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· 专题研究 ·

## 加速康复外科对腹腔镜胃癌根治术患者肿瘤细胞免疫、炎症因子及应激激素的影响

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### 摘要

**背景与目的:** 加速康复外科 (ERAS) 对外科手术患者的益处已被证实, 但是, ERAS 对胃癌根治术患者细胞免疫功能及应激反应在分子水平上的影响仍鲜见报道。本研究探讨 ERAS 理念和措施对腹腔镜胃癌根治术患者肿瘤细胞免疫、炎症因子及应激激素的影响。

**方法:** 纳入 2018 年 1 月—2020 年 12 月行腹腔镜胃癌根治术胃癌患者 90 例, 分为 ERAS 组 (43 例) 和对照组 (47 例)。ERAS 组患者接受 ERAS 理念行围手术期管理, 对照组患者行传统围手术期管理。比较两组在一般资料 (性别、年龄、BMI、ASA 体格情况评估分级、TNM 分期、肿瘤大小), 手术相关指标 (手术方式、吻合方式、手术时间、术中出血量、淋巴结清扫数) 及术后指标 (术后下床活动时间、术后肛门首次排气时间、住院时间及术后并发症) 的差异。比较两组患者术后 1 d 及术后 7 d 两组患者外周血中肿瘤正向免疫调控细胞 (CD3<sup>+</sup>CD4<sup>+</sup>T 细胞、CD3<sup>+</sup>CD8<sup>+</sup>T 细胞、CD16<sup>+</sup>CD56<sup>+</sup>NK 细胞); 负向免疫调控细胞 [中性粒细胞型骨髓源性抑制细胞 (G-MDSC)、单核细胞型骨髓源性抑制细胞 (M-MDSC)、T-调节细胞 (Treg)] 及调节性 B 细胞 (Breg) 细胞数量百分比, 以及两组患者术前及术后 24 h 应激指标皮质醇 (COR)、促肾上腺皮质激素 (ACTH)、肾上腺素 (EPI) 及炎症因子 C 反应蛋白 (CRP)、白细胞介素 6 (IL-6) 水平的差异。

**结果:** ERAS 组与对照组在性别、年龄、BMI、ASA 分级、TNM 分期、肿瘤大小、手术方式、吻合方式、手术时间、术中出血量及淋巴结清扫数方面差异均无统计学意义 (均  $P>0.05$ )。ERAS 组术后下床活动时间和术后肛门首次排气时间均早于对照组 (25.01 h vs. 37.01 h,  $P=0.000$ ; 74.51 h vs. 135.31 h,  $P=0.000$ ), ERAS 组住院时间短于对照组 (7.01 d vs. 9.81 d,  $P=0.000$ )。ERAS 组总术后并发症率小于对照组 (9.3% vs. 19.1%,  $P=0.027$ )。在术后 1 d 及 7 d, ERAS 组 CD3<sup>+</sup>CD4<sup>+</sup>T 细胞、CD3<sup>+</sup>CD8<sup>+</sup>T 细胞、CD16<sup>+</sup>CD56<sup>+</sup>NK 细胞所占百分比高于对照组, 而 G-MDSC、M-MDSC 和 Treg 细胞及 Breg 细胞所占百分比均低于对照组 (均  $P<0.05$ )。两组术前 COR、ACTH、EPI 以及 CRP、IL-6 水平差异均无统计学意义 (均  $P>0.05$ ), 术后 24 h, ERAS 组以上指标的水平均低于对照组 (均  $P<0.05$ )。

**结论:** 围手术期采用 ERAS 理念行腹腔镜下胃癌根治术可降低手术创伤对机体细胞免疫的干扰, 促进肿瘤正向免疫调节同时抑制负向免疫调控, 减轻炎症和应激反应。

### 关键词

胃肿瘤; 胃切除术; 腹腔镜; 快速康复外科; 免疫, 细胞; 炎症; 应激, 生理学

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## Effects of enhanced recovery after surgery on tumor cell immunity, inflammatory factors and stress hormones in patients undergoing laparoscopic radical gastrectomy

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### Abstract

**Background and Aims:** It has been proven that enhanced recovery after surgery (ERAS) offers advantages for patients undergoing surgery. However, the effects of ERAS on cellular immune function and stress response at the molecular level in patients undergoing radical gastrectomy are still rarely reported. Therefore, this study was conducted to investigate the effects of ERAS concept and protocol on tumor cell immunity, inflammatory factors and stress hormones in patients undergoing laparoscopic radical gastrectomy.

