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腹腔镜手术联合新辅助化疗对结直肠癌患者血清 CEA、CA242、CA19-9、CA724、ICAM-1 及 VCAM-1 水平的影响

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[摘要] **目的:**对结直肠癌患者在采用腹腔镜手术的基础上给予新辅助化疗方案进行治疗,探讨该方案对患者血清癌胚抗原(CEA)、CA242、CA19-9、CA724、细胞间黏附分子-1(ICAM-1)及血管细胞黏附分子-1(VCAM-1)水平的影响。**方法:**回顾性分析自2012年1月至2015年1月我院收治的120例结直肠癌患者,分为对照组和观察组,每组60例患者。所有患者给予腹腔镜手术治疗,观察组患者在腹腔镜手术前给予新辅助化疗(FOLFOX4方案)4个周期,于治疗前后清晨取患者空腹静脉血进行离心处理,运用ELISA法检测两组患者血清CA242、CA19-9、ICAM-1及VCAM-1水平并进行比较,运用MEIA法检测两组患者血清CEA水平并进行比较,运用ECLI法检测两组患者血清CA724水平并进行比较。**结果:**(1)治疗前,两组患者血清CEA、CA242、CA19-9及CA724水平之间无显著性差异($P>0.05$);治疗后,与同组治疗前相比,两组患者血清CEA、CA242、CA19-9及CA724水平均明显降低,差异具有显著性($P<0.05$),且观察组患者血清CEA、CA242、CA19-9及CA724水平降低程度均明显优于对照组,两组之间具有显著性差异($P<0.05$);(2)治疗前,两组患者血清ICAM-1、VCAM-1水平之间无显著性差异($P>0.05$);治疗后,与同组治疗前相比,两组患者血清ICAM-1、VCAM-1水平均明显降低,差异具有显著性($P<0.05$),且观察组患者血清ICAM-1、VCAM-1水平降低程度均明显优于对照组,两组之间具有显著性差异($P<0.05$)。**结论:**对结直肠癌患者采用新辅助化疗联合腹腔镜手术的治疗方案能够有效降低血清CEA、CA242、CA19-9、CA724、ICAM-1及VCAM-1水平,该方案可通过调节癌症相关的肿瘤标志物及相关因子的表达,促进患者自身免疫系统的恢复,缓解患者病情,安全可靠,值得临床应用。

[关键词] 腹腔镜手术;新辅助化疗;直肠癌;血清指标

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Effects of laparoscopic operation combined neoadjuvant chemotherapy on serum levels of CEA, CA242, CA19-9, CA724, ICAM-1 and VCAM-1 in patients with colorectal carcinoma

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View from specialist: It is creative, and of certain scientific and educational value.

[ABSTRACT] **Objective:** To observe the effects of neoadjuvant chemotherapy on the basis of laparoscopic operation on colorectal carcinoma patients, serum CEA, CA242, CA19-9, CA724, ICAM-1 and VCAM-1 levels. **Methods:** A total of 120 cases of colorectal carcinoma in our hospital from January 2012 to January 2015 were retrospectively analyzed and divided into control group and observation group, with each group of 60 patients. All patients were given laparoscopic operation, and the patients in the observation group were given neoadjuvant chemotherapy (FOLFOX4 regimen) four cycles before laparoscopic surgery, and fasting venous blood was taken and centrifuged before and after treatment in the morning. The serum CA242, CA19-9, ICAM-1 and VCAM-1 levels were measured by ELISA, the serum CEA levels were measured by MEIA, and the serum CA724 levels were measured by ECLI, and then compared with those of the two groups. **Results:** (1) Before treatment, there was no statistically significant difference in the serum CEA, CA242, CA19-9 and CA724 levels between the two groups ($P>0.05$). After treatment, compared with the same group before treatment, the serum CEA, CA242, CA19-9 and CA724 levels of the two groups were significantly lower ($P<0.05$), and those levels of observation group were significantly better than the control group, there was significant difference between the two groups ($P<0.05$); (2) Before treatment, there was no statistically significant difference in the serum ICAM-1, VCAM-1 levels between the two groups ($P>0.05$). After treatment, compared with the same group before treatment, the serum ICAM-1, VCAM-1 levels of the two groups were significantly lower ($P<0.05$), and those levels of observation group were significantly better than the control group, there was significant difference between the two groups ($P<0.05$). **Conclusions:** The treatment of colorectal cancer patients with neoadjuvant chemotherapy combined with laparoscopic operation can effectively reduce serum CEA, CA242, CA19-9, CA724, ICAM-1 and VCAM-1 levels, which indicates that the program can regulate cancer-related tumor markers and the expression of relative factors, promote the recovery of patients with autoimmune system and ease the patient's condition. It is safe and reliable, worthy of clinical application.

