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·综 述·

肝癌肝动脉化疗栓塞及肝动脉灌注化疗术后疼痛的治疗进展

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[摘 要] 肝动脉化疗栓塞(TACE)及肝动脉灌注化疗(HAIC)等转化治疗是目前将不可切除晚期肝癌降期转化为可切除肝癌的主要治疗方法,不仅可以有效提高患者生存率,同时可为患者提供肝移植的机会。然而,疼痛为肝癌TACE和HAIC治疗的主要并发症,TACE术后腹痛的发生率为19.3%~71.2%,HAIC治疗过程中近64.6%的患者会出现不同程度的疼痛,严重影响患者的生活质量,缩短患者的生存期。目前,TACE和HAIC引起疼痛的发生机制尚不明确,可能与栓塞剂阻塞肿瘤供血动脉后局部肝组织肿胀、肝组织被膜压力增高或肿块包膜被牵拉、栓塞剂与抗肿瘤药物对肝动脉的化学刺激、邻近正常脏器的误栓及肠管缺血所致的内脏痛觉敏化有关。疼痛的干预措施主要有两种,一种是利多卡因、阿片类药物、非甾体抗炎药物及糖皮质激素等干预措施;另一种是腕踝针、中药汤剂等其他干预措施,但治疗效果参差不齐。本文就肝癌TACE及HAIC治疗所致疼痛情况及治疗现状进行综述,以期为其临床治疗提供参考。

[关键词] 肝动脉化疗栓塞;肝动脉灌注化疗;疼痛;肝癌
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Treatment progress of pains caused by transcatheter arterial chemoembolization and hepatic arterial infusion chemotherapy in hepatocellular carcinoma

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Abstract: Conversion therapy such as transcatheter arterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC) is the main treatment method to transform unresectable advanced liver cancer into resectable liver cancer, which can not only effectively increase the survival rate of patients, but also provide patients with the opportunity of liver transplantation. However, pain is a major complication of TACE and HAIC in the treatment of liver cancer, and the incidence of abdominal pain after TACE is from 19.3% to 71.2%, and nearly 64.6% of patients have different degrees of pain during HAIC, which seriously affects the quality of life of patients and shortens their survival time. At present, the mechanism of pains caused by TACE and HAIC is not clear, and it may be related to local liver tissue swelling after embolic agents block the tumor blood supply artery, increased pressure in the liver tissue envelope or traction of the mass capsule, chemical stimulation of the hepatic artery by embolic agents and antineoplastic drugs, thrombosis adjacent to the normal organs, and visceral pain sensitization caused by intestinal ischemia. There are two main intervention measures for pain, one of which is lidocaine, opioids, non-steroidal anti-inflammatory drugs and glucocorticoids, and the other is wrist and ankle acupuncture and traditional Chinese medicine decoction, but their treatment effects are uneven. This article summarizes the status and treatment of pain caused by TACE and HAIC therapies for liver cancer, in order to provide reference for its clinical treatment.

Keywords: transcatheter arterial chemoembolization; hepatic arterial infusion chemotherapy; pain; liver cancer

研究显示,在世界范围内,原发性肝癌发生率在恶性肿瘤中居第6位,病死率居第3位[1]。肝癌起病隐匿,多数无临床症状,39.0%~53.6%的肝癌患者初诊即处于晚期。且肝癌患者多伴有肝血管侵犯及肝外转移,患者1年生存率仅为12.0%~38.3%,多数指南不推荐手术切除治疗[2-5]。即使是可切除的肝癌,也仅5.0%~10.0%的患者具有外科手术切除指征,且由于肿瘤播散和肿瘤切除后仍有新生病灶的可能,患者术后5年复发率可达70%[6]。研究显示,不可切除晚期肝癌行肝动脉化疗栓塞(transcatheter arterial chemoembolization,TACE)及肝动脉灌注化疗(hepatic arterial infusion chemotherapy,HAIC)等转化治疗后,8.0%~18.0%的患者可以降低肿瘤分期,从而获得手术切除机会,患者术后5年生存率为24.9%~57.0%[7-8]。但是肝癌TACE及HAIC治疗均会引起不同程度的疼痛,且疼痛控制效果欠佳,进而影响患者对治疗方法的选择以及预后。本文就肝癌患者TACE及HAIC术后疼痛情况及治疗现状进行综述,以期为临床疼痛的管理和治疗提供参考。