**Methods:** From January 2018 to December 2020, 90 patients with gastric cancer undergoing laparoscopic radical gastrectomy were selected and divided into ERAS group (43 cases) and control group (47 cases). The patients in ERAS group received ERAS perioperative management, while those in control group received the traditional perioperative management. The general clinical data (sex, age, BMI, ASA grade, TNM stage, and tumor size), surgery related variables (surgical procedure, anastomosis method, operative time, intraoperative blood loss, and lymph node dissection), and postoperative variables (time to postoperative ambulation, time to postoperative anal gas passage, length of hospitalization, and postoperative complications) were compared between the two groups. The percentages of positive immunoregulatory cells (CD3<sup>+</sup>CD4<sup>+</sup>T cells, CD3<sup>+</sup>CD8<sup>+</sup>T cells and CD16<sup>+</sup>CD56<sup>+</sup>NK cells), negative immunoregulatory cells [granulocytic myeloid-derived suppressor cells (G-MDSC), monocytic myeloid-derived suppressor cells (M-MDSC) and regulatory T cells (Treg)] and regulatory B cells (Breg) in the peripheral blood at 1 and 7 d after operation, as well as the levels of stress response indexes that included cortisol (COR), adrenocorticotropic hormone (ACTH), epinephrine (EPI) and C-reactive protein (CRP) and the inflammatory factors that included the interleukin-6 (IL-6) before and 24 h after operation were compared between the two groups.

**Results:** There was no significant difference in terms of sex, age, BMI, ASA grade, TNM stage, tumor size, surgical procedure, anastomosis method, operative time, intraoperative blood loss and number of lymph node dissection between ERAS group and control group (all  $P > 0.05$ ). Both times to postoperative ambulation and first postoperative anal gas passage in ERAS group were significantly earlier than those in control group (25.01 h vs. 37.01 h,  $P = 0.000$ ; 74.51 h vs. 135.31 h,  $P = 0.000$ ), the length of hospitalization in ERAS group was significantly shorter than that in control group (7.01 d vs. 9.81 d,  $P = 0.000$ ), and the overall incidence rate of postoperative complications in ERAS group was significantly lower than that in control group (9.3% vs. 19.1%,  $P = 0.027$ ). At 1 and 7 d after operation, the percentages of CD3<sup>+</sup>CD4<sup>+</sup>T cells, CD3<sup>+</sup>CD8<sup>+</sup>T cells and CD16<sup>+</sup>CD56<sup>+</sup>NK cells in ERAS group were higher than those in control group, while the percentages of G-MDSC, M-MDSC and Treg cells as well as Breg cells in ERAS group were lower than those in control group (all  $P < 0.05$ ). There was no significant difference in concentrations of COR, ACTH and EPI as well as CRP and IL-6 between ERAS group and control group before operation (all  $P > 0.05$ ), but above parameters were significantly lower in ERAS group than those in control group at 24 h after operation (all  $P < 0.05$ ).

**Conclusions:** Using ERAS concept during perioperative period of laparoscopic radical gastrectomy can decrease the interference of surgical trauma on cellular immunity, enhance the positive immune regulation, inhibit negative immune regulation, and reduce the inflammatory and stress responses.