[KEY WORDS] Laparoscopic operation; Neoadjuvant chemotherapy; Colorectal carcinoma; Serum parameter

结直肠癌是常见的消化道恶性肿瘤之一,占胃肠道肿瘤的第二位^[1]。随着国民经济近年来的快速发展,结直肠癌的发病率也呈现逐年增加的趋势,且恶性肿瘤死亡率的排名也由 20 世纪 70 年代的第五位上升至目前的第四位,因此应引起政府及医疗单位的高度重视^[2]。目前手术治疗仍是治疗结直肠癌的首选方法,但由于一般患者在癌症晚期才予以确诊,因此导致术后生存率大幅度降低。近年来,随着医疗技术及医疗器械的不断发展及应用,极大增加了结直肠癌的治愈率^[3]。自上世纪 80 年代,新辅助化疗作为结直肠癌围术期的辅助治疗手段,有效使肿瘤降级、临床发展降期,提高了肿瘤的治愈率,给患者及家庭降低了生活负担^[4]。结直肠癌的诊断依赖于机体多种炎性因子及肿瘤标志物的,可通过其变化对病情的发展、术后过程予以辅助判断^[5,6]。本文通过对结直肠癌患者在采用腹腔镜手术的基础上给予新辅助化疗方案进行治疗,观察联合治疗方案对患者血清癌胚抗原(CEA)、CA242、CA19-9、CA724、细胞间黏附分子-1(ICAM-1)及血管细胞黏附分子-1(VCAM-1)水平的影响,现报道如下。

1 资料与方法

1.1 一般资料

本研究选取自 2012 年 1 月至 2015 年 1 月我院收治的 120 例结直肠癌患者为研究对象,随机分为两组,分别为观

察组和对照组,每组患者 60 例。其中观察组男性 33 例,女性 27 例,患者平均年龄为(52.7±12.1)岁;肿瘤部位分布:结肠癌 23 例,直肠癌 37 例;临床分期:Ⅱ期 12 例,Ⅲ期 43 例,Ⅳ期 5 例;病理类型:高分化癌 17 例,中分化癌 32 例,低分化癌 11 例。对照组男性 29 例,女性 31 例,患者平均年龄为(51.4±13.8)岁;肿瘤部位分布:结肠癌 20 例,直肠癌 40 例;临床分期:Ⅱ期 15 例,Ⅲ期 42 例,Ⅳ期 3 例;病理类型:高分化癌 15 例,中分化癌 36 例,低分化癌 9 例。以上分组情况均得到患者及家属的知情同意,并通过了医院伦理委员会的批准。两组患者在性别比例、年龄、肿瘤部位分布、肿瘤病理类型及肿瘤临床分期等一般资料的比较均无统计学差异($P>0.05$),因此具有可比性。

