭的时间间隔为13.1 d(8~16 d),术后未出现任何并发症;同时,所有患者从根治术到开始辅助性治疗的时间为5.37周(5~8.1周),并未延迟正常术后开始放化疗的时间。因此,该研究认为行直肠癌根治术+预防性回肠造瘘的患者在内镜检查和影像学检查确保吻合口完全愈合并且无其他明显并发症时,可以在术后14 d内关闭回肠造瘘口。然而,在一项随机对照试验中,当把关闭造瘘口时间选定在术后1个月时,与常规术后3个月关闭造瘘口相比并不安全,术后1个月闭瘘的总并发症发生率显著较高,因此该研究认为不应该在术后1个月左右关闭造瘘口[36]。但需要注意的是该研究中早期闭瘘的时间为术后1个月,与其他研究者的时间点选择不一样,并且为单中心研究,因此需要更多的研究来证明该结论的可信度。基于以上研究,在行直肠癌低位前切除术+预防性末端回肠造瘘术后14 d时,对于没有并发症或明显禁忌的患者而言,实现早期还纳造瘘口是可行的。

4 早期闭瘘的优势

4.1 早期闭瘘可减少相关并发症发生

有研究显示,造瘘口保留的时间越长,出现的相关并发症越多[30-31]。由上述研究可知,在造瘘术后14 d关闭造瘘口,可明显缩短造瘘口保留的时间,提前缓解患者的心理负担,且不会增加围术期的并发症发生率[14,27,33-34]。早期闭瘘还可以减少低位前切除综合征(low anterior resection syndrome,LARS)的发生。临床对许多直肠癌患者都进行了预防性末端回肠造瘘以避免LARS立即发生,但大多数患者最终会在回肠造瘘口关闭后发生LARS。而且预防性末端回肠造瘘术被发现是直肠切除术后LARS发生的危险因素,这在LARS评分和Jorge-Wexner量表中都得到了证实[37-38]。此外,来自LAARIS试验管理组的数据表明,从初始造

瘘手术到关闭造瘘口的长时间间隔增加了 LARS 的发生率[39]。在吻合口完整的情况下,仅为预防 LARS 而保留回肠造瘘口是很少见的,对于行预防性转流的患者,早期关闭造瘘口的满意度可以超过 LARS 带来的不适,同时可缩短造瘘口保留的时间。

4.2 早期闭瘘可促进患者早期康复

早期闭瘘符合加速康复外科(enhanced recovery after surgery,ERAS)对手术患者的管理要求。多年来,ERAS 一直在各领域寻求新的发展和改进,如微创方法、药物和干预措施。事实上,每种新的临床方法只要可以加快术后康复速度都可以视为 ERAS 方案的一部分。早期关闭回肠末端造瘘口的患者住院时间、费用以及对肿瘤的疗效均与常规时间行闭瘘的患者相似,应该作为 ERAS 方案的一部分来实施[40-41]。

5 早期闭瘘的局限性

5.1 早期闭瘘对化疗周期的影响

对于直肠癌患者,尤其是中晚期患者,需要考虑术后的辅助性化疗。肠道肿瘤化疗目前使用最多的是 Folfox(叶酸、5-氟尿嘧啶和奥沙利铂)方案[42],14 d 为 1 个化疗周期,通常在手术后持续 4 ~ 6 个月。但是,药物的不良反应是影响患者坚持用药的重要因素,主要包括过敏反应、神经毒性反应、骨髓抑制、胃肠道反应、静脉炎等,同时,药物的不良反应也会给患者带来痛苦,甚至威胁患者生命。早期的共识是关闭回肠造瘘口手术应推迟至辅助化疗完成之后[43-44]。因为在辅助化疗期间行闭瘘术可能会因为部分潜在原因而增加风险:首先,最重要的是化疗是否会影响到患者回肠闭瘘术后切口的愈合;其次,由于回肠造瘘口的关闭而导致化疗中断或延迟,可能会影响化疗的效果并导致生存期缩短[45-47];另外,如果发生严重的并发症,辅助化疗的周期可能会延长,会对患者生存率和生活质量产生负面的影响[48-49]。

临床工作中往往在直肠癌根治术后尽早给予化疗,故有研究认为术后 14 d 内行闭瘘术会影响化疗的开始时间[47]。但也有研究显示,胃肠道肿瘤术后化疗时间窗为术后 6 ~ 8 周[50-51],即在一期术后 6 ~ 8 周内任何时间点开始化疗最终疗效都不存在统计学差异,所以早期闭瘘并不会对患者化疗的最终疗效产生影响。近来许多研究证实了在化疗开始之前或化疗周期内关闭造瘘口的安全性和可行性[27,41,52-53]。Zhou 等[52]在一项包含 123 例患者的回顾性研究中发现,化疗并不是关闭造瘘口术后并发症发生的危险因素,化疗期间关闭造瘘口是安全可行的。此外,Lee 等[27]的前瞻性研究和 Choi 等[54]的研究皆认为在化疗期间关闭造瘘口是安全可行的,化疗并不会对手术产生负面影响,而手术对患者的化疗效果和最终的生存率没有影响,反而对患者术后生存质量有益。胃肠道肿瘤的化疗效果主要与肿瘤的分期和患者自身其他疾病的影响有关,患者造瘘口关闭的时间选择与其最终的生存率并没有直接关系[55]。

尽管目前在临床上关闭回肠造瘘口的时间与化疗周期及疗效之间的关系尚存在争议,但由上述可知,越来越多的研究者在化疗前或者化疗周期内行造瘘口关闭取得了满意的效果。而早期关闭回肠造瘘口对肿瘤患者的化疗效果无不利影响,相反,其可以提高患者的生活质量。故对于化疗不良反应不重的患者不必担心早期关闭造瘘口对化疗效果的影响。