**Key words**

Stomach Neoplasms; Gastrectomy; Laparoscopes; Enhanced Recovery After Surgery; Immunity, Cellular; Inflammatory; Stress, Physiological

**CLC number:** R753.2

胃癌是常见的消化道肿瘤，也是癌症相关死亡的主要原因。胃癌发病有很强的地域性特点，好发于东亚地区且病死率较高，其中男性每10万中24例死亡，女性每10万中9.8例死亡<sup>[1-2]</sup>。随着胃镜、手术、分子靶向及免疫治疗的进步，早期胃癌生存率大幅改善，但晚期胃癌病死率仍在25%~30%之间<sup>[3]</sup>。由于胃癌患者常伴有营养不良及其他慢性病，传统的围手术期处理常导致较高的术后并发症发生率，12.5%~39%<sup>[4]</sup>。加速康复外科（enhanced recovery after surgery, ERAS）是基于循证医学证据的一系列围手术期多学科技术的综合运用，包括快速通道麻醉、微创技术、最佳镇痛技术及强有力的术后护理（如术后早期进食、运动）等，以达到减轻围手术期患者心理和生理上的应激和炎症反应，改善患者营养和机体免疫状态，达到快速康复的目的<sup>[5-6]</sup>。ERAS在肝胆外科、胃肠外科、减重外科、妇产科及甲乳外科均有应用<sup>[7-8]</sup>。较多研究<sup>[9]</sup>报道ERAS可缩短住院时间、减少住院费用、改善营养状态、加快术后康复、提高生活质量、减少疼痛及改善心理状态。即便如此，加速康复外科对胃癌根治术患者细胞免疫功能及应激反应在分子水平上的影响仍鲜见研究和报道。本文旨在分子水平上研究接受ERAS的胃癌切除手术患者肿瘤正向及负向免疫调控细胞及调节性B细胞（regulatory B cell, Breg）数量变化、对应激反应激素促肾上腺皮质激素（adrenocorticotrophic hormone, ACTH）、皮质醇（cortisol, COR）和肾上腺素（epinephrine, EPI）及对炎症因子C反应蛋白（c-reactive protein, CRP）和白细胞介素6（interleukin 6, IL-6）的影响，以在分子水平上阐述ERAS对胃癌细胞免疫功能、炎症因子及应激反应的影响。

## 1 资料与方法

### 1.1 纳入及排除标准

本研究纳入2018年1月—2020年12月间扬中市人民医院普外科收治的胃癌患者90例，分为ERAS组和对照组。其中ERAS组43例患者在ERAS理念指导下行围手术期管理，对照组47例患者接受常规围术期处理。入组标准：(1)所有研究对象均经病理确诊为胃癌；(2)术前未行放疗和（或）化疗；(3)患者术前未发现明显远处转移，肿瘤分期在T3及以下，可手术切除；(4)患者存在完整的术前检查和术后随访资料；(5)既往无胃镜下胃黏膜剥离手术史或上腹部手术史。剔除标准：(1)患者存在其他部位的恶性肿瘤；(2)接受姑息性手术切除患者；(3)经评估患者无法耐受手术治疗者；(4)中途不能完成研究者；(5)有炎症性或自身免疫性疾病者，如：IBD肠病等。医院同一外科医疗组医师完成两组患者腹腔镜胃癌根治术。本研究方案经医院伦理委员会审查批准。

### 1.2 干预方法

**1.2.1 对照组** 对照组按常规围手术期方案给予术前、麻醉及术后指导。术后2~3 d待首次肛门排气后给予拔除胃管，术后5 d内给予进流食，术后6 d过渡至正常饮食。

**1.2.2 观察组** ERAS理念用于指导观察组患者围手术期处理，其干预措施参考2016版专家共识<sup>[10]</sup>。术前：(1)患者被告知ERAS实施内容，并对患者进行全面心理辅导，降低患者焦虑和紧张情绪，并宣教负面情绪管理，提高医护配合度；(2)术前6 h内禁食，术前2 h饮用≤400 mL碳水化合物，对糖尿病患者口服500 mL果糖溶液；(3)术前无常规胃肠道准备；(4)麻醉后放置胃管，防止术中胃胀气。术中：(1)麻醉成功后导尿；(2)手术操作轻柔仔细，按照ERAS原则轻柔精细操作和麻醉，尽量减少组织损伤，缩短操作时间，减轻创伤应激反应；

