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改良乳腺癌根治术联合表柔比星治疗乳腺癌的疗效及对血清抵抗素、脂联素水平的影响*

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摘要 目的：探究改良乳腺癌根治术联合表柔比星治疗乳腺癌的疗效及对血清抵抗素、脂联素水平的影响。**方法：**收集 2019 年 1 月～2020 年 1 月我院确诊为乳腺癌的 60 例患者资料，使用随机数字法将患者分为对照组、观察组，每组 30 例。两组患者均接受改良乳腺癌根治术，对照组患者在此基础上接受阿霉素、环磷酰胺、5- 氟尿嘧啶治疗，观察组接受表；柔比星与环磷酰胺联合化疗方案治疗，比较两组患者治疗效果、不良反应发生率、3 年生存率、血清抵抗素、脂联素水平。**结果：**观察组临床疗效（93.33 %）高于对照组患者（60.00 %）：（*P*<0.05）；观察组心脏毒性、中性粒细胞减少发生率（13.33 %，73.33 %）低于对照组患者（30.00%，86.67 %）（*P*<0.05）。两组患者恶心呕吐、肝功能损害发生率相比，差异无统计学意义（*P*>0.05）。观察组术后 3 年生存率（76.67 %）高于对照组患者（63.33 %）（*P*<0.05）。两组患者治疗后血清抵抗素及脂联素水平均有好转（*P*<0.05），观察组血清抵抗素水平低于对照组（*P*<0.05），观察组脂联素水平高于对照组（*P*<0.05）。**结论：**改良乳腺癌根治术联合表柔比星治疗乳腺癌疗效较好，可有效改善血清抵抗素水平、脂联素水平。

关键词：改良乳腺癌根治术；表柔比星；血清抵抗素；脂联素

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Effect of Modified Radical Mastectomy Combined with Epirubicin in the Treatment of Breast Cancer and Research Progress on Serum Resistin and Adiponectin Levels*

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ABSTRACT Objective: To explore the effect of modified radical mastectomy combined with epirubicin in the treatment of breast cancer and its influence on serum resistin and adiponectin levels. **Methods:** The data of 60 patients with breast cancer diagnosed in our hospital from January 2019 to January 2020 were collected and randomly divided into control group and observation group, 30 cases in each group. Two groups of patientsreceived modified radical mastectomy, the control group received adriamycin, cyclophosphamide, 5-fluorouracil on the basis of the treatment, the observation group received epirubicin and cyclophosphamide combined chemotherapy. The treatment effect, adverse reaction rate, 3-year survival rate, serum resistin and adiponectin levels were compared between the two groups. **Results:** The clinical efficacy of the observation group (93.33 %) was higher than that of the control group (60.00 %) (*P*<0.05); the incidence of cardiotoxicity and neutropenia in the observation group (13.33 %, 73.33 %) was lower than that in the control group (30.00 %, 86.67 %) (*P*<0.05). There was no significant difference in the incidence of nausea, vomiting and liver function damage between the two groups (*P*>0.05). The 3-year survival rate of the observation group (76.67 %) was higher than that of the control group (63.33 %) (*P*<0.05). After treatment, the serum resistin and adiponectin levels of the two groups were improved (*P*<0.05), the serum resistin level in the observation group was lower than that in the control group (*P*<0.05), and the adiponectin level in the observation group was higher than that in the control group (*P*<0.05). **Conclusion:** Modified radical mastectomy combined with epirubicin is effective in the treatment of breast cancer, which can effectively improve the levels of serum resistin and adiponectin.

Key words: Modified radical mastectomy; Epirubicin; Serum resistin; Adiponectin

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前言

乳腺癌是临床上常见的恶性肿瘤之一，如今临床上治疗方式主要包括手术治疗及化疗，改良乳腺癌根治术较传统根治术相比，可提高患者 5 年生存率，改善患者疗效，但化疗方式尚未统一[1]。表柔比星可干扰肿瘤细胞转录过程，从而抑制癌细胞分化，治疗效果较好[2]。脂联素由脂肪细胞分泌，可改善胰岛素敏感性，有效减轻体内炎症，与乳腺癌发展过程关系密切[3,4]。血清抵抗素是一种富含半胱氨酸的蛋白质，可拮抗胰岛素、升高血糖，作用于血管内皮细胞及平滑肌细胞，可随着乳腺癌患者病情发展出现明显升高，从而刺激内皮细胞管道生成，促进肿瘤细胞分化[5,6]。因此，通过治疗方式改变血清抵抗素、脂联素水平可能成为乳腺癌患者的一种治疗方法。

