·专家论坛·

加压腹腔气溶胶化疗的若干问题与争议

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【摘要】 加压腹腔气溶胶化疗(pressurized intraperitoneal aerosol chemotherapy, PIPAC)是一种新型的腹腔内局部治疗技术,适用于初诊或复发性腹膜转移癌的治疗。该疗法具有药物分布广泛、组织渗透深入以及摄取效率高等优势。现有证据表明,PIPAC 在临床应用中展现出良好的可行性、安全性及耐受性,并有望改善患者的生活质量和预后。国外逾 14 年的初步临床应用结果显示其具有积极疗效,且已有多部相关共识发布。然而,PIPAC 在国内外均仍处于临床研究阶段,全球范围内仍亟需高级别的循证医学证据。鉴于此,本文旨在对 PIPAC 临床应用中的关键问题与争议进行系统性述评。

【关键词】 加压腹腔气溶胶化疗；　问题；　争议

Problems and controversies in pressurized intraperitoneal aerosol chemotherapy

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【Abstract】 Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a novel locoregional intraperitoneal treatment modality for newly diagnosed or recurrent peritoneal metastasis. This therapy offers advantages such as wide drug distribution, deep tissue penetration, and high uptake efficiency. Clinical evidence supports the favorable feasibility, safety, and tolerability of PIPAC, suggesting its potential to improve patient quality of life and prognosis. Preliminary results from over 14 years of clinical application abroad indicate good efficacy, and multiple relevant consensus guidelines have been published. However, PIPAC remains in the clinical research stage both internationally and domestically, and there is a global imperative for higher-level evidence-based medical evidence. This article aims to provide a systematic review and critical commentary on several issues and controversies regarding the clinical application of PIPAC.

【Key words】 Pressurized intraperitoneal aerosol chemotherapy;　Questions;　Controversies

腹膜癌是指恶性肿瘤在腹膜的原发性或继发性发生/发展,前者包括原发性腹膜癌和恶性腹膜间皮瘤，后者通常指来自胃肠道和卵巢的腹膜转移癌[1]。腹膜转移恶性肿瘤预后极差,未经治疗的患者中位生存时间仅为 3 个月[2-3]。由于血浆-腹膜屏障的存在以及肿瘤内间质压力的升高，与其他远处转移相比，腹膜转移癌对全身化疗的反应性低,治疗难度高[4-5]。早在 20 世纪 50 年代,腹腔内化疗就被应用于腹膜转移癌的治疗。此后,研究者探索了多种腹腔内化疗方法,包括经导管腹腔内灌注化疗和腹腔热灌注化疗(hyperthermic

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intraperitoneal chemotherapy, HIPEC)[6]。目前,细胞减灭术(cytoreductive surgery, CRS)联合 HIPEC 已成为部分腹膜转移癌的标准治疗方案,并可能带来治愈希望[7-9]。然而,HIPEC 较高的并发症发生率、死亡率及其疗效的不确定性,制约了其临床推广应用[6,10-11]。

加压腹腔气溶胶化疗(pressurized intraperitoneal aerosol chemotherapy, PIPAC)是一种新型的腹膜转移癌腹腔内局部治疗技术,源于 2000 年德国学者 Reymond 等[12]提出的“治疗性气腹”概念,并于 2011 年首次应用于人体[13]。该技术借助高压将液态化疗药物雾化为微米级气溶胶,并在 12 mmHg CO_2 气腹压力下将其均匀喷洒至腹腔内,从而发挥腹腔灌注的治疗作用[14-15]。气腹压力梯度和气体动力学特性驱动气溶胶颗粒进行布朗运动和多向扩散,形成独特的“气溶胶内循环”机制[16]。与传统腹腔灌注化疗相比,PIPAC 具有以下优势:①气溶胶形态和独特的内循环机制使药物分布更为均匀;②12 mmHg气腹压力有助于克服腹膜/肿瘤间质压力[5],提升药物渗透深度,增加局部药物摄取;③用药剂量仅为全身化疗或 HIPEC 的 10%~30%[13],但组织药物浓度和渗透深度却优于 HIPEC [17],具有广阔的应用前景。目前,世界范围内正在进行多项 PIPAC 临床研究,有望提供更高级别循证医学证据[18-19]。自 2021 年起,欧洲已通过多项德尔菲研究就PIPAC 治疗的安全性、技术、方案及患者选择达成共识 [19-22]。作为一种新兴的腹腔内化疗方法,PIPAC 尚缺乏与其他腹腔内局部治疗方法对比的高级别随机对照试验数据支持。PIPAC 的临床应用仍存在诸多问题与争议。本文旨在梳理 PIPAC 应用中的若干问题与争议,以期增进临床医师对该技术的理解。