(3)保温,维持手术室温度(25±2)℃,患者体温保持≥36℃;(4)液体治疗,按目标导向控制术中和术后液体管理;(5)引流管放置,放置1根腹腔引流管至吻合口;(6)镇痛,采用自控式静脉止痛泵(PCA)+口服非甾体抗炎药,减少阿片类止痛药使用。术后:(1)拔除导尿管时间在术后1d,对前列腺增生患者可依情况口服盐酸坦索罗辛胶囊,0.2mg,1次/d,或延后至术后2~3d拔除导尿管。拔除腹腔引流管时间在术后第2d;(2)术后清醒活动,术后1d沿床边站立慢走,活动时间在1~2h;术后2d活动时间增加至2~4h,以后维持每日活动时间4~6h;(3)手术后当天咀嚼口香糖,饮水量200~300mL,进流食时间在术后1d,术后2d流食量维持在1000~1500mL,术后3d增至2000~2200mL,半流质饮食开始时间为肛门首次排气后;(4)每日补液量随着流质饮食量递减,2000~2500mL为每日总入量,口服入量≥2000mL时,静脉输液即停止。抗生素使用:术前30min和术后当天各使用1次。

1.3 观察指标

1.3.1 手术相关指标 记录并比较两组患者一般资料,包括:性别、年龄、体质量指数(body mass index, BMI)、美国麻醉医师协会(American society of Anesthesiologists, ASA)体格情况评估分级、TNM分期、肿瘤大小;手术相关指标,包括:手术方式、吻合方式、手术时间、术中出血量、淋巴结清扫数;术后指标,包括:术后下床活动时间、术后肛门首次排气时间、住院时间及术后并发症。

1.3.2 循环中T、B细胞免疫相关指标 术后1d和7d清晨抽取患者外周静脉血10mL,取3mL加入CD3、CD4、CD8、CD11b、CD14、CD15、CD16、CD25、CD33、CD56、CD127(美国Invitrogen公司)荧光抗体及破膜剂后,离心,上流式细胞仪检测正向免疫调节细胞(CD3+CD4+T细胞、CD3+CD8+T细胞、CD16+CD56+NK细胞);负向型免疫调节细胞[中性粒细胞型骨髓源性抑制细胞G-MDSC, CD11b+CD15+CD33+CD14-G-MDSC)、单核细胞型骨髓源性抑制细胞(M-MDSC, CD11b+CD15-CD33+CD14+、T-调节细胞(Treg, CD4+CD25+CD127<sup>low</sup>)]及Breg细胞的百分比。

1.3.3 炎症及应激指标 采集ERAS组及对照组患者于术前及术后24h清晨静脉血20mL,离心后取上清,采用化学发光法测定COR、ACTH、EPI浓

度,采用ELISA试剂盒(美国Invitrogen公司)测定CRP及IL-6的浓度。

1.4 统计学处理

数据分析采用SPSS 20.0软件处理,均数±标准差( $\bar{x} \pm s$ )表示正态分布的计量资料,t检验用于组间比较。例数(百分比)[n(%)]用于表示计数资料,组间比较采用 $\chi^2$ 检验或Fisher确切概率法。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 两组研究对象临床资料比较

ERAS组与对照组在性别、年龄、BMI、ASA分级、TNM分期、肿瘤大小、手术方式、吻合方式、手术时间、术中出血量及淋巴结清扫数方面差异均无统计学意义(均 $P > 0.05$ ),具有可比性(表1)。

表1 ERAS组与对照组临床资料比较[n(%)]  
Table 1 Comparison of the general clinical data between ERAS group and control group [n(%)]

