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腹腔镜对结直肠癌患者血清基质金属蛋白酶、胃肠激素及应激激素水平的影响

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摘要 目的:探讨腹腔镜对结直肠癌患者血清基质金属蛋白酶、胃肠激素及应激激素水平的影响。**方法:**将 110 例结直肠癌患者纳入本研究,随机分为对照组和观察组,均 55 例,分别给予对照组和观察组患者开腹手术治疗和腹腔镜手术治疗,对比治疗前后患者的血清基质金属蛋白酶、胃肠激素及应激激素水平。**结果:**治疗前,两组血清基质金属蛋白酶(Matrix metalloproteinase, MMP) MMP-2、MMP-9、血清胃动素(Motilin, MTL)、胃泌素(Gastrin, GAS)、皮质醇(Cortisol, Cor)、去甲肾上腺素(Noradrenaline, NE)水平比较差异均无统计学意义 ($P>0.05$); 与组内治疗前相比, 两组治疗后血清 MMP-2、MMP-9、MTL、GAS 水平均显著降低, 血清 COR、NE 水平均显著升高, 差异有统计学意义($P<0.05$); 观察组治疗后血清 MMP-2、MMP-9、NE、COR 水平均明显低于对照组, 血清 GAS、MTL 水平均明显高于对照组, 差异对比均有显著性($P<0.05$)。**结论:**腹腔镜治疗结直肠癌可有效降低患者血清基质金属蛋白酶水平, 促进胃肠功能恢复, 减轻机体应激损伤。

关键词:结直肠癌;腹腔镜;基质金属蛋白酶;胃肠激素;应激激素

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Effects of Laparoscopy on the Serum Levels of Matrix Metalloproteinases, Gastrointestinal Hormones and Stress Hormones in Patients with Colorectal Cancer

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ABSTRACT Objective: To investigate the effects of laparoscopy on the serum levels of matrix metalloproteinases, gastrointestinal hormones and stress hormones in patients with colorectal cancer. **Methods:** 110 cases of colorectal cancer patients were selected as the research object, based on the random data table method they were divided into control group and observation group, 55 cases in each group, the control group were treated with open surgery, observation group were treated with laparoscopic surgery, before and after treatment the serum levels of matrix metalloproteinases, gastrointestinal hormones and stress hormone of the two groups were compared. **Results:** There was no significant difference in the serum levels of matrix metalloproteinase (MMP, MMP-2, MMP-9), motilin (MTL), gastrin (GAS), cortisol (Cor) and noradrenaline (NE) between the two groups before the treatment ($P>0.05$). Compared with levels in the group before treatment, after treatment, the serum levels of MMP-2, MMP-9, MTL and GAS in the two groups were significantly decreased, and the serum levels of COR and NE were significantly increased, differences was statistically significant ($P<0.05$). After treatment, the serum levels of MMP-2, MMP-9, NE and COR in the observation group were significantly lower than those in the control group, and the serum GAS, MTL levels were significantly higher than those in the control group, all the difference between the two groups was significant ($P<0.05$). **Conclusion:** Laparoscopic treatment of colorectal cancer can effectively reduce the serum levels of matrix metalloproteinases, promote the recovery of gastrointestinal function and relieve the level of stress hormones, which has certain clinical value.

Key words: Colorectal cancer; Laparoscopy; Matrix metalloproteinases; Gastrointestinal hormones; Stress hormones

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前言

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结直肠癌是全球性最常见一种恶性消化道肿瘤,具有高发病率及致死率,已成为严重威胁人类健康的主要原因之一。流行病学研究显示随着人们生活水平的提高及生活方式的转变,结直肠癌的发生率呈逐年升高趋势^[1-3]。目前,外科手术治疗是治愈结直肠癌的主要方法,其常用手术术式有开腹手术及微创手术,微创治疗主要为腹腔镜手术。近年来,腹腔镜手术在临床中应用较为广泛,众多研究已证实腹腔镜手术较开腹手术具有

创伤小、术后恢复快的优势^[4,5]。然而,目前关于其对患者血清学指标影响的研究相对较少。因此,本研究主要探讨了腹腔镜手术对结直肠癌患者基质金属蛋白酶、胃肠激素及应激激素水平的影响,具体结果报道如下。