1.2 纳入及排除标准

纳入标准:本研究的研究对象需按照 2016 年 11 月 23 日美国国立综合癌症网络(National Comprehensive Cancer Network, NCCN)在线发布的 2017. V1 版《NCCN 结直肠癌诊治指南》中的相关规定进行严格诊断^[7]。术前根据结直肠癌、病理组织诊断、肿瘤标记物等辅助手段检查结果确诊为结直肠癌。排除标准^[8,9]:患有严重的脏器(心、肺、肝、肾等)功能不全者;有血液系统疾病,严重的感染性疾病者;合并其它严重肿瘤者;重度肥胖,对本手术及所用化疗药物不能耐受者。

1.3 治疗方案

入院后两组患者均给予结直肠癌的常规治疗,主要包括营养支持及常规基础疾病的干预。对照组(腹腔镜手术组)^[10]:患者采用气管插管进行全麻,具体手术方法及瘤组

织切除范围的确定严格参照腹腔镜直肠癌手术标准指南。术中需严格遵守无瘤原则,切除的组织标本经标本袋套扎,自小切口取出后进行病理学检查,术后1个月进行辅助化疗,共化疗12个周期。观察组(新辅助化疗+腹腔镜手术组)^[11,12]:该组患者在术前给予新辅助化疗(FOLFOX4方案)4个周期,14 d/周期;具体方案为第1天静脉滴注注射用奥沙利铂(齐鲁制药,国药准字H20093168),剂量按照体表面积 $130\text{ mg}/\text{m}^2$ 持续滴注2~6 h,第1、2天静脉滴注亚叶酸钙注射液(江苏恒瑞医药股份有限公司,国药准字H20000584),剂量按照体表面积 $200\text{ mg}/\text{m}^2$ 持续滴注2 h以上,第1、2天静脉滴注5-氟尿嘧啶注射液(天津金耀药业有限公司,国药准字H12020959),剂量按照体表面积 $500\text{ mg}/\text{m}^2$ 的剂量,通过输液泵以 $5\text{ mL}/\text{h}$ 的速率持续静脉给药并维持24 h;化疗期间须严格检测患者出现的不良反应并给予对症治疗。连续化疗4个周期结束后进行腹腔镜手术治疗,具体治疗方法同对照组。

术后两组患者均服用抗菌药物以预防伤口感染,同时严密监测患者各项生命体征并给予对症的支持治疗。

1.4 观察指标

分别抽取两组患者治疗前后清晨空腹静脉非抗凝血8 mL,离心($3\ 000\text{ r}/\text{min}$,10 min)分离得血清,放置在一 20°C 条件进行保存,备用。CEA测定采用微粒子酶联免疫分析法(MEIA法),CA242、CA19-9、ICAM-1及VCAM-1测定均采用酶联免疫吸附试验法(ELISA法),CA724测定采用电化学发光免疫法(ECLIA法)^[13]。

1.5 统计学处理

采用SPSS19.0统计学软件对试验数据进行处理,计量资料采用均数±标准差($\bar{x}\pm s$)的表示形式,组间比较采用 t 检验, $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 血清CEA、CA242、CA19-9及CA724水平

治疗前,两组患者血清CEA、CA242、CA19-9及CA724水平之间无显著性差异($P>0.05$);治疗后,与同组治疗前相比,两组患者血清CEA、CA242、CA19-9及CA724水平均显著降低($P<0.05$),对照组患者血清CEA、CA242、CA19-9及CA724水平分别为(6.80 ± 2.24)ng/mL、(18.46 ± 6.47)IU/mL、(33.86 ± 14.33)U/mL、(5.64 ± 1.32)IU/mL,观察组患者分别为(5.32 ± 1.97)ng/mL、(15.11 ± 6.65)IU/mL、(25.40 ± 11.42)U/mL、(4.66 ± 1.35)IU/mL,均明显低于对照组,两组差异具有统计学意义($P<0.05$),见表1。

表1 治疗前后两组患者血清CEA、CA242、CA19-9及CA724水平的变化($n=60, \bar{x}\pm s$)