参数	ERAS组 (n=43)	对照组 (n=47)	$\chi^2/t$	P
性别[n(%)]				
男	23(53.5)	30(63.8)	0.51	0.42
女	20(46.5)	17(36.2)		
年龄(岁, $\bar{x} \pm s$ )	59.45±10.35	61.24±9.36	-1.73	0.48
BMI(kg/m <sup>2</sup> , $\bar{x} \pm s$ )	21.72±1.57	22.85±1.92	-1.46	0.59
ASA 分级				
I级	21(48.9)	23(48.9)	0.26	0.51
II级	22(51.1)	24(51.1)		
TNM分期[n(%)]				
I期	13(30.2)	13(27.7)	1.37	0.82
II期	20(46.5)	25(53.2)		
III期	10(23.3)	9(19.1)		
肿瘤大小(cm, $\bar{x} \pm s$ )	3.1±1.1	3.2±0.8	0.65	0.78
手术方式[n(%)]				
腹腔镜辅助远端胃切除术	20(46.5)	22(46.8)	2.34	0.62
腹腔镜辅助全胃切除术	23(53.5)	25(53.2)		
吻合方式[n(%)]				
食管空肠Roux-en-Y吻合	23(53.5)	25(53.2)	1.53	0.59
残胃十二指肠Billroth I式吻合	12(27.9)	10(21.3)		
残胃空肠Roux-en-Y吻合	8(18.6)	12(25.5)		
手术时间(min, $\bar{x} \pm s$ )	234.45±21.67	239.54±19.58	1.34	0.22
术中出血量(mL, $\bar{x} \pm s$ )	125.01±50.01	115.05±60.01	0.79	0.44
淋巴结清扫数(枚, $\bar{x} \pm s$ )	24±7	25±6	1.86	0.25

## 2.2 两组患者术后临床参数比较

ERAS组术后下床活动时间和术后肛门首次排气时间均早于对照组[(25.01±3.20) h vs. (37.01±5.81) h,  $t=11.38$ ,  $P=0.000$ ; (74.51±10.81) h vs. (135.31±15.11) h,  $t=12.63$ ,  $P=0.000$ ], ERAS组住院时间短于对照组[(7.01±0.72) d vs. (9.81±0.31) d,  $t=16.40$ ,  $P=0.000$ ] (表2)。

## 2.3 两组患者术后并发症比较

ERAS组伤口感染1例, 肺部感染1例, 胃瘫1例, 吻合口漏1例, 对照组伤口感染3例, 肺部感染3例, 胃瘫1例, 吻合口漏1例, 腹腔脓肿1例, ERAS组

总术后并发症率小于对照组(9.3% vs. 19.1%,  $P=0.027$ ) (表3)。

表2 ERAS组与对照组患者术后临床参数比较( $\bar{x} \pm s$ )

Table 2 Comparison of the postoperative clinical parameters between ERAS group and control group ( $\bar{x} \pm s$ )

组别	术后下床活动时间(h)	术后肛门首次排气时间(h)	住院时间(d)
ERAS组	25.01±3.20	74.51±10.81	7.01±0.72
对照组	37.01±5.81	135.31±15.11	9.81±0.31
$t$	11.38	12.63	16.40
$P$	0.000	0.000	0.000

表3 ERAS组与对照组患者术后并发症对比[n (%)]

Table 3 Comparison of postoperative complications between ERAS group and control group [n (%)]

组别	n	术后并发症					总并发症(%)
		伤口感染	肺部感染	胃瘫	吻合口漏	腹腔脓肿	
ERAS组	43	1(2.3)	1(2.3)	1(2.3)	1(2.3)	0(0.0)	4(9.3)
对照组	47	3(6.4)	3(6.4)	1(2.1)	1(2.1)	1(2.1)	9(19.1)
$\chi^2$	—	—	—	—	—	—	18.37 <sup>1)</sup>
$P$	—	—	—	—	—	—	0.027