1 加压腹腔气溶胶化疗适应证

1.1 姑息治疗

目前,PIPAC 主要用于不可切除腹膜转移癌的局部姑息治疗[18]。既往超过 10 年的国外应用数据显示,PIPAC 具有良好的安全性和可行性[15,18]。2024 年德尔菲共识推荐 PIPAC 的适应证包括不可切除腹膜转移癌、美国东部肿瘤协作组(Eastern Cooperative Oncology Group, ECOG)评分≤2 分、预期寿命≥3 个月;禁忌证包括预期寿命<3 个月或PIPAC 术中出现腹水进展[19]。该共识亦支持将PIPAC 作为化疗耐药或不耐受患者的姑息治疗选择。

1.2 根治术后腹膜复发的预防

除对腹膜转移癌的姑息治疗外,PIPAC 在肿瘤根治术后局部复发的预防性应用也在探索中,PIPAC-OPC4 研究表明腹腔镜 D2 胃切除术联合 PIPAC 具有良好的安全性及可行性[23]。此外,PLUS 研究显示 PIPAC 联合其他手术与单纯 PIPAC 治疗相比,并未显著增加并发症发生率[24]。上述初步结果提示 PIPAC 联合根治性手术在高危复发患者中具有应用潜力。然而,PIPAC 降低术后局部复发率的有效性尚需长期随访数据及更高级别的循证医学证据加以验证。此外,高危复发患者的界定标准亦有待明确。笔者认为,相较于预防性 HIPEC,预防性 PIPAC 具备操作简便、用药剂量低等特点,提示其在临床应用中具有广阔的探索潜力。

1.3 转化治疗

回顾性研究表明,PIPAC 可使部分不可切除的腹膜转移癌或腹膜间皮瘤转化为可切除状态。例如法国里昂的单中心数据显示,共有 146 例不可切除腹膜转移癌患者接受了 PIPAC 治疗,其中 26 例患者(17.8 %)接受了 76 次 PIPAC,在腹膜负荷减轻后可择期行 CRS 和 HIPEC,且在完成 CRS 和 HIPEC 的患者中有 66.7%(14/21) 的患者未出现复发[25]。另一项针对恶性腹膜间皮瘤的研究显示,54%(14/26)的患者成功实现转化,且接受手术治疗的患者其无进展生存期延长(33.5 个月比 7.4 个月)[26]。综上所述,对于经过严格筛选的不可切除腹膜转移癌患者,PIPAC 或可作为一种潜在的转化治疗策略,并有望成为 HIPEC 联合 CRS 的“新辅助治疗”手段。

2 雾化器的选择

雾化器作为 PIPAC 治疗的核心部件,其性能对药物分布和渗透深度具有至关重要的影响。2023 年,PIPAC 试验研究组发布相关推荐意见:①雾化器应能在 10~20 bar (1 bar=100 kPa)注射压力下产生气溶胶;②气溶胶的平均液滴直径应为 3 μm,且 95%的液滴直径应在 0~10 μm 范围内;③喷洒锥角应大于 70°[27]。然而,笔者注意到,关于第②点,现有文献多采用体积中位粒径(x_{50})对雾化器气溶胶粒径进行表征和描述,且多数雾化器产生的气溶胶 x_{50} 值介于 25~30 μm,远大于理想值 1.2 μm[28-30]。当前,为优化药物分布及渗透效

果,各类新型雾化器的研发工作正在持续深入,包括旋转加压腹腔气溶胶化疗 (rotational intraperitoneal pressurized aerosol chemotherapy, RIPAC),相较于传统 PIPAC, 其药物分布与渗透性能更优[31]; QuattroJet®(四喷头),在正常猪模型中,可显著提升腹腔组织药物的浓度和渗透, 尤其是在壁腹膜[32]; Medspray®(八喷头),具有更大的喷雾范围,从而改善药物在腹腔顶部的分布[33];CapnoTip®(撞针式),雾化角达 155°,药物分布更为均匀[34](表 1)。然而,新型雾化器能否应用于临床实践,以及是否可切实提升 PIPAC 疗效, 仍有待更多的临床试验证据支持。目前,以 CapnoPen®为代表的单孔雾化器仍是 PIPAC 领域的主流雾化器。