1 材料与方法

1.1 材料

收集 2019 年 1 月 ~2020 年 1 月我院确诊为乳腺癌的 60 例患者资料，使用随机数字法将患者分为对照组、观察组，每组 30 例。对照组年龄 24~65 岁，平均(45.28±10.28)岁；对照组年龄 25~64 岁，平均(45.39±10.07)岁。本研究经医学伦理会批准通过，两组患者年龄、肿瘤分期相比，差异有可比性(χ^2=0.906，χ^2=0.228，P>0.05)。见表 1。

表 1 比较两组患者一般资料[n,(%)]

Table 1 The general data of the two groups were compared [n, (%)]

Groups	n	Tumor stages		Ages(years)	
		IIIa	IIIb	<50	≥ 50
Obseravtion group	30	18(60.00)	12(40.00)	13(43.33)	17(56.67)
Control group	30	16(53.33)	14(46.67)	12(40.00)	18(60.00)
χ^2	/	0.906		0.228	
P	/	0.341		0.633	

纳入标准：(1)所有患者均诊断为乳腺癌患者[7]，且接受改良乳腺癌根治术；(2)患者心电图、血常规均表现正常；(3)患者入院前未接受药物治疗。排除标准：(1)合并肝肾功能障碍、心力衰竭者；(2)合并其他肿瘤者；(3)中断研究者。

1.2 方法

两组患者均接受改良乳腺癌根治术，患者取仰卧位，包围乳头乳晕行一梭形切口。若患者肿瘤位于乳腺上方，距离乳头乳晕较远，可采用包围复合体的 S 形切口；若肿瘤位于乳腺下方，距离乳头乳晕较远，可采用纵型切口。患者全麻后根据标记皮肤将皮肤切开，并分离皮下组织。沿皮肤与乳腺之间的脂肪间隙将腺体分离出来，于乳腺腺体与胸大肌筋膜间进行剥离，将乳腺腺体摘除，防止引流管，缝合皮肤，并使用加压绷带包扎。

对照组患者在此基础上接受阿霉素、环磷酰胺、5- 氟尿嘧啶治疗，患者接受环磷酰胺(浙江海正药业股份有限公司，国药准字 H20093392)500 mg/m^2、氟尿嘧啶(山东明仁福瑞达制药股份有限公司，国药准字 H37020120)500 mg/m^2、阿霉素(奥地利依比威药物有限公司，国药准字 H20070131)75 mg/m^2 静脉滴注，其中氟尿嘧啶在第 1d、第 8d 进行治疗，其与药物在第 1d 进行治疗。上述治疗过程为 1 个疗程，每个疗程间隔时间为 28d，一共进行 4~6 个疗程。

观察组接受表柔比星与环磷酰胺联合化疗方案治疗，表柔比星(辉瑞制药(无锡)有限公司，国药准字 H20000497)60 mg/m^2，1 次 /d，环磷酰胺与对照组给药方式一致。上述治疗过程为 1 个周期，连续治疗 6 个周期。并对两组患者进行 3 年随访。

1.3 疗效判定标准

患者疗效根据 WHO 标准[8]进行判定：痊愈：患者切片标本显示原位癌细胞完全消失，浸润癌细胞完全清除；显效：患者治疗后肿瘤消失；有效；患者肿瘤水平直径与垂直直径乘积减少 50%以上；无效：与上述标准不符者。临床总疗效 = 痊愈率 + 显效率 + 有效率。

1.4 观察指标

比较两组患者不良反应发生率、3 年生存率；使用酶联免疫吸附法[9]检测患者治疗前后血清抵抗素、脂联素水平。

1.5 统计学分析

使用统计学软件 SPSS22.0 对数据进行统计学分析，计数资料使用例数 n 及(%)进行表示，组间数据使用 χ^2 进行检验；计量资料使用($\bar{x}\pm s$)进行表示，组间数据使用 t 进行检验。P<0.05，表示差异有统计学意义。

2 结果

2.1 比较两组临床疗效

观察组临床疗效(93.33 %)高于对照组患者(60.00 %)，组间数据相比差异有显著性差异(χ^2=31.048，P<0.05)。见表 2。

2.2 比较两组患者不良反应发生率

观察组心脏毒性、中性粒细胞减少发生率（13.33 %，73.33 %)低于对照组患者(30.00 %，86.67 %)，组间数据相比差异有统计学意义(χ^2=8.187，χ^2=5.561，P<0.05)。两组患者恶心呕吐、肝功能损害发生率相比，差异无统计学意义(χ^2=2.057，χ^2=0.273，P>0.05)。见表 3。

2.3 比较两组患者术后 3 年生存率

观察组术后 3 年生存率(76.67 %)高于对照组患者(63.33 %)，组间数据相比差异有统计学意义(χ^2=4.237，P<0.05)。见表 4。

2.4 比较两组患者血清抵抗素及脂联素水平

两组患者治疗后血清抵抗素及脂联素水平均有好转(P<0.