5.2 早期闭瘘切口感染的问题

造瘘口关闭后切口感染是其常见并发症,这是由于 2 次手术间隔时间短,机体恢复和免疫力下降,并且已有研究证实,大手术或外伤后免疫防御机制的改变会使宿主容易通过多种细胞因子活动而感染传染性并发症[56]。据报道,在预防性造瘘术后常规时间闭瘘的患者切口感染率为 1.5% ~ 5%[57]。然而,在选择早期关闭造瘘口的患者中,均出现了切口感染增多的情况,感染率为 15.5% ~ 26%[12,25-26,28,58],这必然导致患者住院时间及护理成本增加等问题。因此,为了提高患者的治疗效果并使患者选择早期关闭造瘘口时更具成本效益,应在术前评估患者机体免疫情况,术中严格遵守无菌操作,术后加强术区护理,以减少切口感染。早期关闭造瘘口导致切口感染增加,其影响常局限于造瘘口周围,并不会引起更多更严重的并发症。相对于造瘘口引起的身体和心理上的负面影响,早期关闭造瘘口所带来的便利可使患者满意度更高。

5.3 早期闭瘘患者的筛选

在行预防性末端回肠造瘘的患者中,有 21% ~ 28% 的患者会由于各种原因失去闭瘘的机会,最终导致需要永久性造瘘[59-60]。在关闭造瘘口之前,评估患者吻合口愈合的完整性十分重要,临床上常通过内镜、造影、CT 等影像学检查来判断吻合口的愈合情况。在确保患者吻合口愈合良好、无吻合口漏或者狭窄、自身无其他并发症时,才能考虑早期关闭回肠末端造瘘口。

直肠癌术后并发症的总发生率达到 40%,其中 20% 以上的患者会出现严重并发症[61-62],因此,一期术后 14 d 内关闭造瘘口只能在部分患者中进行。根据现有的文献可得出以下结论:①在欲早期为患者关闭造瘘口时,必须告知患者相关事项,并征得患者本人知情同意[14];②所有患者在关闭造瘘口之前需行内镜、造影或影像学检查以保证吻合口无瘘、无愈合不良迹象[14,26,36];③患者在一期手术后一般情况差、不能承受短期内再次手术打击时,不作为早期关闭造瘘口的

选择[36];④虽然高龄不是闭瘘的绝对禁忌证,但考虑到高龄患者身体素质的原因,需谨慎;⑤对于已经开始化疗的患者,如其化疗反应较轻,可不做处理,但当患者出现严重胃肠道反应、白细胞数 $<2\times10^9$/L 以及血小板数量 $<70\times10^9$/L 等严重骨髓抑制时,机体对再次手术承受能力弱,易出现术中出血、切口愈合困难甚至全身感染等并发症,不应在化疗期间关闭造瘘口;⑥高血糖本身具有损害中性粒细胞抗菌功能的趋势,易使患者体征失稳,增加手术风险,同时,由于糖尿病患者通常营养水平低下,会一定程度上加大切口不愈合和感染的概率,故糖尿病患者不建议早期闭瘘[63];⑦术后使用类固醇激素的患者,即使是晚期闭瘘也会有较大的风险,所以也是早期闭瘘的禁忌。

另外,患者自身的依从性也会影响造瘘口保留时间的长短,即使临床医师评估后可以早期关闭造瘘口,患者的选择也会因为居住环境、经济条件、社会地位等各方面的因素而受到影响[59]。因此,在行预防性末端回肠造瘘的患者中,除了永久性造瘘和术后出现其他情况,由于需要对患者的自身基础情况进行评估和医疗环境等原因,最终只有部分患者能够满足早期关闭造瘘口的条件。

6 总结

综上所述,直肠癌低位前切除术后行预防性末端回肠造瘘的患者生活质量受到较大的负面影响,尽管目前临床关于早期关闭预防性末端回肠造瘘的时机尚未统一,对于无吻合口愈合不良及其他严重术后并发症的患者可选择在术后 14 d 行早期闭瘘,缩短造瘘口保留的时间,减少由于长期保留造瘘口带来的生理及心理负担。

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·综 述·

全身麻醉对昼夜节律的影响研究

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[摘 要] 哺乳动物的昼夜节律生物钟是一种分子振荡表达循环,是生物在长年的演化过程中被自然选择出来的一种内源性计时机制,使生物能够预见环境的周期性改变。机体的多种行为和生理功能都表现出明显的昼夜节律现象,而生物钟的紊乱会严重影响机体的健康及生存。全身麻醉会扰乱昼夜节律,引起生物钟的改变。本研究通过回顾生物钟的大体分子机制,从分子水平和生理行为阐述麻醉对昼夜节律的潜在影响。

[关键词] 昼夜节律;生物钟;全身麻醉;光照;PER;丙泊酚;七氟烷;休息/活动节律
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Advances in effect of general anesthesia on circadian rhythms

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Abstract: The circadian clock of mammals is a molecular oscillatory expression cycle, which is an endogenous timing mechanism selected by nature during the evolution of organisms over a long period of time, and enables organisms to foresee the periodic changes of the environment. Many behaviors and physiological functions of the body are showing an obvious circadian rhythm phenomenon, and the disorder of the biological clock will seriously affect the health or survival of the body. Studies have shown that general anesthesia (GA) can disrupt circadian rhythms and cause changes of the biological clock, which indicates that anesthesia can cause circadian rhythm disorders in patients. This study retrospected the general molecular mechanism of the biological clock, to explain the potential effects of anesthesia on the circadian rhythm from the molecular level and physiological behavior.

Keywords: circadian rhythm; biological clock; general anesthesia; lighting; PER; propofol; sevoflurane; rest/activity rhythm

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