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内镜黏膜下剥离术治疗早期胃癌的疗效及对患者预后和血清抗凋亡因子、表皮生长因子的影响*

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摘要 目的:探讨内镜黏膜下剥离术(ESD)治疗早期胃癌(EGC)的疗效及对患者预后和血清抗凋亡因子(Livin)、表皮生长因子(EGF)的影响。**方法:**选取我院于2014年1月~2015年12月期间收治的EGC患者98例为研究对象,根据随机数字表法将患者分为对照组(n=32)和研究组(n=66),对照组给予腹腔镜微创手术治疗,研究组患者给予ESD治疗,比较两组患者术后临床指标,比较两组患者手术前后血清Livin、EGF水平,观察两组患者术中及术后并发症发生情况,随访2年,记录两组患者随访期间的生存率及复发率。**结果:**研究组患者手术时间、住院时间均较对照组短,住院费用、术中出血量均较对照组少($P<0.05$),但两组患者整块切除率、治愈性切除率比较差异无统计学意义($P>0.05$)。两组患者术后血清Livin、EGF水平均较术前降低,且研究组低于对照组($P<0.05$)。研究组术中及术后并发症总发生率为3.03%(2/66),低于对照组的15.63%(5/32)($P<0.05$)。两组患者随访期间生存率、复发率比较无统计学差异($P>0.05$)。**结论:**ESD治疗EGC的预后效果与腹腔镜微创手术相当,但其能够更有效地降低血清Livin、EGF水平,加快患者的恢复,并发症少,临床应用价值较高。

关键词:内镜黏膜下剥离术;早期;胃癌;疗效;预后;抗凋亡因子;表皮生长因子

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Efficacy of Endoscopic Submucosal Dissection for Early Gastric Cancer and Its Influence on Prognosis, Serum Anti-apoptotic Factor and Epidermal Growth Factor*

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ABSTRACT Objective: To investigate the efficacy of endoscopic submucosal dissection (ESD) in the treatment of early gastric cancer (EGC) and its influence on prognosis, serum anti-apoptotic factor (Livin) and epidermal growth factor (EGF). **Methods:** 98 patients with EGC who were admitted to our hospital from January 2014 to December 2015 were selected as the research objects. According to the digital table method, the patients were randomly divided into control group (n=32) and research group (n=66). The control group received laparoscopic minimally invasive surgery, and the research group was given ESD treatment. The clinical indicators of the two groups were compared. The serum levels of Livin and EGF were compared before and after operation. The complications during and after operation were observed. The two groups were followed up for 2 years. The survival rate and recurrence rate were observed. **Results:** The operation time and hospitalization time of the research group were shorter than those of the control group, and the hospitalization expenses and intraoperative bleeding volume were less than those of the control group ($P<0.05$), but there were no significant differences in the total resection rate and the cure resection rate between the two groups ($P>0.05$). The levels of serum Livin and EGF in both groups were lower than those before operation, and the level of Livin and EGF in the research group was lower than those in the control group ($P<0.05$). The total incidence rate of intraoperative and postoperative complications in the research group was 3.03%(2/66), which was significantly lower than that in the control group 15.63%(5/32)($P<0.05$). There were no significant differences in survival rate and recurrence rate between the two groups during the follow-up period ($P>0.05$). **Conclusion:** The prognostic effect of ESD on EGC is similar to that of laparoscopic minimally invasive surgery, but it can effectively reduce the level of serum Livin and EGF, accelerate the recovery of patients, reduce complications, and have high clinical value.