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1 肝癌TACE术后疼痛

1.1 TACE所致疼痛现状

TACE是指将带有化疗药物的碘化油乳剂或载药微球、补充栓塞剂(明胶海绵颗粒、空白微球、聚乙烯醇颗粒)等经肿瘤供血动脉支的栓塞治疗。根据栓塞剂的不同,可分为常规TACE和药物洗脱微球TACE(又称载药微球TACE)[9],二者在肝癌治疗有效性、安全性上并无明显差异,但是药物洗脱微球TACE术后中重度腹痛发生率较常规TACE低(2.2% *vs.* 22.7%,0 *vs.* 18.2%)[10]。疼痛为肝癌患者TACE术后的主要并发症[11]。一项荟萃分析显示,TACE术后腹痛的发生率为19.3%~71.2%[12]。TACE术后疼痛常表现为局限于肝的胀痛和烧灼感[13]。Zhou等[14]的研究显示,约75.0%的肝癌患者TACE术后出现严重疼痛,数字评分量表(numerical rating scale,NRS)评分为7~10分,约93.0%的患者在TACE术后12 h内需要阿片类药物镇痛治疗。

1.2 TACE术后疼痛的发生机制及影响因素

目前,TACE术后疼痛的原因尚不明确,可能由于栓塞剂阻断肿瘤主要供血动脉,导致肿瘤组织迅速坏死,所在局部肝组织肿胀,进一步导致肝被膜紧张、压力增高。抗肿瘤药物与碘油混合物对肝动脉的化学刺激和邻近胆囊等正常脏器的误栓也可能引起术后疼痛。患者对疼痛敏感性较高也与疼痛的发生有一定关联[15-17]。此外,周德贤等[18]采用结扎大鼠结肠系膜动脉的方法建立了缺血性内脏痛模型,从内脏缺血的角度验证了NMDA受体NR2B亚基在肠管缺血引起的内脏痛敏形成机制中起重要作用。因此,我们推测TACE术后疼痛可能与肠管缺血引起内脏痛觉敏化有关。

Bian等[19]分析了TACE术后急性腹痛的危险因素,并基于分类和回归树分析数据集建立栓塞后疼痛的预测模型,在疼痛预测模型中,血管侵犯、TACE史、TACE方法、TACE术后腹痛史是TACE术后急性中重度疼痛的预测因素,其中血管侵犯是最重要、最强的预测因子。Yang等[20]建立的乙肝相关原发性肝癌TACE术后剧烈腹痛预测模型显示,TACE治疗史、肿瘤最大直径、梗死程度、术前美国东部肿瘤协作组体力状况评分是术后疼痛的独立影响因素。Benzakoun等[21]的研究表明,肝癌患者年龄在55岁及以下、无潜在慢性肝病及术中多柔比星剂量高均与TACE术后发生明显疼痛有关。

1.3 TACE术后疼痛的治疗策略

目前肝癌TACE术后疼痛治疗主要分为两种:一种是利多卡因、阿片类药物、非甾体抗炎药物及类固醇类药物等的干预;另一种是腕踝针、中药汤剂等其他干预措施。

1.3.1 动脉内给予利多卡因 多项研究显示,动脉内给予利多卡因可以明显减少TACE术中和术后镇痛药物的需求频率和用量[17,22-24]。Hartnell等[22]的研究表明,动脉内给予利多卡因不仅可以减少额外镇痛药物用量,而且可以缩短住院时间。但Fiorentini等[25]的研究显示,动脉内给予利多卡因并不能缩短住院时间。Lee等[17]分析了动脉内给予利多卡因给药时机对术后疼痛的影响,结果显示,与术后立即动脉内给予利多卡因相比,术前动脉内给予利多卡因能显著降低患者术后疼痛发生率和疼痛程度,减少术后镇痛药物用量。Wang等[26]的研究显示,与TACE术前即刻动脉内注射利多卡因相比,TACE术中给予利多卡因-表柔比星-碘油乳剂(油包水技术)控制TACE术中和术后疼痛的有效性和安全性更高。

