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单孔腹腔镜直肠癌根治术的临床疗效及对患者血清 HO-1、CEA、YKL-40 和 sIL-2R 的影响 *

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摘要 目的:探讨单孔腹腔镜直肠癌根治术的临床疗效及对患者血清血红素氧化酶(HO)-1、癌胚抗原(CEA)、人类软骨糖蛋白 39(YKL-40)、可溶性白介素-2 受体(sIL-2R)的影响。方法:选择 2013 年 1 月至 2015 年 1 月我院接诊的 92 例直肠癌患者,通过随机数表法分为观察组(n=46)和对照组(n=46),对照组使用传统多孔腹腔镜直肠癌根治术,观察组使用单孔腹腔镜直肠癌根治术。比较两组围术期情况及术后并发症的发生情况,手术前 24 h、手术后 24 h 血清 HO-1、CEA、YKL-40、sIL-2R 水平的变化,并随访 2 年,比较两组的生存率。结果:两组手术时间、淋巴结切除个数比较差异无统计学意义($P>0.05$),观察组术中出血量显著少于对照组,术后排气时间、住院时间明显短于对照组($P<0.05$)。手术后 24 h,两组血清 HO-1、YKL-40、sIL-2R 水平均较术前显著升高($P<0.05$),血清 CEA 水平较术前明显降低($P<0.05$),且观察组血清 HO-1、YKL-40、sIL-2R 水平均明显低于对照组($P<0.05$),两组手术后血清 CEA 水平比较差异无统计学意义($P>0.05$);观察组吻合口瘘、尿潴留、切口感染、肺部感染总发生率明显低于对照组($P<0.05$),两组术后 2 年生存率比较差异无统计学意义($P>0.05$)。结论:采用单孔腹腔镜直肠癌根治术治疗直肠癌患者的临床效果明显优于传统多孔腹腔镜直肠癌根治术,且安全性更高,患者术后恢复更快,可能与其有效降低患者血清 HO-1、YKL-40、sIL-2R、CEA 水平有关。

关键词: 直肠癌根治术;单孔腹腔镜;血红素氧化酶-1;癌胚抗原;人类软骨糖蛋白 39;可溶性白介素-2 受体

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Clinical Efficacy of Single-port Laparoscopic Radical Resection in Treatment of Rectal Cancer and Effect on Serum HO-1, CEA, YKL-40 and sIL-2R Levels*

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ABSTRACT Objective: To study the clinical efficacy of single-port laparoscopic radical resection in the treatment of rectal cancer and its effect on the serum heme oxygenase(HO)-1, carcinoembryonic antigen(CEA), chitinase-3-like protein 1(YKL-40) and soluble interleukin-2 receptor (sIL-2R) levels. **Methods:** 92 patients of rectal cancer who were treated from January 2013 to January 2015 in our hospital were selected. According to random number table, those patients were divided into the observation group (n=46) and the control group (n=46). The control group was treated with traditional porous laparoscopic radical resection of rectal cancer, while the observation group was treated with single-port laparoscopic radical resection of rectal cancer. The perioperative period and postoperative complications were compared between the two groups, the fasting venous blood was taken at 24 h before operation and at 24h after operation, the expressions of serum HO-1, CEA, YKL-40 and sIL-2R were detected, the survival rate was recorded after 2 years of follow-up. **Results:** The operation time and the number of resected lymph nodes showed no significant difference between the two groups ($P>0.05$), the amount of bleeding in the observation group was significantly less than that of the control group, the postoperative exhaust time and hospitalization stay of observation group were significantly shorter than those of the control group ($P<0.05$); at 24h after operation, the serum HO-1, YKL-40 and sIL-2R levels in both groups were significantly higher than those before operation, and the serum CEA level was significantly lower than that before operation ($P<0.05$), the serum HO-1, YKL-40 and sIL-2R levels in the observation group were significantly lower than those of the control group ($P<0.05$), there was no significant difference in the serum CEA between the two groups ($P>0.05$); the total incidence of anastomotic leakage, retention of urine, incision infection and pulmonary infection in the observation group was significantly lower than that of the control group($P<0.05$); there was no significant difference in the survival between the two groups during the two-year follow-up($P>0.05$). **Conclusion:** The clinical effect of single-port laparoscopic radical resection of rectal

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cancer was better than that of traditional porous laparoscopic radical resection of rectal cancer, and the security was higher, the patient recovered more quickly after surgery, it may be related to the decrease of serum HO-1, YKL-40, sIL-2R and CEA levels.