表 2 比较两组患者临床疗效[n,(%)]

Table 2 Comparison of clinical efficacy between the two groups [n, (%)]

Groups	n	Recovery	Excellent	Valid	Invalid	Overall response rate
Obseravtion group	30	5(16.67)	11(36.67)	12(40.00)	2(6.67)	28(93.33)
Control group	30	3(10.00)	10(33.33)	5(16.67)	12(40.00)	18(60.00)
χ^2	/	/	/	/	/	31.048
P	/	/	/	/	/	0.000

表 3 比较两组患者不良反应发生率[n,(%)]

Table 3 The incidence of adverse reactions between the two groups was compared [n, (%)]

Groups	n	Nausea and vomiting	Cardiotoxicity	Neutropenia	Liver function lesion
Obseravtion group	30	19(63.33)	4(13.33)	22(73.33)	9(30.00)
Control group	30	16(53.33)	9(30.00)	26(86.67)	8(26.67)
χ^2	/	2.057	8.187	5.561	0.273
P	/	0.151	0.004	0.018	0.601

表 4 比较两组患者术后三年生存率[n,(%)]

Table 4 The three-year survival rates were compared between the two groups[n,(%)]

Groups	n	First years	Second years	Third years
Obseravtion group	30	28(93.33)	26(86.67)	23(76.67)
Control group	30	27(90.00)	24(80.00)	19(63.33)
χ^2	/	0.726	1.602	4.237
P	/	0.394	0.206	0.040

05)。观察组治疗后血清抵抗素水平低于对照组(t=3.040,*P*<0.05),观察组脂联素水平高于对照组,组间数据相比,差异有统计学意义(t=4.426,*P*<0.05),见表 5。

表 5 比较两组患者血清抵抗素及脂联素水平($\bar{x}\pm s$)

Table 5 Serum resistin and adiponectin levels were compared between the two groups($\bar{x}\pm s$)

Groups	n	Before tratment		After treatment	
		Resistin(μg/L)	Adiponectin(mg/L)	Resistin(μg/L)	Adiponectin(mg/L)
Obseravtion group	30	27.48±3.82	8.47±2.95	21.92±3.21*	10.45±2.73*
Control group	30	27.81±3.27	8.52±2.73	24.37±3.03*	7.02±3.25*
t	/	0.360	0.068	3.040	4.426
P	/	0.721	0.946	0.004	0.000

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

3 讨论

乳腺癌是一种全身性疾病,患者治疗效果取决于是否出现远处的微小转移灶。改良乳腺癌根治术可有效保留胸肌,明显改善患者胸廓外形,还可降低胸肌皮瓣坏死几率[10]。临床研究显示,改良乳腺癌根治术患者接受度较高,且保留胸肌,较为美观[11]。Hu[12]对患者进行随机分组,分别采取乳腺癌根治术及改良乳腺癌根治术进行治疗,结果显示改良组患者术后复发率比传统组更低。此外,临床上可根据患者肿瘤大小、淋巴结情况、细胞学分级指导患者的临床化疗,从而有效筛选适用人群[13]。

目前乳腺癌患者的新辅助化疗方案尚无统一方案,《乳腺癌临床实践指南》[14]指出,炎性乳腺癌患者主要使用蒽环类药物为基础,联合紫杉类进行新辅助化疗。且蒽环类及紫杉类联合使用可有效提高新辅助化疗的有效率及保乳手术成功率,疗效较好[15]。Qin[16]对患者使用多西他赛及表柔比星治疗,结果显示两种药物保乳率差异无统计学意义,且表柔比星缓解率高于多西他赛。另 Sakurada[17]对患者使用 ET 方案(表柔比星)及 EC(蒽环类联合环磷酰胺)方案治疗,结果显示 ET 方案治疗后 pCR 率高于 EC 组。ET 方案主要的毒副反应包括脱发、恶心呕吐,但均可耐受[18]。新辅助化疗已经成为了乳腺癌患者的标准治疗手法,可有效降低肿瘤分期,提高患者疗效。表柔比星可有效干扰肿瘤细胞转录过程,从而阻止 mRNA 的形成,抑制癌细