组别	时间	CEA (ng/mL)	CA242 (IU/mL)	CA19-9 (U/mL)	CA724 (IU/mL)
观察组	治疗前	10.27±3.02	25.13±9.85	42.99±18.71	7.09±2.84
	治疗后	5.32±1.97* [#]	15.11±6.65* [#]	25.40±11.42* [#]	4.66±1.35* [#]
对照组	治疗前	9.68±3.56	24.85±10.12	43.28±16.27	7.43±3.01
	治疗后	6.80±2.24*	18.46±6.47*	33.86±14.33*	5.64±1.32*

注:与同组治疗前相比,* $P<0.05$;与对照组同期相比,[#] $P<0.05$ 。

2.2 血清ICAM-1和VCAM-1水平

治疗前,两组患者血清ICAM-1、VCAM-1水平之间无显著性差异($P>0.05$);治疗后,与同组治疗前相比,两组患者血清ICAM-1、VCAM-1水平均显著降低($P<0.05$),对照组患者血清ICAM-1和VCAM-1分别为(310.26 ± 36.45) $\mu\text{g}/\text{L}$ 、(600.9 ± 48.7) $\mu\text{g}/\text{L}$,观察组患者分别为(242.16 ± 32.45) $\mu\text{g}/\text{L}$ 、(458.4 ± 42.9) $\mu\text{g}/\text{L}$,均明显低于对照组,两组差异具有统计学意义($P<0.05$),见表2。

表2 治疗前后两组患者血清ICAM-1和VCAM-1水平的变化($n=60, \mu\text{g}/\text{L}, \bar{x}\pm s$)

组别	时间	ICAM-1	VCAM-1
观察组	治疗前	382.71±40.22	860.1±59.2
	治疗后	242.16±32.45* [#]	458.4±42.9* [#]
对照组	治疗前	376.50±42.48	873.6±55.4
	治疗后	310.26±36.45*	600.9±48.7*

注:与同组治疗前相比,* $P<0.05$;与对照组同期相比,[#] $P<0.05$ 。

3 讨论

结直肠癌(Colorectal Carcinoma, CRC)在消化道恶性肿瘤中的复发率及转移率均较高,因此早发现、早诊断、早治疗对该病显得尤为重要;目前临床上主要依靠窥镜、电子影像及组织病理检测等方法对其进行诊断、病情监测及的预后评估^[14]。腹腔镜手术尽管属于一种微创手术,具有手术创伤小,手术视野清晰,患者术后疼痛小、利于恢复等优点,但手术不能完全清除癌细胞,导致患者术后复发率较高,因此需要配合其他治疗方法^[15];新辅助化疗是指在实施腹腔镜手术前所做的全身化疗,该化疗手段可使肿块缩小、尽早杀灭无法看见的转移细胞。两种手段联合能够有效地控制患者局部复发率,提高疗效。近年来,肿瘤标志物及相关的细胞因子在肿瘤诊断、病情监测、疗效评价、预后评估等方面已成为一种不可或缺的手段^[16-18]。尤其是在结直肠癌的治疗过程中具有重要意义。

癌胚抗原CEA(carcinoembryonic antigen)是一种细胞表面相关糖蛋白,在胃肠道出现恶性肿瘤时患者血清中该指标均可出现高表达,并且其他恶性肿瘤或非肿瘤性疾病也可升高,因此高指标针对结直肠癌的表达不具有特异性;但是该指标可以作为肿瘤发生转移系统性治疗监测疗效的一个重要指标^[19]。糖链抗原CA242(carbohydrate antigen 242)是一种经唾液酸化的黏蛋白型糖类抗原,和肿瘤宿主的抗肿瘤免疫反应相关,该指标的血清水平可随结直肠癌分期的递增而逐渐升高,但其与肿瘤的类型、部位以及细胞的分化程度无明显相关性^[20]。糖链抗原CA19-9(carbohydrate antigen 19-

