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肿节风注射液辅助治疗晚期食道癌的疗效及对患者血清 VEGF、S100A4 水平的影响 *

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摘要 目的：探讨肿节风注射液辅助治疗晚期食道癌的疗效及对患者血清血管内皮细胞生长因子 (VEGF)、钙结合蛋白 S100A4 (S100A4)水平的影响。**方法：**选取 2015 年 12 月 ~2018 年 12 月我院收治的晚期食道癌患者 61 例，采用随机数字表法将患者分为两组。对照组患者采用 TP 方案进行化疗，观察组在对照组的基础上给予肿节风注射液。比较两组患者的临床治疗效果，治疗前后的症状积分、生存质量评分和血清 VEGF、S100A4 水平的变化以及不良反应的发生情况。**结果：**治疗后，观察组总有效率和疾病控制率分别为 93.55%、87.1%，均显著高于对照组(70%、60%，$P<0.05$)。两组患者治疗后的症状积分、血清 VEGF、S100A4 水平均较治疗前显著下降，且观察组以上指标均显著低于对照组($P<0.05$)。对照组患者治疗后的生存质量评分明显下降，而观察组生存质量评分较治疗前无明显变化，但显著高于对照组($P<0.05$)。两组患者白细胞减少、血小板减少、贫血、恶心呕吐及肝肾功能异常等不良反应发生率比较差异无统计学意义($P>0.05$)。**结论：**肿节风注射液联合化疗可显著提高晚期食道癌患者的临床疗效，改善患者的生存质量，可能与其有效降低患者血清 VEGF、S100A4 水平有关。

关键词：肿节风注射液；晚期食道癌；效果；血管内皮细胞生长因子；钙结合蛋白 S100A4
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Clinical Efficacy of Zhongjiefeng Injection in the Treatment of Patients with Advanced Esophageal Cancer and Its Effect on the Serum VEGF and S100A4 Levels*

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ABSTRACT Objective: To investigate the curative effect of zhongjiefeng injection in the treatment of advanced esophageal cancer and its effect on the serum VEGF and S100A4 levels. **Methods:** 61 patients with advanced esophageal cancer admitted to our hospital from December 2015 to December 2018 were selected. The patients were divided into two groups by the random number table method. Patients in the control group were given chemotherapy with TP, while patients in the observation group were given zhongjiefeng injection on the basis of control group. The clinical efficacy, symptom score, quality of life score, changes of serum VEGF and S100A4 and adverse reactions before and after treatment were compared between the two groups. **Results:** After treatment, the total effective rate and disease control rate in the observation group were 93.55% and 87.1%, respectively, which were significantly higher than those in the control group (70%, 60%, $P<0.05$). The symptom scores, serum VEGF and S100A4 levels of the two groups of patients after treatment were significantly lower than those before treatment, and the above indicators in the observation group were significantly lower than those in the control group ($P<0.05$). The quality of life score of patients in the control group decreased significantly after treatment, which showed no significant change in the observation group before and after treatment, but it was significantly higher than that in the control group ($P<0.05$). There was no significant difference in the incidence of adverse reactions including leukopenia, thrombocytopenia, anemia, nausea and vomiting, and liver and kidney dysfunction between the two groups ($P>0.05$). **Conclusion:** Zhong-jiefeng injection combined with chemotherapy can significantly improve the clinical efficacy and quality of life of patients with advanced esophageal cancer, which may be related to its effective reduction of serum VEGF and S100A4 levels.

Key words: Zhongjiefeng injection; Advanced esophageal cancer; Effects ; VEGF; S100A4
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前言

食道癌是我国常见的消化道恶性肿瘤之一，随着人们生活环境和饮食习惯的变化，食道癌的发病率逐年升高，且随着年龄的增长发病率增加，其死亡率位居我国恶性肿瘤死亡率第2位[1-3]。食道癌早期的临床症状不明显，大部分患者就诊时已发展为中晚期，且发生转移，错过手术的最佳时期，失去手术根治的机会[4,5]。中晚期食道癌患者进食进水困难，水电解质代谢紊乱，身体极度虚弱，严重影响患者的健康和生活质量[6,7]。国内外对食道癌的发病原因进行了大量的调查研究，目前认为与多种因素协同作用有关，如吸烟、过量摄入亚硝酸盐、微量元素摄入不足、大量饮酒和营养因素有关[8-10]。

目前，晚期食道癌的治疗主要采取化疗，旨在延长患者的生存期，提高患者的生活质量[11-13]。有研究显示[14,15]TP化疗方案可抑制晚期食道癌患者的病灶扩散，具有较好的治疗效果。但化疗的不良反应明显，患者的耐受性较差，治疗的依从性较低[16,17]。祖国传统医学认为食道癌属"噎隔"范畴，以气、血、痰互结于食管为病机，痰气交阻多见于早期，而痰淤互结多见于中晚期，痰气交阻，淤血内结是食道癌患者的主要症候类型，化痰散瘀法是中医治疗的基本方，中药作用靶点多，不良反应少，与西药联合应用具有增效减毒的作用[18,19]。本研究主要探讨了肿节风注射液辅助治疗晚期食道癌的疗效及对患者VEGF、S100A4水平的影响，以期为食管癌的临床用药提供更多的参考。