Key words: Endoscopic submucosal dissection; Early; Gastric cancer; Efficacy; Prognosis; Serum anti-apoptotic factor; Epidermal growth factor

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前言

早期胃癌(Early gastric cancer, EGC)是指癌组织位于胃黏膜层及黏膜下层,且不论其范围大小以及有无淋巴结转移的一类疾患,是我国的多发病、常见病^[1-3]。随着社会老龄化、人们生活方式的改变,EGC的发病率逐年升高,且呈年轻化趋势,严重危害人类健康^[4]。由于EGC病变范围只局限于黏膜或黏膜下层,如能在早期得到有效治疗,很大程度上可降低患者死亡率,改善患者预后。近年来随着内镜技术的发展,EGC早期诊断率逐年上升,在其基础上发展的腹腔镜微创手术及内镜黏膜下剥离术(Endoscopic submucosal dissection, ESD),具有一次性完全整块切除或剥离病变、微创、减少组织残留复发等优势,逐渐获得国内外临床医师的认可^[5-7]。本研究对我院收治的EGC患者分别行腹腔镜微创手术以及ESD,观察两组手术效果,以期选择合适的临床术式提供参考,现报道如下。

1 资料与方法

1.1 临床资料

选取我院于2014年1月~2015年12月期间收治的EGC患者98例为研究对象,纳入标准:(1)均行内镜及病理学检查确诊为EGC;(2)胸腹部CT显示未见淋巴结转移;(3)肿瘤直径 ≤ 30 mm,无溃疡糜烂;(4)患者及其家属知情本次研究并已签署同意书;(5)均具备手术指征者。排除标准:(1)合并凝血功能障碍者;(2)合并心肝肾等脏器功能障碍者;(3)合并其他恶性肿瘤者;(4)术前诊断为EGC,但术后病理证实已侵犯肌层及以下;(5)既往有腹部手术史者;(6)合并精神疾患无法配合本次研究者;(7)随访期间失联者。根据随机数字表法将患者分为对照组($n=32$)和研究组($n=66$),其中对照组男13例,女19例,年龄48~76岁,平均 (63.29 ± 3.48) 岁;病程1~5年,平均 (2.37 ± 0.46) 年;肿瘤直径0.8~2.0 cm,平均 (1.13 ± 0.18) cm;肿瘤部位:胃底及贲门8例,胃角12例,胃窦12例;浸润深度:粘膜内癌18例,粘膜下癌14例;病理类型:低分化5例,中分化11例,高分化16例。研究组男30例,女36例,年龄50~78岁,平均 (64.09 ± 4.22) 岁;病程1~6年,平均 (2.44 ± 0.53) 年;肿瘤直径0.6~1.9 cm,平均 (1.08 ± 0.13) cm;肿瘤部位:胃底及贲门16例,胃角28例,胃窦22例;浸润深度:粘膜内癌31例,粘膜下癌35例;病理类型:低分化11例,中分化20例,高分化35例。两组患者临床资料比较无差异($P>0.05$)。

1.2 治疗方法

对照组患者给予腹腔镜微创手术,常规禁饮食、全麻,取平卧位,于脐孔处穿刺,气腹压力维持15 mmHg,取4个穿刺套管操作器械,经左右中上腹部切口置入,根据患者病灶位置大小选择胃切除方式,所有患者均采用全腹腔镜内手术吻合。研究组患者给予ESD,具体操作如下:(1)环周标记:采用染色或放大内镜等方法,于距离病变边界处约3~5 mm处使用电刀进行标记,两个标记点间隔约为2 mm;(2)黏膜下注射:取由远至近的顺序,在病变周围进行多点黏膜下注射,分离黏膜层与固有肌层;(3)环形切开:病变充分抬举后,使用电刀在标记点外约3 mm处,由远端开始环周切开病变黏膜;(4)黏膜下剥离:采用电刀于病变下方进行黏膜剥离,直至完全剥离,剥离过程中使用混合液反复注射,以确保剥离层处于粘膜下层。黏膜完全剥离后,采用电热止血钳对显露的血管进行凝固。两组术后给予常规止血、补液抗感染等治疗。

1.3 观察指标

(1)比较两组患者术后临床指标,包括手术时间、住院时间、住院费用、术中出血量、整块切除率、治愈性切除率。其中整块切除标准:一次性切除大部分病灶,治愈性切除标准:病变黏膜完全切除且其水平及基底切缘均未见肿瘤细胞。(2)于术前、术后采集患者外周静脉血4 ml,枸橼酸抗凝,2800 r/min离心10 min,以6 cm为离心半径,取上清液置于-80℃冰箱中待测。血清抗凋亡因子(Livin)、表皮生长因子(Epidermal growth factor, EGF)水平的检测采用酶联免疫吸附试验,试剂盒购于上海酶联生物科技有限公司,严格遵守试剂盒说明书进行操作。(3)观察两组术中及术后并发症发生情况,包括出血、术后穿孔、感染等,采用电话询问以及门诊复查等方式对所有患者进行为期2年的随访,记录两组患者随访期间的生存率及复发率。

