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· 文献综述 ·

自膨式金属支架在结直肠梗阻中的应用进展

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摘要

结直肠恶性梗阻的患者通常需要急诊手术治疗解除梗阻, 然而传统的急诊手术并发症发生率及病死率高, 尤其对于左半结肠癌及直肠癌患者。自膨式金属支架自应用 20 余年来, 已较广泛的应用于结直肠的各种良恶性狭窄, 但支架置入是否会影响患者的长期生存及肿瘤转移目前仍有很大争议。笔者从金属支架置入的适应证与禁忌证、支架在结直肠良恶性梗阻中的应用等方面结合最新研究进展做一综述, 为临床诊疗提供参考。

关键词

结直肠肿瘤; 肠梗阻; 支架; 姑息疗法; 综述文献
中图分类号: R735.3

Advances in application of self-expandable metallic stenting for colorectal obstruction

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Abstract

Patients with malignant colorectal obstruction usually need an emergency surgery to restore luminal patency. However, traditional emergency surgery has high rates of complications and death, especially in patients with left colon cancer and rectal cancer. Self-expandable metallic stenting has been widely used in various benign and malignant colorectal strictures for more than 20 years. However, whether stent implantation will affect the long-term survival of patients and cause tumor metastasis are still highly controversial. Hence, the authors address the indications, contraindications and application of metal stent placement in colorectal benign and malignant obstruction, and combine the latest research advances, so as to provide reference for clinical treatment.

Key words

Colorectal Neoplasms; Intestinal Obstruction; Stents; Palliative Care; Review
CLC number: R735.3

结直肠癌 (colorectal cancer, CRC) 是常见

的实体恶性肿瘤之一, 其发病率和病死率较高^[1], 是高龄患者最常见的肠梗阻病因之一, 有报道指出, 7%~29%的CRC患者会发生急性肠梗阻^[2]。由于回盲瓣的存在, 结直肠癌引起的肠梗阻通常为闭袢性梗阻, 若不及时解除梗阻, 有发生肠管缺血、坏死甚至穿孔等风险, 故需急诊行肠道减压术。然而急诊手术 (emergency surgery, ES) 的并发症发生率及病死率明显高于择期手术^[3-4]。

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1991年, Dohmoto^[5]首先报道了自膨式金属支架 (self-expandable metallic stenting, SEMS) 应用于无法切除或远处转移的直肠癌伴梗阻患者, 并取得了成功。我国于1992年也开始采用记忆合金支架治疗结直肠恶性梗阻, 取得了良好的肠道减压效果^[6]。目前, SEMS置入已应用于结直肠的各种良恶性梗阻, 有多项研究证明其作为结直肠癌梗阻的姑息性治疗手段以及手术桥接 (bridge of surgery, BTS) 都是安全和有效的^[7-8], 但考虑到支架置入相关的并发症以及其可能对患者带来的肿瘤学结果的影响^[9-11], SEMS置入仍存在争议。近年来也有报道SEMS置入应用于右半结肠梗阻^[12], 本文就其在结直肠梗阻中的应用做一综述。

1 SEMS 的置入方式、适应证及禁忌证

SEMS的置入方式: X线辅助结肠镜下金属支架置入^[13-14]: 肠道准备后, 将肠镜送达狭窄处, 经内镜活检管道插入导丝, X线引导下通过狭窄段, 导丝引导下置入导管, 经导管注入造影剂, 根据狭窄情况选择合适的支架 (支架覆盖狭窄段全部及其近端2 cm以上和远端1 cm以上范围), 沿导丝送入并确认狭窄处位于支架中部, 释放支架。SEMS置入的适应证: (1) SEMS置入作为结直肠恶性肿瘤梗阻患者术前的过渡治疗。过去的20年来, SEMS置入已经作为左半结肠癌所致梗阻择期手术的过渡治疗手段, 即手术桥接 (bridge of surgery, BTS), Tomito等^[15]认为, SEMS置入作为BTS在围手术期是安全有效的, 但长期肿瘤学效果仍需大量临床研究加以论证。(2) 结直肠恶性肿瘤的姑息性治疗, 不可切除的CRC患者的姑息治疗是SEMS置入的一项重要适应证^[16], SEMS置入可避免行姑息性手术 (腹壁造口) 及其并发症。(3) 应用于具有高危手术因素的患者, 如心脑血管疾病、糖尿病、凝血机制障碍等, 作为永久或者暂时的治疗措施。(4) 治疗肠道的各种良性狭窄^[17]。(5) 治疗肠道外肿瘤压迫引起的肠道梗阻。(6) 拒绝行肠造瘘, 同意或者要求行支架治疗的患者。SEMS置入的禁忌证: 消化道穿孔、肠坏死以及生命体征不平稳或不能耐受操作者。

