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依泽替米贝辅助腹腔镜微创术联合治疗胆囊结石患者对炎症因子及血清 CCK-A 表达的影响 *

黄怀银 刘昌军 周 宁 郭 超 李 佳 何自力[△]

(湖南省人民医院(湖南师范大学第一附属医院) 湖南 长沙 410005)

摘要 目的:探讨依泽替米贝辅助腹腔镜微创术联合治疗胆囊结石患者对炎症因子及胆囊收缩素 A(Cholecystokinin-A, CCK-A)表达的影响。**方法:**以 2016 年 2 月-2018 年 2 月我院收治的 100 例胆囊结石患者作为研究对象,按随机数字表法分为对照组(腹腔镜微创术)和观察组(腹腔镜微创术+依泽替米贝),每组各 50 例。观察并比较治疗前后两组患者临床疗效、胆囊结石数量和直径的变化、炎症因子 TNF- α 、IL-1 水平以及血清 CCK-A 水平的变化。**结果:**术后观察组感染 2 例,胰腺炎 1 例,观察组发生感染 3 例,两组患者并发症发生情况差异无统计学意义($P < 0.05$),观察组患者的治疗有效率明显高于对照组(94.0% vs 58.0%)($P < 0.05$);治疗前两组患者胆囊结石平均数量、直径差异无统计学意义($P > 0.05$),治疗后观察组和对照组患者胆囊结石数量(5.16 ± 2.35 vs 9.18 ± 2.82)、直径(0.78 ± 0.29 cm vs 1.26 ± 0.36 cm)明显降低,观察组低于对照组($P < 0.05$);治疗前两组患者血清 TNF 和 IL-1 水平无明显差异($P > 0.05$),治疗后观察组和对照组患者血清 TNF- α [15.28 ± 4.28 (ng/mg) vs 22.19 ± 5.02 (ng/mg)], IL-1 [63.38 ± 8.27 (μ g/mg) vs 89.59 ± 7.39 (μ g/mg)]水平明显降低,且观察组明显低于对照组($P < 0.05$);治疗前两组患者血清 CCK-A 水平无明显差异($P > 0.05$),治疗后观察组和对照组患者血清 CCK-A 水平 [121.36 ± 10.47 (ng/mg) vs 115.39 ± 10.39 (ng/mg)]明显升高,且观察组高于对照组($P < 0.05$)。**结论:**依泽替米贝辅助腹腔镜微创术能有效减少胆囊结石患者的结石数量、降低结石直径,并且可以降低患者血清炎症因子水平,促进 CCK-A 表达,减轻胆囊炎症反应,缓解患者痛苦,有较好的临床效果。

关键词:胆囊结石;依泽替米贝;腹腔镜微创术;CCK-A

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Effect of Ezetimibe-assisted Laparoscopic Minimally Invasive Surgery on Inflammatory Factor and Serum CCK-A Expression in Patients with Cholecolithiasis*

HUANG Huai-yin, LIU Chang-jun, ZHOU Ning, GUO Chao, LI Jia, HE Zi-li[△]

(Hunan Provincial People's Hospital/The First Affiliated Hospital of Hunan Normal University, Changsha, Hunan, 410005, China)

ABSTRACT Objective: To investigate the effect of ezetimibe-assisted laparoscopic minimally invasive surgery on inflammatory factors and serum CCK-A expression in patients with gallstones. **Methods:** 100 patients with gallstones admitted to our hospital from February 2016 to February 2018 were divided into control group (laparoscopic minimally invasive surgery) and observation group (laparoscopic minimally invasive surgery + ezetimibe), 50 cases in each group. The clinical efficacy, the number and diameter of gallstones, the levels of TNF- α , IL-1 and serum CCK-A were observed and compared before and after treatment. **Results:** There were 2 cases of infection, 1 case of pancreatitis and 3 cases of infection in the observation group and there was no significant difference in complications between the two groups ($P < 0.05$). After operation, the effective rate of the observation group was higher than that of the control group (94.0% vs 58.0%). Before taking medicine, there was no significant difference in the average number and diameter of gallstones between the two groups; after four weeks of treatment, the number of gallstones in the observation group and the control group (5.16 ± 2.35 vs 9.18 ± 2.82) and the diameter of gallstones (0.78 ± 0.29 cm vs 1.26 ± 0.36 cm) in the observation group and the control group were increased and the observation group was higher than the control group. There was no significant difference in the levels of serum TNF- α and IL-1 between observation group and control group before treatment. After four week of treatment, the levels of serum TNF- α (15.28 ± 4.28 ng/mg vs 22.19 ± 5.02 ng/mg) and IL-1 (63.38 ± 8.27 μ g/mg vs 89.59 ± 7.39 μ g/mg) in the observation group were lower than those in the control group. There was no significant difference in serum CCK-A level between the two groups before treatment; after four week of treatment, the serum CCK-A level of the observation group and the control group increased significantly and the observation group was higher than the control group. **Conclusion:** Ezetimibe-assisted laparoscopic minimally invasive surgery can effectively reduce the number and diameter of gallstones in patients with gallstones, reduce the level of serum inflammatory factors, promote the expression

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作者简介:黄怀银(1984-),男,住院医师,硕士研究生,研究方向:肝胆外科

[△] 通讯作者:何自力,男,主任医师

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of CCK-A, alleviate gallbladder inflammation, alleviate the pain of patients, and has a good clinical effect.