1.4 统计学方法

研究数据录入SPSS25.0软件处理,计量资料用 $(\bar{x} \pm s)$ 表示,行t检验,计数资料以率(%)表示,行 χ^2 检验, $\alpha=0.05$ 设置成检验标准。

2 结果

2.1 两组患者术后临床指标情况

研究组患者手术时间、住院时间均短于对照组,术中出血量、住院费用少于对照组($P<0.05$),但两组患者整块切除率、治愈性切除率比较差异无统计学意义($P>0.05$),详见表1。

表1 两组患者术后临床指标情况

Table 1 Postoperative clinical indicators in two groups

Groups	Operation time (min)	Hospitalization time(d)	Hospitalization expenses(ten thousand yuan)	Intraoperative bleeding volume (mL)	Total resection rate (%)	Cure resection rate (%)
Control group($n=32$)	125.79 $\pm$ 7.65	12.67 $\pm$ 2.95	2.23 $\pm$ 0.25	167.53 $\pm$ 61.87	31(96.88)	30(93.75)
Research group($n=66$)	73.26 $\pm$ 8.02	6.14 $\pm$ 1.79	1.71 $\pm$ 0.36	138.98 $\pm$ 58.95	63(95.45)	62(93.94)
t/χ^2	30.859	13.585	7.348	2.212	0.111	0.004
P	0.000	0.000	0.000	0.029	0.739	0.971

2.2 两组患者手术前后 Livin、EGF 水平比较

术前两组患者血清 Livin、EGF 水平比较无差异($P>0.05$),

两组患者术后血清 Livin、EGF 水平均低于术前,且研究组较对照组低($P<0.05$),详见表2。

表 2 两组患者手术前后 Livin、EGF 水平比较($\bar{x} \pm s$)Table 2 Comparison of Livin and EGF levels before operation and after operation in two groups($\bar{x} \pm s$)

Groups	Livin($\mu\text{mol/L}$)		EGF($\mu\text{g/L}$)	
	Before operation	After operation	Before operation	After operation
Control group(n=32)	12.09 $\pm$ 1.94	9.31 $\pm$ 0.69*	1.73 $\pm$ 0.85	1.31 $\pm$ 0.51*
Research group(n=66)	11.98 $\pm$ 1.87	6.67 $\pm$ 0.71*	1.69 $\pm$ 0.96	0.93 $\pm$ 0.34*
t	0.270	17.418	0.201	4.379
P	0.788	0.000	0.841	0.000

Note: Compared with before operation, * $P < 0.05$.

2.3 两组术中及术后并发症发生情况比较

对照组的 15.63%(5/32)($P < 0.05$), 详见表 3。

研究组术中及术后并发症总发生率为 3.03%(2/66), 低于

表 3 两组术中及术后并发症发生情况比较[n(%)]

Table 3 Comparisons of intraoperative and postoperative complications between the two groups[n(%)]

Groups	Bleeding	Postoperative perforation	Infect	Total incidence rate
Control group(n=32)	3(9.38)	0(0.00)	2(6.25)	5(15.63)
Research group(n=66)	2(3.03)	0(0.00)	0(0.00)	2(3.03)
χ^2				5.263
P				0.023

2.4 两组患者随访期间生存率、复发率情况

($P > 0.05$), 详见表 4。

两组患者随访期间生存率、复发率比较无统计学差异

表 4 两组患者随访期间生存率、复发率情况[n(%)]

Table 4 Survival rate and recurrence rate during follow-up in two groups[n(%)]