注: 1) 采用Fisher确切概率法

Note: 1) Using Fisher's Exact test

## 2.4 两组患者细胞相关免疫指标比较

在术后1 d及7 d, ERAS组肿瘤正向免疫调控细胞(CD3<sup>+</sup>CD4<sup>+</sup>T细胞、CD3<sup>+</sup>CD8<sup>+</sup>T细胞、CD16<sup>+</sup>CD56<sup>+</sup>NK细胞)所占百分比高于对照组(均

$P<0.05$ ) (表4)。ERAS组肿瘤负向免疫调控细胞(G-MDSC、M-MDSC和Treg)所占百分比以及抑制肿瘤免疫相关的Breg细胞所占百分比低于对照组(均 $P<0.05$ ) (表5)。

表4 ERAS组与对照组患者术后1 d和7 d肿瘤正向免疫调控细胞百分比比较(%,  $\bar{x} \pm s$ )

Table 4 Comparison of the percentages of positive immunoregulatory cells between ERAS group and control group at 1 and 7 d after operation (%,  $\bar{x} \pm s$ )

组别	n	CD3 <sup>+</sup> CD4 <sup>+</sup> T细胞		CD3 <sup>+</sup> CD8 <sup>+</sup> T细胞		CD16 <sup>+</sup> CD56 <sup>+</sup> NK细胞	
		术后1 d	术后7 d	术后1 d	术后7 d	术后1 d	术后7 d
ERAS组	43	41.83±5.34	48.83±5.44	27.81±3.12	31.81±4.91	11.12±2.93	14.63±2.23
对照组	47	33.84±5.12	34.12±5.95	21.84±4.44	24.82±5.95	7.83±2.44	10.73±4.13
$t$		4.071	4.587	3.187	4.843	4.431	4.921
$P$		0.011	0.013	0.010	0.021	0.011	0.007

表5 ERAS组与对照组患者术后1 d和7 d肿瘤负向免疫调控细胞百分比比较(%,  $\bar{x} \pm s$ )

Table 5 Comparison of the percentage of negative immunoregulatory cells between ERAS group and control group at 1 and 7 d after operation (%,  $\bar{x} \pm s$ )

组别	n	G-MDSC		M-MDSC		Treg		Breg	
		术后1 d	术后7 d	术后1 d	术后7 d	术后1 d	术后7 d	术后1 d	术后7 d
ERAS组	43	18.83±1.95	14.83±1.87	2.83±0.45	1.93±0.32	3.41±0.29	1.83±0.25	22.89±3.45	18.83±4.75
对照组	47	22.34±1.32	18.33±1.95	4.83±0.95	3.73±1.05	5.86±0.95	4.78±0.65	31.83±2.95	25.73±4.34
$t$		1.591	1.801	1.544	1.348	1.872	1.564	1.570	1.578
$P$		0.016	0.012	0.014	0.013	0.014	0.012	0.017	0.019

## 2.5 两组患者炎症及应激指标的比较

术前, ERAS组COR、ACTH、EPI浓度与对照组差异无统计学意义(均 $P>0.05$ );术后24 h, ERAS组COR、ACTH、EPI浓度均明显低于对照组

(均 $P<0.05$ );术前, ERAS组CRP、IL-6浓度与对照组差异均无统计学意义(均 $P>0.05$ ),术后24 h, ERAS组CRP、IL-6浓度均明显低于对照组(均 $P<0.05$ )(表6)。

表6 ERAS组与对照组手术前后应激及炎症指标比较( $\bar{x} \pm s$ )

Table 6 Comparison of stress and inflammatory indexes between ERAS group and control group before and after operation ( $\bar{x} \pm s$ )