Key words: Radical resection of rectal cancer; Single-port laparoscope; Heme oxygenase-1; Carcinoembryonic antigen; Chitinase-3-like protein 1; Soluble interleukin-2 receptor

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前言

直肠癌是一种消化系统最为常见的恶性肿瘤,对人类身体健康造成严重威胁,目前仍主要以手术治疗为主,同时配合积极化疗、放疗^[1]。传统的多孔腹腔镜直肠根治术可得到令人满意的淋巴结清扫效果,但该术式对患者造成创伤较大,对机体应激反应、免疫功能均会造成一定影响,影响术后恢复^[2-3]。随着内镜技术的不断发展,单孔腹腔镜直肠根治术可经过肚脐实施操作,不仅隐蔽手术瘢痕,还可以减少多孔操作中对胃、阴道、直肠等的伤害,但该术式操作要求较高^[4]。近年来,研究表明手术前后血清血红素氧化酶(HO)-1、癌胚抗原(CEA)、人类软骨糖蛋白 39(YKL-40)、可溶性白介素-2 受体(sIL-2R)的变化有助于评价手术效果以及围术期患者免疫功能及机体炎症反应^[5,6]。本研究主要探讨了单孔腹腔镜直肠根治术的治疗效果及其对患者血清 HO-1、CEA、YKL-40、sIL-2R 水平的影响,现将结果报道如下。

1 资料与方法

1.1 一般资料

选择 2013 年 1 月至 2015 年 1 月我院接诊的 92 例直肠癌患者。纳入标准^[7]:①符合直肠癌诊断标准,肿瘤位置处于直肠中上段,肿瘤直径 $<6\text{ cm}$;②符合手术适应证;③知情同意此次研究,并完成随访。排除标准^[8]:①存在远处转移;②合并心、肝、肺、肾等严重脏器功能障碍;③脑功能障碍。通过随机数表法分为 2 组,各 46 例。观察组男 28 例,女 18 例;年龄 42~69 岁,平均 (55.89 ± 3.10) 岁;TNM 分期 I 期 15 例,II 期 22 例,III 期 9 例;肿瘤直径 2.2~5.9 cm,平均 $(3.97\pm 0.42)\text{ cm}$;Miles 术 25 例,Dixon 术 21 例。对照组男 30 例,女 16 例;年龄 40~68 岁,平均 (56.04 ± 3.02) 岁;TNM 分期 I 期 14 例,II 期 24 例,III 期 8 例;肿瘤之间 2.0~5.9 cm,平均 $(4.03\pm 0.39)\text{ cm}$;Miles 术 22 例,Dixon 术 24 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 方法

1.2.1 传统多孔腹腔镜直肠根治术 对照组:气管插管全麻,采取截石位,消毒铺巾,于肚脐将 10 mm Trocar 置入,建立 CO₂ 气腹,压力控制在 13 mmHg;在左、右肚脐旁腹直肌外缘作 5 mm 戳孔,并安装器械,于右下腹作 12 mm 戳孔,为主操作孔,可在左下腹作一个 5 mm 戳孔,常规 4~5 孔实施手术。

1.2.2 单孔腹腔镜直肠根治术 观察组:气管插管全麻,采取截石位,消毒铺巾,于肚脐上作切口,长度大约 2.5 cm,将单孔腹腔镜装置置入,建立 CO₂ 气腹,压力控制在 13 mmHg。手术过程均严格参照《中国腹腔镜结直肠癌根治术指南》、《普通外科腹腔镜手术操作规范与指南》进行。

1.3 观察指标

1.3.1 记录围术期情况 包括手术时间、术中出血量、淋巴结切除个数、术后排气时间及住院时间。

1.3.2 血清学指标 于手术前 24 h、手术后 24 h 抽取患者 5 mL 空腹静脉血,将血清分离后置于冷冻箱内以备血清 HO-1、CEA、YKL-40、sIL-2R 的检测;血清 HO-1、YKL-40、sIL-2R 的检测采用酶联免疫吸附法,试剂盒购于北京科瑞美科技有限公司,血清 CEA 的检测使用竞争放射免疫分析法,试剂盒购于中国原子能科学院同位素研究所;均使用美国贝克曼公司提供的全自动生化分析仪 AU5800。

1.3.3 术后并发症 对所有患者进行 2 年随访,记录生存率。

1.4 统计学分析

以 spss18.0 软件包处理,计量资料用均数 $\pm$ 标准差($\bar{x}\pm s$)表示,两组间比较采用 t 检验,计数资料以[例(%)]表示,两组间比较采用 χ^2 检验,以 $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组围术期情况比较