1 资料与方法

1.1 临床资料

选取 2015 年 8 月至 2017 年 10 月南京医科大学附属淮安第一医院收治的结直肠癌患者 110 例作为研究对象,本研究符合医院伦理委员会标准,并取得伦理委员会许可后进行。所有患者均符合:① 经医院常规实验室检查、内镜、影像及病理组织学检查后确诊,符合结直肠癌诊断标准^[6];② 未发生明显浸润及远处转移;③ 无手术禁忌,符合临床手术指征;④ 入院后患者临床资料齐全,患者及家属对研究均知情同意;⑤ 排除肿瘤最大直径已超过 6 cm^[7],腹腔存在严重粘连已不适合手术者,在研究开始前有放化疗史以及不愿加入研究,不签署知情同意书者。依据随机数据表法将 110 例患者平均分为对照组和观察组,每组患者 55 例。对照组中患者年龄为 42~75 岁,平均年龄为(58.47±3.62)岁;男性患者 36 例,女性患者 19 例;肿瘤部位:直肠 34 例,乙状结肠 21 例;肿瘤 TNM 分期:Ⅰ期 14 例,Ⅱ期 22 例,Ⅲ期 19 例。观察组患者年龄为 41~76 岁,平均年龄为(57.68±4.07)岁;男性患者 32 例,女性患者 23 例;肿瘤存在部位:直肠 31 例,乙状结肠 24 例;肿瘤 TNM 分期:Ⅰ期 16 例,Ⅱ期 25 例,Ⅲ期 14 例。两组患者临床资料如年龄、性别、病理 TNM 分期及肿瘤存在部位等对比差异均无统计学意义($P>0.05$),具有可比性。

1.2 研究方法

两组患者均接受结直肠癌根治术治疗,治疗严格按照《结直肠癌诊疗规范》^[8]进行,术前给予患者常规实验室检查,对患者身体状况进行评估,后给予全身麻醉处理。给予对照组传统开腹手术治疗,操作方法:于患者腹部正中做切口,使用超声刀将肠系膜游离暴露肠系膜血管,清扫周围淋巴结,结扎血管,分离肠断,切除病灶及周围组织(距肿瘤 5 cm 处),后进行吻合肠断、冲洗及关腹等后期处理。观察组患者给予腹腔镜手术治疗,

术前常规检查及肠道清洗步骤同对照组,待麻醉成功后,具体操作为,建立二氧化碳气腹,维持气腹压力(15 mmHg 左右)下置入腹腔镜,对肿瘤部位等进行探查,利用超声刀逐层打开结肠系膜及后腹膜,清扫肠系膜下血管及周围淋巴结,结扎血管,在肿瘤近端及远端结扎肠管,依据病灶位置在腹部做切口,常规切除肿瘤处肠管取出,探查肠端吻合情况,待无出血后,常规清洗腹腔,放置引流管做关腹处理。严密监测患者生命体征,并做预防感染处理。

1.3 指标检测

分别于手术前(治疗前)和术后 1 d(治疗后)抽取患者空腹外周静脉血,离心分离血清置于 -70℃ 冰箱待测,检测指标为基质金属蛋白酶(Matrix metalloproteinase, MMP)MMP-2、MMP-9,胃肠激素:血清胃动素(Motilin, MTL)及胃泌素(Gastrin, GAS)以及应激激素[皮质醇(Cortisol, Cor)、去甲肾上腺素(Noradrenaline, NE)],其中 MMP-2、MMP-9、Cor、NE 水平测定方法为 ELISA 法,试剂盒均由上海酶联生物科技有限公司提供,MTL 及 GAS 水平采用放射免疫法测定,检测步骤严格遵循说明书进行。

1.4 统计学处理

研究所得数据经统计学软件 SPSS17.0 软件进行处理及分析,研究中计数资料以例数(%)表示,比较方法为卡方检验,基质金属蛋白酶、胃肠激素及应激激素水平经正态性验证后均符合正态分布,以 $\bar{x} \pm s$ 表示,组间样本均数比较采用独立样本 t 检验,以 $P<0.05$ 表示差异有统计学意义。

2 结果

2.1 两组治疗前后血清 MMP-2 和 MMP-9 水平的对比

治疗前,两组患者血清 MMP-2 和 MMP-9 水平比较差异均无统计学意义($P>0.05$);治疗后,两组血清 MMP-2 和 MMP-9 水平均较组内治疗前显著降低($P<0.05$),且观察组治疗后血清 MMP-2 和 MMP-9 水平水平 [(79.05±10.14)ng/mL, (128.93±35.29)ng/mL] 显著低于对照组 [(148.64±13.16)ng/mL, (202.96±65.82)ng/mL], 差异有统计学意义($P<0.05$)(表 1)。

表 1 两组治疗前后血清 MMP-2 和 MMP-9 水平的对比($\bar{x} \pm s$)

Table 1 Comparison of the serum levels of MMP-2 and MMP-9 levels between the groups before and after treatment($\bar{x} \pm s$)

Groups	Cases	Time of therapy	MMP-2(ng/mL)	MMP-9(ng/mL)
Control group	55	Before treatment	199.55± 15.54	350.11± 147.84
		After treatment	148.64± 13.16	202.96± 65.82
		t1 value/P value	18.541/0.000	6.743/0.000
Observation group	55	Before treatment	198.89± 16.38	346.86± 153.52
		After treatment	79.05± 10.14	128.93± 35.29
		t2 value/P value	46.134/0.000	10.261/0.000
		t3 value/P value	31.065/0.000	7.351/0.000

Note: t1 and t2 represent the comparison of the levels before and after treatment in the control group and the observation group respectively; the value of t3 represents the comparison of the levels after treatment between the two groups.