9)是一种低聚糖类肿瘤相关抗原,当消化系统出现恶性肿瘤时,患者血清中该指标的浓度将明显增高,尤以胰腺癌为最高;在结直肠癌中其水平也随肿瘤分期的递增而升高,并且与Ⅲ和Ⅳ期结肠癌的生存率及预后情况具有密切的相关性^[21]。糖链抗原 CA724(carbohydrate antigen 724)是一种高分子量糖蛋白抗原,对结直肠癌具有较高的特异性和敏感性,并且该指标在正常人的组织、良性肿瘤及渗出物中不具有表达性,当检测出该指标表达后其水平高低可直接反映肿瘤浸润程度和淋巴结转移状况,同时还能一定程度上反映肿瘤的负荷情况,血清中的敏感度明显高于 CEA^[22]。因此肿瘤标志物的检测在临床上辅助诊断结直肠癌及对其病情的检测及预后判断具有重要的作用。此外,黏附分子作为一种生物大分子,其主要的生理功能是维持机体的正常组织结构,参与炎症反应的应答及在恶性肿瘤的转移和浸润中都具有重要的功能,其中细胞间黏附分子-1(intercellular adhesion molecule-1,ICAM-1)和血管细胞黏附分子-1(vascular cell adhesion molecule-1,VCAM-1)则是其中的重要组成部分^[23,24]; ICAM-1 是免疫球蛋白的一种,分布广泛,正常情况时其主要存在于上皮细胞、内皮细胞、淋巴细胞等表面,主要参与机体的免疫反应及炎症反应,并且与体内的多种恶性肿瘤的产生、发展和转移相关;研究表明随着恶性胃肠肿瘤的发生,机体由于原发病灶局部炎症介质的诱导与释放,进而导致机体黏附功能失调,致使肿瘤被浸润并进一步发生转移,而该指标则会随着病情的发展即可出现高表达;VCAM-1 属于一种跨膜糖蛋白,正常情况下该因子在细胞中也不表达或微量表达,但其却在活化的巨噬细胞或内皮细胞中表达;研究表明当机体存在恶性肿瘤细胞时,该因子的水平即可上升,并且随着其表达的升高可进一步促进肿瘤的生长及转移。因此在结直肠癌术后随访及检测过程中,多种指标联合检测具有较高的临床意义和应用价值。

在本次研究中发现,治疗前,两组患者血清 CEA、CA242、CA19-9、CA724、ICAM-1 及 VCAM-1 水平之间均无显著性差异($P>0.05$);而治疗后,与同组治疗前相比,两组患者血清所有检测指标水平平均明显降低($P<0.05$),且采用腹腔镜联合新辅助化疗方案治疗的患者血清 CEA、CA242、CA19-9、CA724、ICAM-1 及 VCAM-1 水平改善程度均明显优于单纯采用腹腔镜手术治疗的患者。说明采用腹腔镜联合新辅助化疗方案,即可提高临床疗效,也可通过影响机体多种肿瘤标志物和相关因子的表达而

起到控制、监测病情发展的作用。

综上所述,对结直肠癌患者采用新辅助化疗联合腹腔镜手术的治疗方案能够有效降低血清 CEA、CA242、CA19-9、CA724、ICAM-1 及 VCAM-1 水平,表明该方案可通过调节癌症相关的肿瘤标志物及相关因子的表达,促进患者自身免疫系统的恢复,缓解患者病情,安全可靠,值得临床推广应用。

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刺联合腹腔镜手术后的免疫应答的程度弱于急诊腹腔镜手术,提示经皮经肝胆囊穿刺能够改善急性重症胆囊炎患者的免疫应答。

经皮经肝胆囊穿刺联合腹腔镜手术用于急性重症胆囊炎的治疗能够较急诊腹腔镜手术更为有效的减轻术后炎症反应、应激反应,改善细胞免疫应答和体液免疫应答。

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