3 气溶胶的分布和药物渗透

PIPAC 的主要优势在于更广泛的药物分布、更深的药物渗透以及更高的组织药物浓度[13,35]。然而,PIPAC 的药物分布均匀性及渗透性仍有提升空间。传统雾化器工作时药物主要集中分布于正对喷头下方的圆形区域[28,36-37],针对这一不足,目前主要的改进策略包括:①采用旋转 PIPAC 给药系统(RIPAC),研究表明,其在大动物模型中能够显著优化药物分布与渗透,且安全性已得到验证[31,38];②采用多喷头雾化器以扩大药物分布范围[32];③静电沉积 PIPAC(electrostatic PIPAC, ePIPAC),已有初步研究证实该方法的可行性及其提高药物渗透的潜力[39];④采用高压气腹(20 mmHg),实验表明,该方法可在不影响药物分布模式的前提下,增加药物渗透深度[40];⑤热疗 PIPAC(hyperthermic PIPAC, hPIPAC), 初步的动物及临床试验结果证明 hPIPAC 安全可行,在 PIPAC 基础上增加热疗并没有增加治疗相关并发症, 且体外实验结果表明 hPIPAC 能够持续显著降低肿瘤细胞活力[41-44]。

4 药物选择及剂量

目前临床上存在 2 种常用的 PIPAC 方案:针对腹膜转移性结直肠/阑尾癌,推荐药物与剂量为奥沙利铂 92 mg/m²(相当于 HIPEC 剂量的 20%)[45];针对其他癌种, 推荐药物与剂量为顺铂 7.5 mg/m² + 多柔比星 1.5 mg/m²(相当于 HIPEC 剂量的 10%)[13]。剂量递增研究显示,顺铂+多柔比星剂量增至 30 mg/m²+ 6 mg/m² 时,未观察到剂量限制性毒性;奥沙利铂剂量增至 120~135 mg/m² 时,患者均表现出良好的耐受性,当剂量增至 140 mg/m² 时,出现 2 例剂量限制毒性[46-48]。在 2022 年发布的一项 PIPAC 共识声明中,多柔比星(2.1 mg/m²)和顺铂(10.5 mg/m²)的组合获得 90.9 %专家(20/22)的认可,同时72.7 % 专家(16/22)支持奥沙利铂 120 mg/m² 的剂量方案[22]。鉴于此,目前所采用的剂量已获得多数专家认可,且其安全性已得到初步验证。此外,针对紫杉醇、丝裂霉素等其他药物的应用研究亦在积极开展。

5 治疗次数以及治疗间隔时间

对于晚期腹膜转移性肿瘤, 多数临床试验方案建议进行 3 次 PIPAC 治疗, 该方案已获得欧洲德尔菲共识的支持[21],但最佳治疗次数仍未明确。研究表明, 疾病进展和并发症是 PIPAC 治疗终止的主要原因,而接受≥3 次 PIPAC 治疗的患者往往预后更佳[49-50]。国际胸膜与腹膜研究学会(International

表 1 各种雾化器的基本参数

参数	CapnoPen®	HurriChem™	MCR-4 TOTOL®	QuattroJet®	DreamPen®	Medspray®	Junlin®	CapnoTip®
产地	德国	美国	捷克	德国	韩国	荷兰	中国	德国
体积流量(ml/s)	0.5	0.5	1.3~2.0	1.5	0.5	1.0	0.7	0.2~1.3
操作压力(bar)	15.7	14.9	7.4~18.1	7.4~18.1	7	NA	13.8~20.7	10~20
压力启动时间(s)	52	100	18~26	94	NA	NA	5	NA
喷孔直径(μm)	200	190	370	170	800	NA	200	NA
体积中位粒径(μm)	28.95	20.99	52.17	24.18	30	NA	25	26
喷射角度(°)	≈72	≈71	≈79	≈67	≈77.2	NA	≈70	155.3
喷孔数量(个)	1	1	1	4	1	8	1	1
喷锥角类型	全锥	全锥	空心锥	全锥	全锥	NA	全锥	全锥
雾化杆直径(mm)	10	10	8	10	10	NA	10	10

