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电子支气管镜下氩气刀联合冷冻疗法治疗晚期肺癌的临床疗效及对患者癌性疼痛和免疫功能的影响 *

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摘要 目的:评价电子支气管镜下氩气刀联合冷冻疗法治疗晚期肺癌的疗效及对患者癌性疼痛和免疫功能的影响。**方法:**选择我院 2016 年 7 月~2018 年 7 月收治的 94 例晚期肺癌患者,按随机数字表法分为对照组(51 例)和 4 研究组(43 例)。对照组采用常规化疗,研究组在对照组基础上联合电子支气管镜下氩气刀和冷冻疗法。治疗后,比较两组的临床疗效,治疗前后疼痛程度、疼痛介质、免疫功能、生活质量的变化和不良反应的发生情况。**结果:**治疗后,研究组疾病控制率显著高于对照组($P<0.05$),两组疼痛 I 级率、 $CD4^+$ 、 $CD4^+/CD8^+$ 及生活质量评分均较治疗前显著上升($P<0.05$),而疼痛介质及 $CD8^+$ 均较治疗前明显下降($P<0.05$),研究组疼痛 I 级率、 $CD4^+$ 、 $CD4^+/CD8^+$ 及生活质量评分明显高于对照组,而疼痛介质及 $CD8^+$ 均显著低于对照组($P<0.05$)。两组总不良反应发生率比较差异无统计学意义($P>0.05$)。**结论:**电子支气管镜下氩气刀联合冷冻疗法用于治疗晚期肺癌的疗效明显优于常规化疗,其可显著减轻癌性疼痛,改善患者免疫功能从而提高患者的生活质量。

关键词:晚期肺癌;电子支气管镜下氩气刀;冷冻疗法;疗效;癌性疼痛;免疫功能

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Curative Efficacy of Argon Argon Knife Combined with Cryotherapy in the Treatment of Advanced Lung Cancer and Its Effect on the Cancer Pain and Immune Function*

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ABSTRACT Objective: To evaluate the efficacy of argon gas knife combined with cryotherapy under electronic bronchoscope in the treatment of advanced lung cancer and its effect on the cancer pain and immune function of patients. **Methods:** 94 patients with advanced lung cancer admitted to our hospital from July 2016 to July 2018 were randomly divided into the control group (51 cases) and the research group (43 cases). The control group was given conventional chemotherapy, while the research group was treated by argon knife and cryotherapy under electronic bronchoscope on the basis of control group. After treatment, the clinical effects, changes of pain degree, pain medium, immune function, quality of life before and after treatment, and incidence of adverse reactions were compared between two groups. **Results:** After treatment, the disease control rate of research group was significantly higher than that of the control group ($P<0.05$). the pain grade I rate, $CD4^+$, $CD4^+/CD8^+$ and quality of life scores of both groups were significantly higher than those before treatment ($P<0.05$), while the pain medium and $CD8^+$ were significantly lower than those before treatment ($P>0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** The therapeutic effect of argon gas knife combined with cryotherapy under electronic bronchoscope in the treatment of advanced lung cancer is obviously superior to the conventional chemotherapy, it can significantly reduce cancer pain, improve the immune function and quality of life of patients.

Key word: Advanced lung cancer; Argon knife under electronic bronchoscope; Cryotherapy; Efficacy; Cancer pain; immune function

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前言

肺癌是临床常见的恶性肿瘤之一, 发病率及死亡率较高, 危及患者生命安全^[1]。手术是早期肺癌患者的首选疗法,但大部

分患者确诊时已错过最佳的手术时机,加上手术治疗可降低机体抵抗力,可能增加肿瘤复发和转移风险性^[2]。目前,化疗已成为晚期肺癌的主要治疗手段,但有研究显示^[3,4]晚期肺癌患者容易受到药物耐受、副反应等因素的影响,疗效不甚理想。目前由

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于肺脏介入医学的进步,经电子支气管镜介入治疗已成为肺癌的重要治疗方式之一,其中氩气刀及冷冻疗法为最新发展的肿瘤微创疗法,其能够快速消除肿瘤组织,减轻瘤负荷,其近期疗效已得到临床认可,但缺乏对相关作用机制的研究^[56]。近年来,有研究报道^[7],电子支气管镜下氩气刀联合冷冻疗法对晚期肺癌患者癌性疼痛的缓解可能有一定作用,癌痛为晚期恶性肿瘤患者的主要症状之一,明显降低患者生存质量,甚至可能缩短患者生存期^[8]。此外,研究显示^[9]晚期肺癌患者可能发生免疫逃逸,降低患者免疫功能。本研究主要探讨了电子支气管镜下氩气刀联合冷冻疗法用于晚期肺癌的疗效及对患者癌性疼痛和免疫功能的影响。