2.2 两组治疗前后血清胃肠激素水平的对比

治疗前,两组血清 MTL 和 GAS 水平比较差异无统计学意

义($P>0.05$);治疗后,两组血清 MTL 和 GAS 水平较同组内治疗前均显著降低($P<0.05$),且观察组治疗后血清 MTL 和 GAS 水

平分别为(277.96± 25.39)ng/L、(127.21± 12.67)ng/L,均显著高于治疗前对照组[(233.59± 21.61)ng/L,(102.16± 13.76)ng/L],差

表 2 两组治疗前后血清胃肠激素水平的对比($\bar{x} \pm s$)Table 2 Comparison of the serum levels of gastrointestinal hormones levels between the groups before and after treatment($\bar{x} \pm s$)

Groups	Cases	Time of therapy	MTL(ng/L)	GAS(ng/L)
Control group	55	Before treatment	316.47± 28.73	145.05± 13.64
		After treatment	233.59± 21.61	102.16± 13.76
		t1 value/P value	17.097/0.000	16.417/0.000
Observation group	55	Before treatment	318.35± 27.57	145.52± 13.72
		After treatment	277.96± 25.39	127.21± 12.67
		t2 value/P value	7.992/0.000	7.271/0.000
		t3 value/P value	9.869/0.000	9.932/0.000

Note: t1 and t2 represent the comparison of the levels before and after treatment in the control group and the observation group respectively; the value of t3 represents the comparison of the levels after treatment between the two groups.

2.3 两组治疗前后血清应激激素水平的对比

如表 3 所示, 两组治疗前血清 COR、NE 水平比较差异均无统计学意义($P>0.05$); 治疗后, 两组血清 COR、NE 水平均较组内治疗前明显升高($P<0.05$); 与治疗前对照组相比[(246.43±

40.41)ng/mL、(374.83± 20.68)ng/mL], 观察组血清 COR、NE 水平[(208.01± 33.73)ng/mL、(337.74± 47.72)ng/mL]均显著降低, 差异有统计学意义($P<0.05$)。

表 3 两组治疗前后血清应激激素水平的对比($\bar{x} \pm s$)Table 3 Comparison of the serum levels of stress hormones levels between the groups before and after treatment($\bar{x} \pm s$)

Group	Cases	Time of therapy	COR(ng/mL)	NE(ng/mL)
Control group	55	Before treatment	191.95± 36.81	316.04± 38.98
		After treatment	246.43± 40.41	374.83± 20.68
		t1 value/P value	7.391/0.000	9.755/0.000
Observation group	55	Before treatment	189.65± 35.16	314.02± 39.38
		After treatment	208.01± 33.73	337.74± 47.72
		t2 value/P value	2.794/0.006	2.843/0.005
		t3 value/P value	5.413/0.000	5.289/0.000

Note: t1 and t2 represent the comparison of the levels before and after treatment in the control group and the observation group respectively; the value of t3 represents the comparison of the levels after treatment between the two groups.

3 讨论

自 1987 年开展的第一例腹腔镜胆囊切除术(laparoscopic cholecystectomy, LC)以来, 腹腔镜技术以其创伤小、恢复快等优势在临床上被广泛应用。1991 年, 英国 Jacobs 报道了首例腹腔镜治疗结直肠癌案例, 距今腹腔镜在结直肠癌的治疗上已有 20 余年的历史。随着腹腔镜的应用逐渐增多, 医务人员对技术的掌握愈加娴熟以及腹腔镜技术的不断发展及完善, 腹腔镜治疗的优势愈加突出。NICE 及 NCCN 指南中明确指出腹腔镜辅助方案可作为结肠癌手术的推荐方案^[9-11]。与传统的开腹手术相比, 腹腔镜手术切口较小, 术后伤口愈合及手术疤痕较小, 能够满足患者对体表美观的需求。此外, 腹腔镜手术其操作更为精细, 手术视野更为清晰, 因此对腹腔内血管、神经及组织脏器创伤小, 术后各脏器功能恢复更快, 可明显缩短住院时间。结直肠癌腹腔镜手术已逐渐取代传统的开腹手术方案, 成为当今

手术的主要术式^[12,13]。相关研究表明与传统开腹手术相比, 腹腔镜手术在清扫淋巴结、切除肿瘤的有效性、肿瘤转移率及患者术后生存率方面无显著差异^[14,15]。