2 SEMS 置入在结直肠恶性梗阻姑息性治疗中的应用

在所有的CRC患者中, 约22%在第一次就诊时已经有肝或其他器官的转移, 80%的结肠癌梗阻患者由于肿瘤广泛浸润、远处转移或严重的伴随疾病等而无法行根治性切除^[18], 传统需急诊行肠道腹壁造口来解除梗阻, 但急诊手术的并发症发生率及病死率高, 且有腹壁永久造口, 患者生活质量低。大量的研究^[14,19]报道了SEMS置入对结直肠癌梗阻姑息性治疗的安全性及有效性。为比较SEMS置入与姑息性手术治疗的效果, Finlayson等^[20]对128例无法根治的IV期结直肠癌患者做了回顾性分析, SEMS组技术成功率为98.5%, 临床成功率为100%, 并发症发生率低, 为23.1% (再梗阻7.7%, 移位7.7%, 穿孔4.6%, 出血3.1%), 仅有7.7%的SEMS组患者需要手术治疗, 在30 d及1、2年生存率及总生存期上, 两组结果无明显差异, 但SEMS组住院时间及造口率明显低于手术组。Ribeiro等^[21]对4项RCT研究共125例患者做了Meta分析显示, SEMS组和ES组的30 d病死率分别为6.3%和6.4% ($RD=0.00$, $95\% CI=0.10\sim0.10$, $I^2=0\%$), 差异无统计学意义, 平均生存时间分别为279 d和244 d ($RD=20.14$, $95\% CI=42.94\sim83.21$, $I^2=44\%$), 差异无统计学意义。ES组和SEMS组的临床成功率分别为96%和86.1% ($RD=0.13$, $95\% CI=0.23\sim-0.02$, $I^2=51\%$), 差异有统计学意义, ES组和SEMS组的永久造口率分别为84%和14.3% ($RR=0.19$, $95\% CI=0.11\sim0.33$, $I^2=28\%$) 差异有统计学意义。SEMS组的住院时间更短 ($RD=5.16$, $95\% CI=6.71\sim-3.61$, $I^2=56\%$), 差异有统计学意义。两组不良事件发生率 ($RD=0.18$, $95\% CI=0.19\sim0.54$)、ICU住院率 ($RD=0.01$, $95\% CI=0.08\sim0.05$, $I^2=7\%$) 均无统计学差异。对晚期结直肠癌梗阻患者, 姑息性支架置入是安全、有效的, 但需要谨慎操作, 减少肠道穿孔、出血等并发症。

3 SEMS 置入作为 BTS 在左半结肠癌及直肠癌梗阻中的应用

左半结肠癌及直肠癌引起的肠梗阻患者通

常全身一般状况差,伴有水电解质、酸碱平衡紊乱、细菌移位等情况,一期吻合率低。对于可根治的左半结肠癌及直肠癌患者,传统一期急诊处理梗阻,行病灶切除加腹壁造口术,二期行造口还纳,然而急诊手术的并发症发生率及病死率高,且患者需要承受更多的手术痛苦,更多的医疗费用,更长的住院时间,且有临时造瘘口,生活质量较差,难以被患者接受。目前,SEMS置入可作为BTS避免行造瘘手术。Crespi-Mir等^[22]对77例(BTS组57例,ES组20例)左半结肠癌及直肠癌梗阻患者做了回顾性分析,BTS组经腹腔镜手术的患者较ES组多(64.9% vs. 5%, $P<0.001$),BTS组一期吻合率较ES组高(91.2% vs. 55%, $P=0.001$),BTS组腹壁造口率较ES组低(10.5% vs. 50%, $P=0.001$),BTS组住院时间较ES组低(7 d vs. 12 d, $P=0.014$),BTS组30 d并发症发生率与ES组没有统计学差异(29.8% vs. 50%, $P=0.104$),BTS组30 d病死率较ES组低(1.8% vs. 20%, $P=0.015$)。Lim等^[23]对102例(BTS组55例,ES组47例)左半结肠癌及直肠癌梗阻患者做了回顾性分析,支架置入的技术成功率为71%,ES组发生严重并发症的可能性较BTS组高,但无明显统计学意义($OR=2.84$, 95% $CI=0.71\sim 11.3$, $P=0.139$),BTS组平均随访48.3(3.1~111)个月,ES组平均随访51.2(1.2~117.1)个月,BTS组与ES组复发率无明显差异(25.6% vs. 21.3%, $P=0.500$),ES组吻合口和腹膜复发较多,BTS组与ES组5年无病生存率(77% vs. 73%, $P=0.708$)和总生存率(86% vs. 62%, $P=0.064$)差异无统计学意义。SEMS置入作为BTS治疗左半结直肠癌梗阻患者的远期疗效与急诊手术组相似。Arezzo等^[24]对8项RCT研究共497例左半结肠癌或直肠癌梗阻患者做了Meta分析,BTS组与ES组的60 d病死率分别为9.6%和9.9% ($RR=0.99$, $P=0.97$),60 d整体并发症发生率分别为33.9%和51.2% ($RR=0.59$, $P=0.023$),临时造口率分别为33.9%和51.4% ($RR=0.67$, $P<0.001$),永久造口率分别为22.2%和35.3% ($RR=0.66$, $P=0.003$),一期吻合率分别为70%和54.1% ($RR=1.29$, $P=0.043$)。SEMS作为BTS有更低的并发症发生率、临时造口率、永久造口率,更高的一期吻合率,更少的住院时间和住院费用,但对肿瘤长期预后似乎没有影响。SEMS可作为左半结肠及直肠