1 资料与方法

1.1 一般资料

94例晚期肺癌患者纳入本研究。纳入标准^[10]:经病史、临床症状、血液检查、病理组织活检确诊为晚期中央型肺癌;TNM分期为ⅢB~Ⅳ期;有可评价或可测量病灶;既往未接受过放疗、化疗、肺部手术;可耐受电子支气管镜检查;肝肾功能、血常规和心电图正常。排除标准:化疗禁忌证;颅内高压、神经压迫、脑转移;合并其他原发性肿瘤;预计生存期<3个月;血液系统疾病。所有患者按随机数字表法分为51例对照组和43例研究组,对照组男31例,女20例;年龄39~73岁,平均(61.29±7.52)岁;TNM分期:ⅢB~C期38例、Ⅳ期13例;平均KPS(77.53±9.37)分;肿瘤类型:非小细胞肺癌17例,小细胞肺癌34例。研究组男28例,女15例;年龄38~75岁,平均(62.61±7.14)岁;TNM分期:ⅢB~C期34例、Ⅳ期9例;平均KPS(75.89±10.31)分;肿瘤类型:非小细胞肺癌13例,小细胞肺癌29例。两组一般资料比较无统计学差异($P>0.05$)。

1.2 治疗方法

对照组采用常规化疗,非小细胞肺癌:静脉滴注25 mg/m²顺铂(厂家:江苏豪森药业集团有限公司,6 mL:30 mg/支,批号:20160519),每周第1~3天;静脉滴注75 mg/m²多西他赛(厂家:浙江海正药业股份有限公司,规格:20 mg/支,批号:20160229),每周第1天,1个周期为21天,持续治疗2个周期。小细胞肺癌:静脉滴注25 mg/m²顺铂,每周第1~3天;静脉滴注60 mg/m²依托泊苷(厂家:江苏恒瑞医药股份有限公司,规格:2 mL:0.1 g,批号:20160821),每周第3~5天。研究组在对照组基础上予以电子支气管镜下氩气刀联合冷冻疗法,于化疗结束后4周进行。所有患者均予以2%利多卡因(厂家:河南遂成药业股份有限公司,规格:5 mL:50 mg,批号:20160803)雾化吸入麻醉,常规监测血压、心率及血氧饱和度等生命体征。

在患者单侧前臂粘贴电极片,接通橡胶电极板及氩气刀导管,于鼻内置入BF-T260型电子支气管镜(奥林巴斯公司),全面检查支气管及气管状态。在电子支气管镜活检孔引出美国康美氩气刀探针,距离病灶5 mm内电凝,功率设定为20~60 W,氧浓度≤40%。将表浅肿瘤组织结痂碳化,探针顶端贴紧结瘤瘤体组织,德国ERBE冷冻3~5 s,取出探头和其黏附肿瘤,病灶较大者可进行多冷冻点处理,待可见病灶完全冷冻。于治疗结束时进行疗效评价,记录不良反应发生情况。

1.3 观察指标

1.3.1 疗效评价 病灶全部消失,同时维持时间超过1个月为完全缓解;可见肿瘤病灶缩小超过50%,无新病灶出现,无其他病灶增大,且维持时间超过1个月为部分缓解;可见肿瘤病灶增大低于25%或者缩小低于50%,无新病灶出现,且维持时间超过1个月为疾病稳定;可见肿瘤病灶增大超过20%或者可见新病灶为疾病进展,疾病控制率=完全缓解率+部分缓解率^[10]。

1.3.2 疼痛程度 I级:轻度不适;II级:疼痛较轻微,可耐受,对正常生活无影响;III级:中度疼痛,明显疼痛,无法忍受,要求接受止痛药处理,影响睡眠;IV级:重度疼痛,需接受止痛药干预,生活受到明显影响;V级:剧烈疼痛,无法忍受,可伴头晕、恶心呕吐及强迫体位^[11]。