1 资料与方法

1.1 一般资料

选取2015年12月~2018年12月我院收治的晚期食道癌患者61例，所有患者均符合《中国早期食管癌筛查及内镜诊治专家共识意见》中关于晚期食道癌的诊断标准。纳入标准：① 所有患者均经胃镜、食管钡餐X线及CT检查确诊；② 年龄40~75岁；③ KPS评分＞70分；④ 不宜或不愿接受手术治疗者。排除标准：① 合并心、肝、肾等重要脏器功能病变者；② 合并精神神经系统疾病者；③ 对本研究所用药物过敏者；④ 近期未接受其他药物治疗者。采用随机数字表法将患者分为两组，对照组30例，男17例，那次13例；年龄41~72岁，平均52.35± 3.57岁；TNM分期：Ⅲ期22例，Ⅳ期8例；病理类型：腺癌12例，鳞癌10例，小细胞癌8例。观察组31例，男16例，那次15例；年龄42~74岁，平均53.64± 3.96岁；TNM分期：Ⅲ期21例，Ⅳ期10例；病理类型：腺癌13例，鳞癌9例，小细胞癌9例。两组一般资料比较差异均无统计学意义(P>0.05)，具有可比性。

1.2 治疗方法

患者均给予维生素B6、维生素C、氨基酸、谷胱甘肽及甲氰咪胍等对症治疗。对照组采用TP方案化疗，第1 d给予紫杉醇150 mg/(m²·d)静脉滴注，顺铂75 mg/m²分别于第1、2、3天静脉滴注，21天为一个化疗周期。观察组在对照组的基础上给予肿节风注射液，4 mL/次，1次/d，两组均连续治疗2个周期。

1.3 观察指标

① 比较两组患者的临床治疗效果。② 比较两组患者临床症状积分及生存质量评分，分别于治疗前后对两组患者的临床症状及生存质量进行评价。③ 比较两组患者治疗前后的VEGF、S100A4水平，分别于治疗前后抽取两组患者的空腹静脉血5ml，采用ELISA法测定VEGF、S100A4水平，试剂盒均由上海恪敏生物科技有限公司提供。④ 比较两组患者的不良反应发生情况。

1.4 疗效评定及症状、生存质量评分标准

疗效评定：完全缓解(CR)：所有病灶消失；部分缓解(PR)：病灶长径总和缩小≥ 30%；疾病稳定(SD)：病灶长径总和缩小＜30%，但未达到PD；疾病进展(PD)：病灶长径总和增加≥ 20%，或出现新的病灶。治疗总有效率 = (CR+PR)/总例数×100%。症状评分标准：参照《中药新药临床研究指导原则(试行)》制定的吞咽困难评分标准，0分：无明显吞咽困难症状；1分：间歇性轻微吞咽困难，粗糙食物或大口吞咽不畅；2分：普通食物吞咽受阻，可吞咽半流食；3分：半流食吞咽受阻，可吞咽流食；4分：流食吞咽受阻，饮水困难；5分：症状无改善或加重。生存质量评分：采用Karnofsky(KPS)功能状态评分标准：0分为死亡，100分为正常，分值越高表示患者的生存质量越好。

1.5 统计学方法

采用SPSS16.0对研究数据进行统计学分析，计数资料以率(%)表示，组间比较行卡方检验，计量资料以($\bar{x}\pm s$)表示，组间比较行t检验，以P<0.05为差异有统计学意义。

2 结果

2.1 两组临床治疗效果的比较

观察组总有效率和疾病控制率分别为93.55%、87.1%，均显著高于对照组(70%、60%，P＜0.05)，见表1。

表1 两组患者临床治疗效果的比较[例(%)]

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

Groups	Cases	CR	PR	SD	PD	Total effective rate	Disease control rate
Control group	30	9(30.00)	9(30.00)	3(10.00)	9(30.00)	18(60.00)	21(70.00)
Observation group	31	19(61.29)	8(25.81)	2(6.45)	2(6.45)	27(87.10)	29(93.55)
x^2						5.785	5.720
P						0.016	0.017

2.2 两组治疗前后症状及生存质量评分的比较

治疗后，两组患者的症状评分均较治疗前显著下降，且观察组显著低于对照组(P＜0.05)。治疗后，对照组患者的生存质量评分明显下降，但观察组无明显变化，且显著高于对照组(P＜0.05)，见表2。

表 2 两组患者治疗前后的症状及生存质量评分比较($\bar{x}\pm s$, 分)

Table 2 Comparison of the symptom and KPS score between two groups before and after treatment($\bar{x}\pm s$, score)

Groups	Cases	Symptom score		KPS score	
		Before treatment	After treatment	Before treatment	After treatment
Control group	30	4.22± 1.15	3.02± 0.85*	75.68± 18.61	61.34± 12.73*
Observation group	31	4.13± 1.02	1.51± 0.41*	73.58± 17.33	70.65± 15.23
t		0.324	8.791	0.452	2.586
P		0.747	＜0.001	0.653	0.012

注:与治疗前相比,*P＜0.05。

Note: Compared with before treatment,*P＜0.05.