恶性梗阻的过渡治疗,已被多项研究^[17-8, 25-28]证实是安全和有效的。

4 SEMS置入在右半结肠癌梗阻患者中的应用

SEMS置入在左半结肠癌及直肠癌中的应用已经较为常见,但在右半结肠癌引起的梗阻中应用较少,主要是因为大多数右半结肠癌引起的梗阻患者通常一期行肿瘤切除加吻合术。但部分研究^[29-31]表明SEMS置入应用于右半结肠癌引起的梗阻较ES有更低的并发症发生率、临时造口率及永久造口率。Ji等^[12]对39例右半结肠癌梗阻患者(SEMS组16例,ES组23例)做了回顾性分析,14例(87.5%)获得技术成功,SEMS组腹腔镜手术率为93%(13/14),ES组为12%(3/25),SEMS组和ES组的住院时间分别为(9.4±3.4) d和(12.4±5.9) d ($P=0.089$),两组术后恢复进食时间分别(3.2±2.1) d和(5.7±3.4) d ($P=0.019$)。Kye等^[32]对74例右半结肠癌梗阻患者(SEMS组25例,ES组49例)进行了回顾性分析显示,两组远侧和近侧切缘长度($P=0.820$ 和0.620)、转移淋巴结数量($P=0.444$)的差异无明显统计学意义,SEMS组和ES组5年总生存率分别为90.7%和73.2% ($P=0.172$),5年无病生存率分别为76.2%和71.9% ($P=0.929$),两组的长期肿瘤学结果相似。Morita等^[33]对201例结直肠癌梗阻患者(SEMS组109例,ES组92例,其中右半68例,左半133例)进行了对比研究,结果显示左半SEMS组一期切除率、一期吻合率、腹腔镜手术率明显高于ES组,而右半SEMS组比ES组仅有较高腹腔镜手术率,但住院时间更长,SEMS置入对左半结肠癌及直肠癌梗阻患者的益处较右半结肠癌梗阻患者大。Amelung等^[34]对14个队列研究共3 028例(ES组2 873例,SEMS组155例)右半结肠癌梗阻患者进行Meta分析,结果显示ES组急诊一期吻合患者病死率为10.8%(8.1%~18.5%),SEMS组支架置入后择期切除吻合的患者病死率为0,ES组和SEMS组主要并发症发生率分别为23.9%(9.3%~35.6%)和0.8%(0~4.8%),病死率和主要并发症发生率有显著差异,SEMS组较ES组有较低的吻合口瘘发生率(0% vs. 9.1%)和较低的永久造口率(0% vs. 1.0%)。综上,SEMS置入

在右半结肠癌引起的梗阻患者的应用似乎是安全和有效的。

5 SEMS 置入在良性结直肠梗阻患者中的应用

良性结直肠狭窄有很多原因,包括术后狭窄、憩室疾病和炎症性肠病等,外科手术一度被认为是良性结直肠狭窄的标准治疗方式,但SEMS置入的出现,为结直肠良性狭窄提供了一种新的治疗手段。Lamazza等^[35]对10例结直肠切除术后出现良性狭窄的患者使用SEMS解除梗阻,10例均成功置入,无严重并发症发生,平均随访18个月,7例成功缓解,其余3例只用球囊扩张治疗成功。Keranen等^[36]对21例良性大肠梗阻患者进行SEMS置入,他们认为与恶性梗阻相比,SEMS在良性狭窄中有更多术后并发症,但对于有手术禁忌证的良性结直肠梗阻患者,SEMS置入是其良好的选择。