注:NA,参数未知。

Society for the Study of the Pleura and Peritoneum, ISSPP)最新发布的 PIPAC 数据库第 3 次年度报告显示,有患者接受治疗的次数高达 33 次[51]。德尔菲共识指南建议:83.67%的专家认为 PIPAC 治疗的最小时间间隔应为 6 周,95.92%的专家认为 PIPAC 与全身化疗(或全身化疗与PIPAC)的间隔时间应为 1~2 周[21]。目前的 PIPAC 治疗方案基本遵循上述建议。尽管目前国际共识和指南未就 PIPAC 治疗次数给予建议,但以上数据表明,重复多次 PIPAC 治疗的患者预后更好,这可能是由于 PIPAC 本身的疗效,也可能是因为全身状态以及肿瘤生物学行为更好的患者能够接受更多次的 PIPAC 治疗,这也提示 PIPAC 治疗次数可以作为评价预后的潜在指标。笔者认为,在身体状态良好且全身治疗后病情稳定的患者中,筛选出肿瘤生物学行为更优、肿瘤负荷更低的病例,重复进行 PIPAC 治疗有助于控制腹膜转移病灶,改善患者生活质量,并可能创造彻底 CRS 的机会。

6 疗效评估工具

目前对于 PIPAC 的疗效评估工具仍然存在争议。客观缓解率(objective response rate, ORR)、无进展生存时间以及总生存 (overall survival, OS)期是评价肿瘤疗效的关键指标。既往研究表明,PIPAC 治疗卵巢癌腹膜转移的 ORR 为 62%~88%,中位 OS 期为 11.0~14.1 个月;胃癌腹膜转移的 ORR 为 50%~91%,中位 OS 期为 8.4~15.4 个月;结直肠癌腹膜转移的 ORR 为 71%~86%,中位 OS 期为 15.7 个月;腹膜间皮瘤的 ORR 为 67%~75%,中位 OS 期为 27 个月[15]。类似研究显示,来源于结直肠癌、胃癌、妇科肿瘤(卵巢癌为主)和肝胆/胰腺癌的腹膜转移患者接受 PIPAC 治疗后的 1 年生存率分别为 53%、25%、59%和 37%[18]。尽管以上 PIPAC 治疗所显示的结果显著优于既往仅使用姑息性全身治疗患者的疗效[15],但鉴于腹膜转移癌患者群体的异质性以及目前缺乏与其他治疗手段的随机对照试验数据,难以准确界定 PIPAC 的独立疗效。传统的肿瘤疗效反应评估手段——实体瘤疗效评价标准(response evaluation criteria in solid tumors, RECIST)规定可测量的靶病灶必须至少有 10 mm[52],但腹膜转移癌患者的病灶常表现为弥漫性粟粒样肿瘤结节或广泛性腹膜增厚,因此,上述规定使得 RECIST 难以适用于此类患者。腹膜癌指数(peritoneal cancer index, PCI)由 Jacquet 等[53]于 1996 年首次提出,通常作为腹膜转移癌患者接受 CRS 的预后指标。然而,一项研究表明病理学 PCI 评分和手术中 PCI 评分存在明显差异[54]。尽管多数 PIPAC 研究采用了重复性 PCI 评分,但 Roensholdt 等[55]指出,PIPAC 治疗后腹膜表面的肉眼评估难以鉴别治疗诱导的纤维化与残余肿瘤结节。因此,PCI 评分主要用于描述基线患者的疾病负荷,而非作为衡量治疗反应的有效指标。2016 年,Solass 等[56]首次提出使用腹膜退缩分级评分(peritoneal regression grading score,PRGS)评估 PIPAC 疗效,其评估依据为显微镜下肿瘤细胞的退缩程度(表 2),而且 PRGS 的评估应辅以腹水或腹腔灌洗液的细胞学检测结果,这对判定完全缓解尤为重要。Solass 等[57]同时建议,为确保评估的准确性超过 80%,每次应至少获取 3 份活检样本。近期,ISSPP 第 3 次年度 PIPAC 报告表明,PRGS≤2 分的患者比 PRGS>2 分的患者预后更好[51]。综上所述,PIPAC 治疗后的疗效评估仍具挑战性。笔者认为,PRGS 结合腹水(或腹腔灌洗液)细胞学检测是当前较为可靠的疗效评估策略。