组别	n	COR(nmol/L)		ACTH(pmol/L)		EPI(pmol/L)		CRP(mg/L)		IL-6(ng/L)	
		术前	术后24 h	术前	术后24 h	术前	术后24 h	术前	术后24 h	术前	术后24 h
ERAS组	43	229.58±24.28	304.58±30.26	12.81±1.31	14.16±1.32	30.17±2.57	41.28±3.46	3.65±0.64	49.26±9.37	9.62±1.83	52.46±8.24
对照组	47	227.4±25.31	380.87±37.42	12.52±1.24	17.98±1.56	30.52±2.74	56.37±4.85	3.58±0.74	83.27±13.51	9.74±1.69	73.83±11.46
t		4.126	19.463	3.927	11.376	3.587	16.379	1.347	8.365	1.257	13.482
P		0.732	0.000	0.859	0.029	0.762	0.000	0.745	0.017	0.826	0.032

## 3 讨论

ERAS理念和微创外科技术的有机融合促进外科向更小创伤发展的同时,也降低了手术风险,使得更多患者受益<sup>[11]</sup>。大量证据显示,采用ERAS理念对患者围手术期管理可减轻手术创伤对患者心理、生理功能及应激反应的影响,保护机体器官功能,减少术后并发症的发生并加速患者康复<sup>[12-14]</sup>。顾亚奇等<sup>[15]</sup>报道对因胰头癌接受胰十二指肠切除术的患者行ERAS管理,ERAS组患者术后并发症低于对照组,术后营养指标转铁蛋白、前清蛋白和白蛋白均优于对照组。程康文等<sup>[16]</sup>报道对接受腹腔镜辅助胃癌根治术患者围手术期管理采用ERAS,ERAS组补液量、肛门首次排气时间、排便时间、输液时间、住院时间及总费用均优于常规组,术后血清白蛋白、CRP、IL-6及降钙素原均优于常规组。腹腔镜微创外科和ERAS理念综合运用,可显著降低机体创伤和应激对患者免疫功能的影响<sup>[17]</sup>。

本研究发现ERAS组术后下床活动及肛门排气时间缩短,住院时间缩短,显示ERAS可加速患者康复过程,本研究结果与前人文献报道结果一致<sup>[16, 18]</sup>。关于ERAS方案的Meta分析显示对胃癌患者围手术期采用ERAS管理,可缩短患者住院时间,降低住院费用<sup>[19]</sup>。尽管如此,此前的研究仅限于探讨机体循环中CD4<sup>+</sup>和CD8<sup>+</sup>细胞数目或百分比变化,尚未对循环中T和B细胞免疫功能进行全面研究。

激活肿瘤免疫、杀死肿瘤细胞是机体清除肿瘤细胞的主要途径,而肿瘤细胞可通过多种机制逃避机体免疫系统的捕杀<sup>[20]</sup>。同时手术操作所带

来的机体急性应激和炎症反应可影响免疫应答功能和免疫细胞的分化和成熟<sup>[21]</sup>。T淋巴细胞是机体参与肿瘤免疫反应的重要细胞亚群,CD3<sup>+</sup>是T细胞的共同分子标志物,在成熟过程中可分为CD3<sup>+</sup>CD4<sup>+</sup>和CD3<sup>+</sup>CD8<sup>+</sup>亚群,而CD3<sup>+</sup>CD8<sup>+</sup>亚群作为重要的抗肿瘤细胞系,可分泌包括IL-2和IFN- $\gamma$ 在内的细胞因子,再经MHC-I类分子信号刺激激活成熟为细胞毒性T细胞,对肿瘤产生杀伤作用和并捕杀循环中的肿瘤细胞<sup>[22]</sup>。本研究发现患者在接受胃癌切除术后第1天和7天,与对照组相比,ERAS组患者循环中具有促进肿瘤免疫、消除肿瘤细胞功能的正向免疫调控T细胞数量增多,体现在CD3<sup>+</sup>CD4<sup>+</sup>、CD3<sup>+</sup>CD8<sup>+</sup>和CD16<sup>+</sup>CD56<sup>+</sup>细胞百分比均显著升高,提示ERAS对T细胞免疫干扰影响较小。T细胞中其他亚群,如G-MDSC、M-MDSC和Treg细胞在肿瘤免疫中也发挥重要作用,其可抑制肿瘤免疫,促进肿瘤细胞免疫逃逸,进而导致肿瘤细胞在循环中存活,促进肿瘤远处转移。T细胞免疫受到G-MDSC、M-MDSC和Treg三种细胞的负性调控<sup>[23-24]</sup>。本研究发现在术后第1和7天,与对照组相比,ERAS组患者G-MDSC、M-MDSC和Treg细胞百分比显著降低。提示ERAS对T细胞负向免疫干扰程度低,有利于肿瘤免疫应答。