6 SEMS 置入在肠外恶性肿瘤引起肠道梗阻患者中的应用

常见的引起肠道梗阻的肠外肿瘤有子宫癌、卵巢癌、胃癌、膀胱癌和肾癌等,目前支架置入对肠外恶性肿瘤所致肠梗阻的疗效还不明确。Faraz等^[37]对187例结肠外恶性肿瘤继发大肠梗阻患者进行研究,142例患者(75.9%)取得了技术成功,102例患者(54.5%)取得了临床成功,手术不良事件12例(6.4%),临床成功者3个月支架闭塞发生率为14.7%(95% CI=7.8%~21.6%),所有患者支架置入后中位总生存期为3.3个月(95% CI=3.0~4.1),姑息性支架置入对肠外恶性肿瘤引起的肠梗阻是安全有效的。

7 SEMS 置入的并发症

支架置入的常见并发症为术后出血、穿孔、再梗阻、支架移位、便意频繁和里急后重等^[9, 38-42],Lee等^[43]的经验认为恶性梗阻伴成角易造成支架置入术后肠穿孔。Lee等^[44]对474例(BTS组164例,姑息性组310例)行支架置入的结直肠癌梗阻患者进行分析,结果显示,技术成功率和临床成功率

分别为90.5%和81%,早期穿孔和迟发性穿孔分别为2.7%(3/474)和2.7%(8/310),21例穿孔患者中,14例行急诊手术(66.7%),穿孔后30d内死亡5例(23.8%),穿孔相关因素分析中,年龄>70岁(OR=3.276,95% CI=1.041~10.309)、支架位于乙状结肠部位(OR=7.760,95% CI=1.681~35.371)与早期穿孔发生独立相关,支架位于脾曲(OR=17.573,95% CI=2.00~154.09)和腹膜外位结肠(OR=6.139,95% CI=1.150~32.770)与延迟穿孔显著相关。李弼民等^[45]对263例结直肠癌梗阻患者进行分析,支架置入成功258例(98.1%),不良反应发生率为:穿孔1.1%(3例),出血3.8%(10例),发热4.6%(12例),支架移位、脱位发生率为3.0%(8例)。穿孔是结直肠支架置入最严重的并发症,平均穿孔率为5%(0~60%),穿孔可能与预后不良有关,此外,穿孔患者的病死率可能高达16%^[46]。

8 SEMS 置入的肿瘤学安全性

支架置入在结直肠肿瘤切除后一期吻合率、腹腔镜手术率及造口率等方面较急诊手术有明显的优势,但其对长期肿瘤学特性的影响仍存在很大的争议。Maruthachalam等^[10]的一项研究认为支架置入会增加外周循环中CEA和CK20mRNA的水平,表明支架置入后肿瘤细胞在血液中扩散。同样,Yamashita等^[9]和Takahashi等^[47]研究均证实SEMS置入增加了血液中游离DNA(cfDNA)和循环肿瘤DNA(ctDNA)的水平,可能是由于支架置入过程中作用于肿瘤上的剪切力致肿瘤细胞入血所致。Sabbagh等^[11]的一项倾向性评分研究认为,支架置入组的总生存期和无病生存期较急诊手术组短,进一步对两组病理结果分析显示,支架组的肿瘤溃疡、瘤周溃疡及神经淋巴管浸润率明显高于急诊手术组。Malgras等^[48]通过构建结肠癌小鼠模型来研究支架置入的肿瘤学安全性,结果表明,支架置入导致小鼠肿瘤转移增加,总生存时间缩短。但部分临床研究^[26, 32]认为,支架置入组与急诊手术组的无病生存期和总生存期无明显差异。一些体外研究^[49-50]表明,施加于结肠癌细胞系生长的多细胞球体(MCSs)上的压力会显著降低其增值率,而这种降低与细胞分裂的减少有关,与细胞凋亡的增加无关。Ki-67参与细胞

周期的调控,其表达被用作细胞增殖的标志物,Matsuda等^[51]研究显示,SEMS置入的机械操作导致了Ki-67的表达水平显著下降,随后他们研究了SEMS置入前后p27_{Kip1}表达的变化,以探讨Ki-67表达降低的机制,结果显示p27_{Kip1}表达显著上调,他们认为SEMS诱导的机械压迫可能导致结直肠癌细胞增殖抑制。

9 总结与展望

近年来随着SEMS置入技术的成熟,其在结直肠良恶性梗阻中的应用逐渐普及,SEMS置入在结直肠癌梗阻的治疗上较急诊手术有明显的优势,提高了手术的成功率,降低了术后并发症,降低了造口率,减少了住院时间及住院费用,但应考虑到其并发症如穿孔和支架移位等风险。对于长期肿瘤学影响,目前争议较大,就目前的研究,虽然支架置入增加了血液中的ctDNA含量,但支架置入似乎可以抑制局部肿瘤的增殖,且并没有降低患者的无病生存期和总生存期。然而,目前仍缺乏高质量的临床研究来评价SEMS置入的长期肿瘤学特性,还需要大规模、多中心的临床前瞻性研究加以证实。

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