1.3.3 实验室指标 酶联免疫法测定P物质(Substance P, SP)、前列腺素E2(Prostaglandin E2, PGE2)水平。于治疗前及治疗结束时采集患者4 mL空腹外周静脉血,常规分离血清,采用美国GE公司FACSCanto II型流式细胞仪测定CD4⁺、CD8⁺细胞数目。

1.3.4 生活质量 于治疗前后采用生活质量综合评定问卷(Generic Quality of Life Inventory-74, GQOLI-74)量表评价生活质量,包含心理健康维度、躯体健康维度、社会功能维度及物质生活维度4个方面,评分越高表明生活质量越好^[12]。

1.3.5 安全性评估 用药期间对血常规、肝肾功能等进行定期检查,并依据世界卫生组织拟定的不良反应评价标准评估毒副反应^[13]。

1.4 统计学分析

数据处理选用SPSS18.0软件包,计量资料用($\bar{x} \pm s$)表示,组间比较选用t检验,计数资料用[(例)%]表示,组间比较用 χ^2 检验, $P<0.05$ 表示差异有统计学意义。

2 结果

2.1 两组临床疗效的比较

治疗后,研究组疾病控制率为90.7%,显著高于对照组,差异有统计学意义($P<0.05$),见表1。

表1 两组临床疗效的比较[例(%)]

Table 1 Comparison of the clinical efficacy between the two groups[n(%)]

Groups	n	Totally Relaxed	Partial Relief	Stable	Progress	Disease Control Rate
Control group	51	0(0.00)	20(39.22)	17(33.33)	14(27.45)	37(72.55)
Research group	43	0(0.00)	23(53.49)	16(37.21)	4(9.30)	39(90.70) ^a

Note: Compared with control group, ^a $P<0.05$.

2.2 两组治疗前后疼痛程度的比较

治疗前,两组疼痛程度比较差异无统计学意义($P>0.05$);治

疗后,两组疼痛程度分级为I级的比例均较治疗前上升,且研究组高于对照组($P<0.05$),见表2。

表 2 两组治疗前后疼痛程度比较[例(%)]

Table 2 Comparison of the degree of pain before and after treatment between the two groups[n(%)]

Groups	n	Time	Degree of pain					
			Level 0	Level I	Level II	Level III	Level IV	Level V
Control group	51	Before treatment	0(0.00)	0(0.00)	0(0.00)	30(58.82)	21(41.18)	0(0.00)
		After treatment	0(0.00)	14(27.45)	22(43.14)	11(21.57)	4(7.84)	0(0.00)
Research group	43	Before treatment	0(0.00)	0(0.00)	0(0.00)	23(53.49)	20(46.51)	0(0.00)
		After treatment	0(0.00)	24(55.81) ^a	12(27.91)	6(13.95)	1(2.33)	0(0.00)

Note: Compared with control group, ^a $P<0.05$; Compared with the same group before treatment, ^b $P<0.05$.

2.3 两组治疗前后免疫功能的比较

治疗前, 两组 $CD4^+$ 、 $CD4^+/CD8^+$ 和 $CD8^+$ 比较差异无统计学意义($P>0.05$); 治疗后, 两组 $CD4^+$ 、 $CD4^+/CD8^+$ 均较治疗前上升, $CD8^+$ 均较治疗前下降, 研究组 $CD4^+$ 、 $CD4^+/CD8^+$ 明显高于对照组, 而 $CD8^+$ 显著低于对照组($P<0.05$)。

3 讨论

肺癌是危及患者生命的常见恶性肿瘤, 早期缺乏特异症状, 多数患者就诊时已进展至中晚期, 预后多不良。目前研究表明^[14]全身化疗为主的综合治疗为晚期肺癌的主要治疗手段, 能够一定程度的延长患者生存时间, 降低死亡风险。但有研究显著^[15]晚期肿瘤患者靶器官化疗药物的浓度较低, 容易发生肿瘤转移, 因此化疗的疗效有限, 加上化疗药物可损伤组织器官, 影响临床疗效。

电子支气管镜下氩气刀联合冷冻疗法因具有微创、操作简便及安全高等优势, 广泛开展于临床, 已成为治疗晚期肺癌的有效方式^[16]。氩气刀通过电离氩气在靶组织输送均匀的高频电流, 氩等离子流可通过侧向、轴向及径向处理角落部位病灶, 通过热效应促进接触病灶干燥挛缩、失活及凝固, 起到止血及消除病灶作用^[17]。氩气刀较传统电刀, 不直接与组织接触, 组织穿透力较为表浅, 可避免组织粘连探头及穿孔^[18]。另外其热传导较不明显, 显著减弱碳化作用, 视野清晰。但有研究认为^[19], 凝固坏死组织形成后继续电凝对深部肿瘤的杀伤力较弱, 因此术中需反复清除凝固坏死组织, 有一定局限性。