MMP-2 和 MMP-9 是基质金属蛋白酶家族(MMPs)中主要成员, 是重要的细胞外基质成分分解降解蛋白酶, 主要通过降解保卫肿瘤细胞的外基质及基底膜, 在肿瘤细胞浸润及迁移过程中起着重要作用^[16,17]。肿瘤细胞突破基质意味着肿瘤的增殖、向正常组织的浸润及转移^[18]。相关研究显示恶性肿瘤患者存在 MMPs 表达增加, 且 MMPs 的表达量与与肿瘤体积、数量、恶性程度及侵袭能力呈显著正相关性^[19-21]。此外, 由于手术过程中操作不娴熟, 或对肿瘤的过渡牵拉等因素均可造成 MMPs 水平的升高, 所以 MMPs 水平测定在一定程度上可反映手术对机体造成的损伤程度^[22]。本研究结果显示两组患者治疗后的血清 MMP-2 和 MMP-9 水平均显著降低, 表明两种方案均是治疗结直肠癌的有效方案, 但腹腔镜组患者 MMP-2 和 MMP-9 水平下

降更为显著,提示腹腔镜手术对肿瘤及周围组织的牵拉作用小,对机体损伤小,其原因可能与腹腔镜手术腹腔内视野清晰、可操作空间较大、操作精确有关。

腹部手术胃肠功能改变受交感神经的影响,手术、麻醉及镇痛药物对胃肠道影响以及胃肠激素改变等多因素影响,其中胃肠激素改变可能最为主要。胃肠激素主要是通过内分泌及神经递质等途径对胃肠功能进行调节。作为胃肠功能状态的主要及有效评估指标,胃肠激素在多种疾病及创伤性研究中应用较多。MTL 和 GAS 均属于兴奋性胃肠激素,前者以促进胃强力收缩,增强小肠分节运动及结肠运动等作用为主,而 GAS 则主要是通过调节胃酸、胃蛋白及胰液分泌,来增强胃肠道运动功能。此外,GAS 还具有促进胃体收缩,加速胃排空等功能。相关研究指出手术创伤可促进儿茶酚胺的分泌,而儿茶酚胺对 MTL 和 GAS 的分泌存在一定的抑制作用,低水平 MTL 和 GAS 可导致机体胃肠功能紊乱,进而影响术后恢复。本研究结果显示与治疗前水平相比,两组患者治疗后 MTL 和 GAS 水平均显著降低,说明手术创伤可导致胃肠功能的降低,但腹腔镜治疗后患者 MTL 和 GAS 水平下降幅度显著低于开腹手术治疗,说明腹腔镜治疗对患者胃肠激素水平影响小,更有利于术后恢复,其原因可能为腹腔镜手术治疗无需绑扎腹带,微创手术对肠功能影响小。

手术引发创伤及疼痛均可导致机体产生全身性非特异性适应反应(即应激反应),应激反应时,机体应激激素异常紊乱,机体应激反应是评估疾病病情及创伤程度的敏感指标,应激激素水平监测对手术疗效及创伤具有极高的临床价值。目前临床上应用较为广泛的应激激素有儿茶酚胺类(肾上腺素、NE、多巴胺)、生长激素、血管紧张素鸡糖皮质激素(皮质酮、COR)等。应激时,机体内糖皮质激素(主要为 COR)及儿茶酚胺类激素释放量会急剧增加,前者主要具有调节机体三大代谢、抗炎、抗过敏等作用,还可多方面抑制机体免疫反应,如破坏及解体 T 淋巴细胞,阶梯阻断 T 淋巴细胞诱导的单核细胞及巨噬细胞募集,诱导中性粒细胞及巨噬细胞凋亡等;后者可促使心跳加快,心输出量增加,收缩内脏血管,扩张冠脉血管等,对免疫功能也存在一定的影响。因此,作为外界干预反应的敏感指标,应激激素水平检测在手术治疗中的研究价值较高,其指标水平不仅可反映手术对机体的创伤程度,评估手术治疗效果,对术后康复效果评价也具有极高价值。本研究结果表明与手术治疗前应激激素水平相比,两种手术方案治疗后患者的应激激素水平均显著升高,然而与治疗前开腹水平相比,腹腔镜治疗后应激激素水平升高幅度显著降低,研究结果与先前报道的内容相一致,进一步证实了腹腔镜手术对患者产生的创伤小,手术不良反应少。

综上所述,开腹手术与腹腔镜手术均是治疗结直肠癌的有效术式,但腹腔镜手术治疗能更有效降低患者基质金属蛋白酶水平,对胃肠激素影响小,机体产生应激反应程度低,更有利于术后康复。

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(上接第 4517 页)

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