Groups	Survival rate		Recurrence rate	
	Follow up for 1 year	Follow up for 2 years	Follow up for 1 year	Follow up for 2 years
Control group(n=32)	32(100.00)	30(93.75)	0(0.00)	1(3.13)
Research group(n=66)	66(100.00)	63(95.45)	0(0.00)	2(3.03)
χ^2	0.000	0.129	0.000	0.001
P	1.000	0.719	1.000	0.980

3 讨论

近年来随着内镜技术的成熟,EGC 的诊断率逐年升高,据相关报道统计,EGC 的诊断率已由 5%提高至 40%~50%,且其术后 5 年生存率高达 90%,大大的提高了患者术后生存质量^[8,9]。以腹腔镜为主的微创技术应用于腹部手术,其优势已得到广泛认可^[10-12],然而关于腹腔镜微创手术能否达到早期胃癌的根治效果,且不增加肿瘤细胞转移尚存在一定争议。ESD 是一种采用高频电原理,一次性完整剥离病灶黏膜部位的新型治疗措施,该术式的出现颠覆了癌前病变、EGC 以及胃肠道间质瘤等消化道疾病仅仅局限于腹部手术的现状^[13,14],但 ESD 作为内镜治疗要求较高的一类微创手术,对操作医生要求具备丰富的消化内镜及手术经验,还要求患者本身具有较高适用征^[15-17],故而本研究设置对照试验,以期为 EGC 术式选择提供相关数据支持。

本研究显示,研究组患者手术时间、住院时间、术中出血

量、住院费用均少于对照组,提示 ESD 相较于腹腔镜微创手术,其优势更为显著。Friedel D 等人^[18]认为,EGC 内镜治疗可获得与传统手术相似的治愈率,且对组织损伤小,患者负担轻,术后生活质量明显提升,这与本次研究结果基本一致。ESD 术式在治疗过程中借助针状切刀或者钩型刀切开黏膜以暴露病灶,且联合混合液注射以促进病灶剥离,缩短操作时间,加之其作为微创手术,切口较小,有效减少术中出血量,患者术后恢复迅速,减少住院时间、住院费用,减轻患者身心及经济上的负担^[19-21]。同时本研究中两组患者整块切除率、治愈性切除率比较无差异,这可能是由于腹腔镜微创手术可最大限度的切除病灶并有效减少病灶残留,同时 ESD 亦可一次性切除大范围病灶,尽量排除淋巴结转移以减少病灶残留^[22-24]。本次研究结果还表明,两组患者术后血清 Livin、EGF 水平均较术前降低,且研究组低于对照组,其中 Livin 是重要的抗细胞凋亡因子,通过阻断凋亡受体及线粒体相关的凋亡途径来发挥抗凋亡作用,其在消化道肿瘤的发生发展起重要作用^[25,26];EGF 与肿瘤的增殖、侵袭

以及转移有关,同时还可抑制肿瘤细胞凋亡^[27,28]。郭霄梅等人^[29]研究证实,早期胃癌患者血清 Livin、EGF 水平均较高,ESD 在降低血清 Livin、EGF 水平中效果更为明显,再一次证实了 ESD 可将病灶黏膜部位一次性完整剥离,且其效果优于腹腔镜微创手术。研究组术中及术后并发症总发生率低于对照组,ESD 在内镜操作下可减少患者损伤,降低患者出血风险,一定程度上降低了并发症的发生几率。本研究中研究组患者复发人数多于对照组,但两组比较无统计学差异。刘晓等学者^[30]研究表明,EGC 术后短期临床效果 ESD 组优于外科组,然而对于长期临床效果,ESD 组术后复发风险高于外科组,这与本次研究结果报道不一致,可能与本次研究样本量偏小或者随访时间太短有关,其准确的生存率、复发率比较有待进一步的大样本量以及延长随访时间的试验来验证。

综上所述,针对 EGC 患者,ESD 术后预后效果与腹腔镜微创手术治疗相当,但其在降低血清 Livin、EGF 水平、并发症发生率、改善部分临床指标等方面效果更为显著,故临床医师在全面评估 EGC 患者手术适应征的情况下,行 ESD 具有一定的安全性和有效性。

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