7 药物泄露风险

自 PIPAC 应用以来,化疗药物职业暴露风险日益受到重视。Solass 等[58]率先提出关键防护措施,包括腹部密封、层流手术室、密闭废气管理系统以及患者头部透明隔离帘,使用以上防护措施

表 2 腹膜退缩分级评分的定义

分级	PRGS	
	肿瘤细胞	退缩特征
PRGS 1-完全反应	无肿瘤细胞	丰富的纤维化和/或无细胞黏蛋白池和/或梗死样坏死
PRGS 2-主要反应	肿瘤细胞以退行性改变为主	纤维化和/或脱细胞黏蛋白池和/或梗死样坏死以肿瘤细胞为主
PRGS 3-次要反应	主要为肿瘤细胞	肿瘤细胞以纤维化和/或无细胞黏蛋白池和/或梗死样坏死为主
PRGS 4-无反应	肿瘤细胞实体生长(最大放大倍数下)	无退缩变化

注:PRGS,腹膜退缩分级评分。

后在术者和麻醉师的工作区域未检测到铂类药物。后续针对 PIPAC 药物泄露的研究普遍沿用上述防护措施，结果显示空气采样的药物浓度始终无法检测到或低于既定安全阈值，且生物监测结果亦未显示医务人员存在可测量的全身化疗药物暴露；尽管在设备和术者手套表面可检测到化疗药物，但其检测水平显著低于 HIPEC 中普遍报道的水平[59-65]。2021 年,ISSPP PIPAC 研究组就安全措施达成共识[20],并划分了 4 类安全措施:①个人防护用品(personal protective equipment, PPE);②环境保护措施;③预防接触雾化的化疗药;④一般预防措施。对高暴露风险人员(手术医师、器械护士及手术助手)推荐 PPE:①眼部保护(塑料护目镜或眼罩);②FFP3 口罩;③加强手术衣;④双层手套,内层为抗化疗药;⑤塑料鞋套。在手术室环境保护方面推荐:地面放置吸水垫(95.7%);将贴有标签的容器放在注射针筒下方以容纳溢出物(95.7%);在高压管线周围包裹一层透明的覆盖物(89.4%);将受污染的一次性用品整体移除(93.6%);使用专用、密封、标记的化疗废物容器(97.9%);在注射器监视器上方使用一次性覆盖物(72.3%)。预防接触雾化的化疗药物的措施包括:使用一次性穿刺器(93.6%);腹部密封(100%);手术室通风系统(91.5%);远程化疗给药(95.7%);远程视频监控雾化(89.4%);安全的有毒气溶胶排空(97.9%)。一般防护包括 PIPAC 过程中对手术室进行标记,限制其他工作人员进入,需备有用于意外接触化疗药物的急救包，延长喷射器清洁程序(例如,对 PIPAC 注射器进行 3 次擦拭)等。笔者认为,基于现有研究结果与共识,并结合严格的培训、标准化操作及必要的防护措施,PIPAC 对医务人员的药物暴露风险较低且可控。

8　加压腹腔气溶胶化疗的国内应用现状及展望

我国腹膜癌患者基数大,2020 年总数约为 76.7 万[66]。目前,国内 PIPAC 治疗尚处于研发和初步临床探索阶段。笔者团队联合高校及企业,成功研制出一种新型腹腔雾化给药系统，该系统采用高压蠕动泵(产生 200~300 psi 压力)以及自主研发的高效雾化器(流量 0.7 ml/s 时雾化角约为 70°,气溶胶 x_{50} 约为 25 μm)[67]。该系统的核心物理参数与国外高压注射泵类似[28],但具备更短的工作压力启动时间和更高的药物装载效率等优势。基于该设备,笔者团队启动一项全国多中心临床研究(NCT06743867),目前研究已完成全部 40 例患者入组,预计将于 2027 年 2 月完成[68],后续研究结果值得关注。

PIPAC 技术发展潜力巨大,超细雾化器/多孔/可旋转雾化器、静电 PIPAC、高温 PIPAC 以及新式载药台(如水凝胶、纳米材料/探针)等将优化药物分布与渗透,提高治疗效率[41-42,69-71]。上述领域亟待深入研究以拓展 PIPAC 的临床应用价值。同时,期待获得更多关于 PIPAC 治疗腹膜转移癌的高级别循证医学证据,并回答当前存在的争议问题,推动其临床应用。

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