冷冻疗法为接触性治疗, 利用超低温作用于靶组织, 通过形成冰球起到力学效应, 导致肿瘤环境及超微结构发生变化, 从而影响肿瘤生长^[20]。有研究发现^[21], 冷冻疗法具有白细胞浸润、炎症反应等多种作用。相关研究认为, 冷冻疗法可增加肿瘤细胞对放化疗的敏感性, 从而提高临床疗效。Chen L 等^[22]报道, 电子支气管镜下氩气刀联合冷冻疗法在手术中反复交替进行可互相弥补不足, 起到协同增效作用。冷冻后的肿瘤组织未完全融化前拔出探针容易出血, 氩气刀的止血作用较好, 冷冻后予以氩气刀电灼可起到良好的止血目的, 且缩短手术时间。另外冷冻后的坏死组织采用氩气刀电凝后再予以冷冻法切除更能有效清除^[23,24]。本研究结果显示氩气刀联合冷冻疗法组疾病控制率较常规治疗组高, 表明两者联合具有协同增效作用, 更有利于肿瘤的控制。

动物实验及临床研究显示^[25,26]经纤支镜下治疗对气管恶性肿瘤的癌性疼痛有调节作用, 局部微波治疗可调控机体疼痛效

应。但电子支气管镜下氩气刀联合冷冻疗法对肺癌患者癌性疼痛的影响尚未完全明确。疼痛是晚期恶性肿瘤最自觉症状之一, 为持续加重的过程, 长期过度剧烈的疼痛能够对机体形成伤害性刺激, 导致身心痛苦, 且可影响患者相关抗肿瘤治疗, 影响预后^[27]。近年来, 由于癌痛动物模型的建立, 晚期癌痛分子的研究发现恶性晚期肿瘤因瘤体增大, 侵犯感觉神经、压迫组织, 诱导癌细胞分泌系列 SP、PGE2 等细胞因子, 刺激痛觉过敏肽的过表达, 导致局部微环境出现改变, 产生疼痛^[28]。本研究结果显示氩气刀联合冷冻疗法治疗后血清 SP、PGE2 水平相对较低, 提示二者可通过调节疼痛介质的表达, 减轻机体疼痛, 进一步分析显示二者联合治疗后疼痛程度改善更为明显, 证实其镇痛效果, 考虑与氩气刀联合冷冻疗法能够清除肿瘤组织, 缓解其对周围组织或神经的压迫及浸润, 从而减轻疼痛。

近年来, 研究显示^[29]氩气刀联合冷冻疗法不仅可通过血管及细胞损伤效应杀灭癌细胞, 抑制肿瘤进展, 且具有增强细胞免疫应答、调节机体免疫功能作用。肺癌进展至中晚期后可明显抑制机体细胞功能, 导致癌细胞发生免疫逃逸。T 淋巴细胞可维持机体正常的免疫功能, 在抵御疾病发生及肿瘤形成中有重要作用^[30]。本研究结果显示氩气刀联合冷冻疗法组治疗后 $C4^+$ 、 $CD4^+/CD8^+$ 相对较高, $CD8^+$ 明显下降, 说明二者联合可增强机体免疫功能, 改善免疫抑制状态, 提高机体抗肿瘤效应。晚期肺癌能够明显影响患者生活, 近年来生存质量已成为评估疗效的主要指标之一, 为临床方案的选择提供依据^[31]。本研究结果显示氩气刀联合冷冻疗法治疗后生存质量评分较高, 说明其对生存质量的改善作用更明显, 可能与二者联合更能控制肿瘤进展、缓解癌性疼痛有关。另外, 两组不良反应经对症处理后均得到有效控制。

综上所述, 电子支气管镜下氩气刀联合冷冻疗法用于晚期肺癌的疗效确切, 可减轻癌性疼痛, 改善免疫功能, 提高患者生活质量。但本研究随访时间较短, 二者联合是否能够改善此类患者的远期疗效仍有待进一步研究。

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