最近研究认为Breg细胞可在肿瘤免疫中发挥负调控作用,即抑制免疫应答<sup>[25-26]</sup>。本研究发现在术后第1和7天,与对照组相比,ERAS组患者Breg细胞百分比显著降低,结果提示ERAS对Breg细胞功能的影响有利于肿瘤免疫应答并杀伤肿瘤细胞。

麻醉及手术创伤是种应激源,创伤应激反应大小与机体所受的损伤密切相关,麻醉及手术创伤可引起机体代谢、炎症因子释放及激素分泌等

发生变化,进而影响患者术后康复。CRP是机体经创伤和炎症反应后释放的非特异性急性时相蛋白,CRP浓度与创伤及应激反应密切相关,术后CRP浓度可用于反映围手术期创伤程度大小<sup>[27]</sup>。IL-6由单核细胞、巨噬细胞和内皮细胞分泌并激活,在手术创伤和应激刺激下,IL-6浓度与创伤严重程度正相关<sup>[28]</sup>。本研究结果发现CRP及IL-6浓度在术前差异无统计学意义,而在术后24h,ERAS组CRP及IL-6浓度低于对照组,提示ERAS可减少围手术期患者创伤,这与程康文<sup>[16]</sup>等人研究结果类似。

手术应激及炎症因子能抑制机体的免疫功能,同时手术应激可激活交感神经系统和下丘脑-垂体-肾上腺轴并诱导神经内分泌反应,促进应激激素,如儿茶酚胺、促肾上腺皮质激素的释放<sup>[29]</sup>,同时严重的手术创伤及应激反应易导致切口感染、肺部感染、尿潴留和尿失禁等并发症的发生<sup>[30]</sup>。COR、ACTH及EPI是常见的应激反应标志物,ERAS组COR、ACTH及EPI与对照组在术前差异无统计学意义,而在术后24h,ERAS组COR、ACTH及EPI浓度低于对照组,这在分子水平上表明ERAS可显著减少患者术后应激反应,使患者处于较温和的生理环境中,便于术后胃肠功能快速恢复。从两组术后并发症率比较来看,ERAS组总术后并发症率也低于对照组,提示ERAS可显著减轻患者术后应激程度,这也解释了ERAS组患者术后下床时间、术后首次肛门排气时间、住院时间短于对照组,ERAS组术后并发症率低于对照组的原因。

诚然,本研究在实施过程中积累了一定的经验,也存在一定的不足:首先,ERAS强调术后早期拔除导尿管及腹腔引流管,对于术后恢复情况良好,无腹腔内出血、脓肿及尿储留等并发症的患者给予术后早起拔除导尿管及腹腔引流管。其次,但对于有排尿困难、前列腺增生的患者适当的给予延迟留置导尿管,并口服盐酸坦索罗辛胶囊治疗。对于伴吻合口漏、腹腔脓肿等并发症的患者,在经过对引流物及腹部CT复查后,综合评估无异常后方给予拔除。最后,由于本研究是单中心研究,不可避免的存在一定的选择偏倚,值得更大规模的多中心研究。

综上所述,围手术期采用ERAS理念行腹腔镜下胃癌根治术可降低手术创伤对机体细胞免疫的干扰,促进肿瘤正向免疫调控,抑制肿瘤负向免疫调控,减少术后并发症,减少机体应激反应及炎症因子释放,有助于患者快速康复。

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