胞增殖[19,20]。因此,行改良乳腺癌根治术的患者应用表柔比星可有效提高患者临床疗效,促进患者恢复。本研究结果显示,观察组临床疗效(93.33 %)高于对照组患者(60.00 %)(P<0.05);观察组心脏毒性、中性粒细胞减少发生率(13.33 %,73.33 %)低于对照组患者(30.00 %,86.67 %)(P<0.05)。两组患者恶心呕吐、肝功能损害发生率相比,差异无统计学意义(P>0.05)。观察组术后 3 年生存率(76.67 %)高于对照组患者(63.33 %)(P<0.05)。提示该种化疗方式安全性较高,因此改良乳腺癌根治术联合表柔比星可有效改善患者预后情况。

肥胖人群患乳腺癌风险性较其余人群更高,尤其是 BMI 指数超过 40kg/m^2 的患者发病率最高[21]。脂肪因子中生长因子及炎症因子可有效促进细胞有丝分裂,而血清抵抗素及脂联素是其中较重要的两种调控因子。血清抵抗素一种富含半胱氨酸的蛋白质,可随着患者病情发展而逐渐升高,与脂肪细胞分化及胰岛素抵抗有一定关系[22]。有研究表明,大鼠下丘脑、垂体部位同样有抵抗素分泌,可能与下丘脑、垂体发育成熟有关[23]。另 Zeidan[24]研究显示,血清抵抗素与炎症标志物有关,且抵抗素基因表达与多种因素调控有关。同时在脂肪、肝脏、骨骼肌组织中,血清抵抗素可减轻胰岛素摄取葡萄糖的能力,从而减弱胰岛素的作用并发生胰岛素抵抗。胰岛素在乳腺癌患者病情发展中,可有效促进有丝分裂,发挥抗细胞凋亡效应,促进细胞分裂等[25,26]。此外,胰岛素可通过上调雌激素水平、增强 IGF-1 活性促进乳腺癌的发生,因此胰岛素与胰岛素抵抗均与乳腺癌进程有一定关系[27]。因此,血清抵抗素不仅导致患者凝血系统亢奋,血管平滑肌细胞异常增殖,还可有效增强血管内皮生长因子分泌能力,从而有效促进肿瘤生长[28]。

脂联素是一种由脂肪细胞分泌的激素。临床研究显示,瘦者脂联素水平高于肥胖者,提示患者体重可随着脂联素水平升高而降低,且脂联素循环水平与肥胖、胰岛素抵抗等恶性肿瘤发病风险程度相关,包括子宫内膜癌、胃癌、大肠癌等[29,30]。这可能是因为脂联素可以通过改变细胞因子水平保护机体,而肥胖患者体内脂联素水平降低,从而导致患者出现胰岛素抵抗等,从而促进患者肿瘤细胞分化[31]。本研究结果显示,两组患者血清抵抗素水平、脂联素水平均有改善(P<0.05),观察组血清抵抗素水平低于对照组(P<0.05),观察组脂联素水平高于对照组(P<0.05)。提示表柔比星联合改良乳腺癌根治术可有效升高脂联素,可抑制有害炎症因子,从而促进体内免疫系统恢复平衡。出现这一结果可能是因为表柔比星可能会上调机体抗氧化酶表达水平,加强对自由基的清除作用[32,33]。此外,Vega[34]选择脂联素这一炎症因子进行研究,结果显示乳腺癌患者脂联素水平低于正常组,且随着患者病情好转,脂联素水平逐渐升高,同时,肿瘤坏死因子 -α(TNF-α)可刺激记忆生成血管,而脂联素水平降低可改变 TNF-α 作用,从而增加患者肿瘤发病率。表柔比星可用过抑制白细胞介素 -12(IL-12)、干扰素(IFN)等表达对组织内炎症反应进行抑制[35,36]。但上述结论还需进一步研究。

综上所述,改良乳腺癌根治术联合表柔比星可有效提高患者疗效,促进患者生存率,且安全性较高。同时改良乳腺癌根治术联合表柔比星可有效降低乳腺癌患者血清抵抗素水平,并提高脂联素水平,表明调控血清抵抗素水平、脂联素水平是手术联合化疗发挥疗效的重要机制之一。这一发现有助于我们对改良乳腺癌根治术联合表柔比星治疗乳腺癌作用机制的理解,且为表柔比星的应用提供一定支持。

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