两组手术时间、淋巴结切除个数比较差异无统计学意义($P>0.05$),观察组术中出血量少于对照组,术后排气时间、住院时间明显短于对照组($P<0.05$),见表 1。

表 1 两组围术期情况比较($\bar{x}\pm s$)

Table 1 Comparison of the perioperative conditions between the two groups($\bar{x}\pm s$)

Groups	Operation time(min)	Amount of bleeding (mL)	Resected lymph nodes s(number)	Postoperative exhaust time(d)	Hospital stay(d)
Observation group (n=46)	155.75 $\pm$ 21.48	78.56 $\pm$ 13.82*	12.37 $\pm$ 1.23	2.34 $\pm$ 0.41*	8.95 $\pm$ 1.16*
Control group(n=46)	150.23 $\pm$ 22.04	137.45 $\pm$ 15.73	12.84 $\pm$ 1.04	3.85 $\pm$ 0.75	10.48 $\pm$ 1.43

Note: Compared with the control group, * $P<0.05$.

2.2 两组手术前后血清 HO-1、CEA、YKL-40、sIL-2R 水平的比较

手术前 24 h, 两组血清 HO-1、CEA、YKL-40、sIL-2R 比较差异无统计学意义($P>0.05$); 手术后 24 h, 两组血清 HO-1、

YKL-40、sIL-2R 水平均较治疗前显著升高($P<0.05$), 血清 CEA 水平较治疗前明显降低($P<0.05$), 且观察组血清 HO-1、YKL-40、sIL-2R 水平明显低于对照组($P<0.05$), 而两组手术后

血清 CEA 水平比较差异无统计学意义($P>0.05$),见表 2。

表 2 两组手术前后血清 HO-1、CEA、YKL-40、sIL-2R 水平的比较($\bar{x}\pm s$)

Table 2 Comparison of the serum HO-1, CEA, YKL-40 and sIL-2R levels between two groups before and after operation($\bar{x}\pm s$)

Groups		HO-1(pg/L)	CEA(ng/mL)	YKL-40(pg/mL)	sIL-2R(pmol/L /mL)
Observation group (n=46)	Before operation	8.45 $\pm$ 1.74	34.73 $\pm$ 4.52	134.73 $\pm$ 25.74	143.84 $\pm$ 16.34
	After operation	21.73 $\pm$ 2.53**	15.73 $\pm$ 2.03*	212.73 $\pm$ 27.35**	178.95 $\pm$ 18.39**
Control group(n=46)	Before operation	18.51 $\pm$ 1.7	34.59 $\pm$ 4.64	135.02 $\pm$ 25.23	144.12 $\pm$ 16.04
	After operation	29.85 $\pm$ 2.83*	15.48 $\pm$ 2.10*	279.45 $\pm$ 30.12*	234.24 $\pm$ 19.45*

Note: Compared with the same group before operation 24 h, * $P<0.05$; Compared with the control group, ** $P<0.05$.

2.3 两组术后并发症发生情况的比较

8.69%,明显比对照组的 26.09%低($P<0.05$),见表 3。

观察组吻合口瘘、尿潴留、切口感染、肺部感染总发生率为

表 3 两组术后并发症发生情况的比较(例,%)

Table 3 Comparison of the incidence of postoperative complications between two groups (n, %)

Groups	Anastomotic leakage	Retention of urine	Incision infection	Pulmonary infection	Total incidence rate
Observation group (n=46)	0(0.00)	1(2.17)	1(2.17)	2(4.35)	4(8.69)*
Control group(n=46)	1(2.17)	3(6.52)	3(6.52)	5(10.87)	12(26.09)

Note: Compared with the control group, * $P<0.05$.

2.4 两组术后 2 年生存率比较

($P>0.05$),见表 4。

在两年的随访过程中,两组生存率比较差异无统计学意义

表 4 两组术后 2 年生存率比较(例,%)

Table 4 Comparison of the survival rate in the 2 years after operation between two groups (n, %)

Groups	1 years	2 years
Observation group(n=46)	41(89.13)	35(76.09)
Control group(n=46)	40(86.96)	36(78.26)