2.3 两组治疗前后血清 VEGF、S100A4 水平的比较

治疗前,两组患者的血清 VEGF、S100A4 水平比较无统计学差异(P＞0.05)。两组治疗后血清 VEGF、S100A4 水平均较治理前显著下降,且观察组以上指标均显著低于对照组(P＜0.05),见表 3。

表 3 两组患者治疗前后血清 VEGF、S100A4 水平的比较($\bar{x}\pm s$)

Table 3 Comparison the serum levels of VEGF and S100A4 between two groups before and after treatment($\bar{x}\pm s$)

Groups	Cases	VEGF(ng/L)		S100A4(ug/mL)	
		Before treatment	After treatment	Before treatment	After treatment
Control group	30	77.25± 20.31	55.64± 15.36*	6.54± 2.01	4.32± 1.54*
Observation group	31	75.33± 18.27	34.28± 10.12*	6.69± 2.03	2.63± 0.66*
t		0.388	-6.392	-0.290	-5.539
P		0.699	＜0.001	0.773	＜0.001

注:与治疗前相比,*P＜0.05。

Note: Compared with before treatment,*P＜0.05.

2.4 两组不良反应发生情况的比较

两组患者白细胞减少、血小板减少、贫血、恶心呕吐及肝肾功能异常等不良反应发生率比较差异无统计学意义(P＞0.05),见表 4。

表 4 两组患者的不良反应发生情况的比较[例(%)]

Table 4 Comparison of the incidence of adverse reactions between two groups[n(%)]

Groups	Cases	Hypoleucocytosis	Thrombopenia	Anemia	Nausea and vomiting	Abnormal liver and kidney
Control group	30	3(10.00)	4(13.33)	5(16.67)	9(30.00)	10(33.33)
Observation group	31	5(16.13)	6(19.35)	8(25.81)	10(32.26)	12(38.71)
x^2		0.503	0.403	0.759	0.036	0.191
P		0.707	0.731	0.384	0.849	0.662

3 讨论

晚期食道癌的预后较差,患者主要表现为吞咽困难,咽下食物时有哽咽感,食后有胸骨后烧灼疼痛,干的食物难以咽下,中期难咽半流食,晚期严重者饮水困难[20,21]。食道癌的发病机制目前认为与食道腺上皮、鳞状上皮的异常增生造成的恶性病变有关。早发现、早治疗能够达到痊愈[22,23]。但由于临床症状不典型,就诊时往往已发展为中晚期。祖国传统医学认为食道癌属 " 噎隔 " 范畴,其发生主要以痰凝、气滞、血瘀为标,以正虚为本。主要是由于外邪长期侵袭机体,正气亏损,气血津液失调,而导致痰凝、气滞、血瘀为标的病理变化,痰淤互结阻于食道,妨碍饮食下咽为本病[24,25]。

肿节风是金粟兰科植物草珊瑚的全株,具有抗菌消炎,祛风通络,活血散结,抗肿瘤的功效。肿节风注射液由肿节风药材提取精制而成,现代药理学研究表明肿节风注射液主要成分延胡索酸、黄酮苷、内脂和香豆素等,具有抗肿瘤、抗菌和免疫调节的作用[30]。肿节风注射液可直接杀死癌细胞并抑制癌细胞的分裂和增殖。本研究结果显示观察组患者的临床症状改善情况及生存质量均显著优于对照组,且疾病总有效率和控制率显著高于对照组,说明肿节风注射液与 TP 化疗方案联合应用对于患者的症状控制,生活质量改善等具有更好的临床效果。这可能与肿节风注射液可调节患者的免疫功能、具有显著抗肿瘤抗

菌活性有关。

血管生成是肿瘤生长、浸润和转移的基础，而新生的血管主要为肿瘤提供营养，并为癌细胞的扩散提供途径。VEGF 是作用最强的血管生长因子，在肿瘤的血管生成过程中起重要作用。VEGF 可削弱血管屏障，诱导毛细血管官腔形成，增加血管的通透性，通过渗透作用使大量癌细胞进入血液循环，从而促进肿瘤血管形成、浸润和转移[26,27]。S100A4 与多种恶性肿瘤密切相关，可调节细胞的增殖与凋亡抑制，并增强细胞的运动，减少粘附，加速血管生成，其高表达与肿瘤的高侵袭、高转移、不良预后密切相关[28,29]。本研究结果显示观察组患者治疗后的血清 VEGF 和 VEGF 水平显著下降，且观察组低于对照组，提示肿节风注射液联合 TP 化疗方案提高疗效的机制可能与显著降低患者血清 VEGF 和 S100A4 水平有关。在不良反应方面，联合肿节风注射液不增加患者的不良反应的发生率，安全性较高。

综上所述，肿节风注射液联合化疗可显著提高晚期食道癌患者的临床疗效，改善患者的生存质量，可能与其有效降低患者血清 VEGF、S100A4 水平有关。

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