1.3.2 口服或静脉给予阿片类药物及非甾体抗炎药物 Zhou等[14]的研究显示,规律口服羟考酮控释片可以降低疼痛评分,缩短住院时间,但轻中度右上腹疼痛的发生率较高,且仍有约16.4%的患者在术后12 h内发生严重疼痛;规律口服不同剂量的羟考酮控释片,患者TACE术后12 h疼痛有显著差异,而术后12~48 h疼痛无明显差异。Prajapati等[15]的研究显示,在不可切除肝癌患者中,口服羟考酮可有效缓解多柔比星药物洗脱微球TACE术后轻中度腹痛。Narayanan等[27]研究发现,在结直肠癌肝转移患者中,伊立替康药物洗脱微球TACE术中静脉给予递增数量的氢吗啡酮(总量为4 mg),可以减少2级和3级腹痛发生率,但是增加了1级腹痛发生率(常见不良反应术语评定标准CTCAE V3.0)。阿片类药物在控制疼痛方面非常有效,但其可能引起呼吸抑制、恶心呕吐、瘙痒、便秘等不良后果及有成瘾的风险,使用存在争议[11]。

另有研究显示,术前、术后规律接受静脉注射选择性环氧化酶-2抑制剂帕瑞昔布钠的患者疼痛NRS评分、疼痛程度分布、吗啡总消耗量及生活质量均显著优于使用生理盐水的患者,且术后并未发生严重不良反应[11]。Guo等[28]对比了常规镇痛方案与多模式镇痛方案应用于TACE术后镇痛,结果显示,与常规镇痛方案相比,多模式镇痛方案患者疼痛缓解更显著,患者满意度更高,不良反应更少。Lyu等[29]研究显示,与手术前后规律使用塞来昔布、羟考酮控释片相比,手术前后规律使用帕瑞昔布钠的患者TACE术后12 h疼痛评分显著降低,发生严重疼痛的患者数也显著减少。在一项前瞻性评分匹配队列研究中,TACE术后给予帕瑞昔布钠可有效缓解肝癌患者发热,促进术后恢复,缩短住院时间[30]。

1.3.3 静脉给予糖皮质激素 一项关于原发性肝癌的随机、双盲、对照试验显示，与接受安慰剂组患者相比，手术前后单独使用地塞米松组、单独使用人参皂苷组、人参皂苷和地塞米松联用组患者TACE术后腹痛发生率均明显降低[31]。Lu等[32]的研究显示，TACE术中使用碘油+地塞米松+抗肿瘤药物混合栓塞乳剂可以降低术后72 h内的腹痛发生率。此外，TACE术前预防性静脉给予地塞米松，术后疼痛程度和镇痛药物平均使用剂量均明显降低[33-34]。但Kogut等[35]的研究显示，术前预防性单次给予地塞米松不能减少TACE术后止痛剂或止吐剂的使用。

1.3.4 其他干预措施 一项随机对照试验结果显示，相较于空白对照组和安慰剂对照组患者，服用由茯苓、白术、党参、枳壳、山楂生果、五叶木通、枳实熬制的中药健脾理气汤剂组肝癌患者TACE术后第2、3天出现严重疼痛的比例更低，且术后肝功能损伤也明显改善[36]。Zeng等[13]研究显示，腕踝针对原发性肝癌患者TACE术后中重度疼痛的缓解效果等同于或大于口服吗啡的效果，还可以降低术后腹胀的发生率。此外，耳穴联合内关、合谷、足三里穴贴敷中药王不留行籽按摩可以有效缓解肝癌患者术后疼痛和恶心呕吐症状，且可提高患者满意度[37]。还有研究显示，3个月的居家有氧运动可以改善肝癌患者TACE术后疼痛–疲乏–睡眠障碍症状群，提高其生活质量[38]。