3 讨论

近年来,直肠癌作为发病率较高的消化系统肿瘤,发病率逐渐升高,且趋于老龄化,患者多以恶心呕吐、食欲不振、疲劳、贫血等为主要症状^[9]。传统多孔腹腔镜直肠癌根治术在临床上应用广泛,但其术后所造成的疼痛大、恢复慢^[10]。单孔腹腔镜直肠癌根治术虽然目前仍处于发展阶段,但国内外均有报道证实该术式在缓解术后疼痛、促进术后恢复中具有优势,且更满足患者对手术切口的美观需求^[11,12],但其治疗有效性临床上仍存在争议。Lurje G 等^[13]认为由于单孔腹腔镜直肠癌根治术手术视野有限,在肿瘤根治效果上不如传统多孔腹腔镜直肠癌根治术,可行性不佳。也有学者提出单孔腹腔镜直肠癌根治术可获得和传统多孔腹腔镜直肠癌根治术相似的肿瘤根治效果^[14]。本研究结果显示使用单孔腹腔镜直肠癌根治术的患者淋巴结切除个数以及两年生存率和传统多孔腹腔镜直肠癌根治术的患者比较均无显著差异,显示出单孔腹腔镜直肠癌根治术可得到和传统多孔腹腔镜直肠癌根治术相似的肿瘤根治效果;此外,使用单孔腹腔镜直肠癌根治术的患者术中出血量明显更少,术后排气时间、住院时间更短,且吻合口瘘、尿潴留、切口感染、肺部感染总发生率为 8.69%,明显比使用传统多孔腹腔镜直肠癌

根治术患者(26.09%)低,分析是由于在单孔腹腔镜直肠癌根治术切口较少,对机体创伤更小,有助于促进术后恢复,并降低并发症,安全性更高,和国外 Danforth RM 等^[15]报道具有相似性。

HO 是一种催化血红素降解所解的微粒体限速酶,在细胞和组织发生应激反应时,机体内多种应激因子均可诱发 HO-1 的表达,参与体内各种氧化应激、炎症反应。Hou N 等^[16]研究显示 HO-1 的表达和炎症反应程度之间呈正相关。Yang PM 等^[17]研究也证实直肠癌患者实施手术后血清 HO-1 的表达会呈明显升高趋势。YKL-40 在细胞分化增殖、炎症反应中作用近年来也受到较多学者重视。Querol-Vilaseca M 等^[18]发现 YKL-40 可作为急性相关蛋白,在遭受到炎症刺激时,其表达可增加 25%以上。Batista KMP 等^[19]也提出在手术的刺激下,YKL-40 可在促炎因子的诱导下释放,和 C 反应蛋白相比具有更佳的敏感性、特异性。sIL-2R 主要由活化的 T 细胞膜产生,其和 IL-2 相互结合,可对肿瘤患者的细胞免疫反应产生抑制效果。在恶性肿瘤患者中,血清 sIL-2R 的表达呈明显升高趋势,且存在肿瘤转移的患者表达更高^[20,21]。Tabata R 等^[22]报道称在行肿瘤根治术过程中,由于对机体免疫系统会产生较大的干扰性,可引发免疫抑制,会进一步增加血清 sIL-2R 的表达,对术后恢复造成影响。在直肠癌患者中,血清 CEA 是一种常用的肿瘤标志物,其在健

康人群中表达较低,而在多种消化道肿瘤如胰腺癌、胃癌、直肠癌患者中呈明显升高。国内外均有研究显示血清 CEA 和直肠癌患者 TNM 分期存在密切关系,可有效反映病变程度,可作为直肠癌手术疗效、预后评价的参考指标^[23,24]。

本研究结果显示两种术式的患者手术后血清 HO-1、YKL-40、sIL-2R 的表达较术前均明显增加,但行单孔腹腔镜直肠癌根治术的患者术后血清 HO-1、YKL-40、sIL-2R 的表达明显比传统多孔腹腔镜直肠癌根治术的患者更低,分析是由于单孔腹腔镜直肠癌根治术由于切口较少,对患者创伤小,产生的应激反应小,这也可能是应用该术式的患者术后恢复更快的内在机制之一。国外 Wijerathne S 等^[25]报道也证实单孔腹腔镜直肠癌根治术产生的炎性反应更低,对免疫系统的影响更小,和本研究具有相似性。两种术式的患者术后血清 CEA 均明显降低,术后血清 CEA 的表达无显著差异,显示出两种术式均有助于降低肿瘤标志物的表达,疗效相似,这可能也是两种术式患者淋巴结清扫个数、生存率比较无显著差异的原因之一。

综上所述,采用单孔腹腔镜直肠癌根治术治疗直肠癌患者的临床效果明显优于传统多孔腹腔镜直肠癌根治术,且安全性更高,患者术后恢复更快,可能与其有效降低患者血清 HO-1、YKL-40、sIL-2R、CEA 水平有关。

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