2 肝癌HAIC术后疼痛

2.1 HAIC所致疼痛现状

肝癌HAIC是化疗药物通过股动脉插管或植入药盒连续注入肿瘤营养动脉，从而发挥局部化疗作用，杀伤肿瘤[39]。一项Meta研究表明，HAIC可能是一种普遍安全的治疗方法，尤其是对于结直肠癌肝转移和晚期肝癌患者，可以延长其总生存期和无病生存期，并改善患者的客观缓解率和疾病控制率[40]。然而，有研究发现，部分患者在HAIC治疗过程中出现了严重疼痛，VAS评分甚至达到10分，导致患者对该治疗方案的依从性和耐受性显著降低；多元线性回归分析显示，在接受肝癌HAIC治疗过程中，约64.6%的患者出现不同程度的疼痛，约43.9%的肝癌患者需要强阿片类镇痛药物，约1.6%的肝癌患者需要额外的吗啡镇痛[41]。一项研究采用改良FOLFOX（奥沙利铂、亚叶酸钙、5-氟尿嘧啶）进行HAIC作为TACE治疗失败或不适合TACE治疗的晚期肝癌患者的替代治疗，结果显示，在采用FOLFOX治疗的患者中，约2.3%的患者发生3级腹痛[42]。Liu等[43]的研究显示，不可切除肝癌患者TACE术后采用以奥沙利铂和雷替曲塞为基础的化疗方案进行HAIC治疗，约32.4%的患者出现不典型1～2级腹痛。一项前瞻性研究显示，与采用单独肝动脉化疗栓塞治疗的不可切除肝癌患者相比，肝动脉TACE联合HAIC治疗患者3~4级腹痛发生率显著增加；有6例采用TACE联合HAIC治疗的患者在奥沙利铂灌注过程中出现上腹部剧痛（VAS评分为8~10分，多发生在化疗后2～4 h）[44]。Boilève等[45]的研究表明，采用奥沙利铂进行HAIC治疗最常见的3级毒性是中性粒细胞减少症(40.0%)、神经毒性(12.0%)和腹痛(3.0%)。Xu等[46]的研究也发现，HAIC中腹痛发生率达45.9%，是最常见的治疗相关不良事件之一。此外，HAIC治疗初期，多数患者在输注奥沙利铂期间会出现不同程度的腹痛，8.2%的患者发生3～4级严重腹痛；延长灌注时间和动脉内给予利多卡因可以有效缓解疼痛。在一项肝动脉输注奥沙利铂联合雷替曲塞与奥沙利铂联合5-氟尿嘧啶治疗不可切除结直肠癌肝转移的随机Ⅱ期试验中，2组患者均有约50.0%的患者在输注药物期间出现3～4级严重腹痛，而口服阿片类药物或经肝动脉泵入利多卡因可明显缓解疼痛[47]。

2.2 HAIC术后疼痛发生机制及影响因素

在HAIC治疗过程中，奥沙利铂作为常用化疗药物，不同于顺铂和卡铂，其通过诱导核糖体生物应激来杀死癌细胞[48]。既往研究表明，奥沙利铂对晚期肝细胞癌具有较强的抗肿瘤活性，且患者耐受性良好[48-49]。一项回顾性研究结果显示，疼痛在出现胃十二指肠溃疡和肝外灌注的患者中较为常见，并且主要出现在肝动脉灌注化疗过程中。在未进行肝外灌注的情况下，使用奥沙利铂进行HAIC时，可出现剧烈的腹痛[50]。Wu等[41]的研究也证实，奥沙利铂是影响肝癌患者HAIC术后疼痛程度的重要因素，且奥沙利铂配制时间及其生产厂家均是肝癌患者HAIC术后疼痛的潜在影响因素。推测造成患者HAIC术后疼痛的原因可能是：奥沙利铂配制时间过长，导致草酸沉淀刺激血管，而草酸盐是在接受奥沙利铂治疗而非接受顺铂治疗的患者中观察到的冷诱导超敏反应的原因，其引起的疼痛是细胞外钙离子螯合的结果；肝动脉直径过小时，化疗药物对肝动脉的刺激会引起术后疼痛；肝供血不足会导致缺血，化疗药物输注时也可以引发疼痛[41,51]。

2.3 HAIC术后疼痛的治疗策略

目前，肝癌HAIC术后疼痛治疗大致分为两种：口服阿片类药物及经肝动脉泵入利多卡因[46-47]。Wu等[41]的研究显示，传统的镇痛方法通常对HAIC引起的疼

痛效果不佳,且大剂量强阿片类药物可能引起呼吸抑制等严重不良反应。

3 总结与展望

肝癌TACE及HAIC引起的疼痛难以避免,严重影响患者的生活质量,延长住院时间,增加住院费用,甚至导致相关并发症的发生风险增高[14]。因此,对肝癌TACE及HAIC所致疼痛的发生机制及干预措施进行研究是必要的,但目前相关研究较少,未来可进一步探索肝癌TACE及HAIC所致疼痛的具体发生机制,寻找相关的治疗靶点,以期为其临床治疗提供参考。

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