Key words: Cholecystolithiasis; Ezetimibe; Minimally invasive laparoscopy; CCK-A

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前言

胆囊结石是肝胆外科常见的疾病,常可引发胆囊炎症,其发病机制与饮食、体脂率、雌激素水平等因素相关。近年来,随着人们生活水平及肥胖率的不断提高,胆囊结石的发病率正逐年攀升^[1-3]。腹腔镜保胆取石术具有对患者损伤较小,且术后不良反应和并发症少的特点,成为临床的主要治疗方案之一。但是对于结石数量较多且体积较大的患者单纯手术的治疗效果并不理想,因此药物治疗辅助镜下取石的治疗方案越来越受到重视^[4]。其中依泽替米贝是一种新型调脂药物,能够通过阻断肠道对胆固醇的吸收从而减少胆汁中胆固醇含量,达到抑制胆固醇结晶形成的目的^[5]。CCK-A是由小肠粘膜分泌的一种激素,可促进胆囊收缩和胆汁排出^[6,7]。有研究表明^[8],胆囊结石患者血CCK受体表达明显降低,导致此类患者胆囊排空延迟,易于造成胆囊残渣淤积。监测患者CCK-A水平可评估患者胆囊收缩功能,对评价患者术后胆囊功能、预测胆囊结石复发的风险有重要意义。故本研究探讨依泽替米贝辅助腹腔镜微创术联合治疗胆囊结石患者对炎症因子及血清CCK-A表达的影响。

1 资料和方法

1.1 一般资料

选取2016年2月-2018年2月我院收治的100例胆囊结石患者,观察组和对照组各50例。纳入标准:(1)符合胆囊结石诊断标准患者^[9],①右上腹或右中腹绞痛,或放射至肩胛区,偶有黄疸、发烧。②胆囊区有轻压痛或叩击痛或墨菲征阳性。③超声可见胆囊壁粗糙增厚,胆囊内可见结石。凡具备①、②两项,且具备③、④项中任意一项者,即可诊断。(2)近6个月内未用过该方案相关药物治疗者;(3)胆囊收缩功能良好,胆囊收缩功能大于30%;(4)术前胆囊壁厚度<4cm;(5)自愿参与本研究,并签署知情同意书。排除标准:(1)有腹腔镜手术禁忌证者;(2)本次入院有急性胆囊炎表现或胆囊结石出现梗阻、嵌顿等外科急诊手术指征者;(3)既往合并有肺、肾、肝等脏器功能性疾病;(4)妊娠或哺乳期女性;(5)合并有恶性肿瘤者。观察组男19例,女31例,平均年龄(48.5±7.2)岁;对照组男18例,女32例,平均年龄(48.3±6.9)岁。两组性别、年龄比较无统计学差异($P>0.05$),本研究经我院伦理委员会批准。

1.2 治疗方法

对照组患者采用常规溶石疗法,服用消炎利胆片(广州白

云山和记黄埔中药有限公司,批准文号:国药准字Z44022243),6片/次,每天3次。观察组患者在对照组治疗基础上加用依泽替米贝(武汉联合药业有限责任公司,批准文号:国药准字Z20110032),10mg/次,每日1次。两组患者均治疗4周。治疗4周后对两组患者行胆囊结石微创术,腹腔镜探查以了解患者胆囊及周围炎症情况,并取出胆囊结石。术后予以两组患者常规护理干预,密切观察患者心率、血压、呼吸、体温等情况,常规应用抗生素,术后第1-3天口服33%硫酸镁10mL,每日3次。

1.3 观察指标

1.3.1 临床疗效 术后比较两组患者治疗效果(有效、显效、无效),计算总有效率。有效:临床主要症状(右上腹绞痛,黄疸,腹胀等)消失和(或)结石数量减少1/3以上;显效:临床主要症状明显减轻和(或)结石数量减少1/4以上;无效:未达到上述标准。总有效率=(有效例数+显效例数)/总例数×100%^[9]。

1.3.2 胆囊结石数量、直径 治疗前通过彩超测量并记录患者胆囊内结石数量和直径。治疗4周后行胆囊结石微创手术取出结石,测量并记录结石的数量和直径。

1.3.3 炎症因子指标 分别于治疗前和治疗后抽取患者空腹静脉血10mL,3000r/min离心取上清,行酶联免疫吸附试验法检测血清TNF、IL-1水平。

1.3.4 CCK-A水平 分别于治疗前和治疗后取患者空腹静脉血5mL,3000r/min离心取上清,采用放射免疫法检测血清CCK-A水平。

1.3.5 安全性评价及不良反应 治疗前和治疗后4周检测两组患者血常规、尿常规、便常规、肝肾功能、心电图。观察并记录治疗过程中,患者是否存在腹胀、恶呕、腹泻等消化道不良反应。

1.4 统计学分析

本研究采用SPSS 19.0软件对数据进行统计学分析。计数资料以率[n(%)]的形式表示,比较采用 χ^2 检验;计量资料以均数±标准差($\bar{x} \pm s$)表示,比较采用配对资料t检验或独立资料t检验,检验标准 $\alpha=0.05$, $P<0.05$ 表示差异有统计学意义。

2 结果

2.1 疗效比较

术后观察组感染2例,胰腺炎1例,观察组发生感染3例,两组患者并发症发生情况差异无统计学意义($P<0.05$),观察组胆囊结石患者的治疗有效率为94.0%,高于对照组的58.0%($P<0.05$)。见表1。

表1 两组患者疗效比较(例)

Table 1 Comparison of curative effect between two groups (case)

Groups	Number of cases	Effective	Significant effece	Invalid	Effective rate
control group	50	14	15	21	58.00
Observation group	50	35	12	3	94.00
u/χ^2			$u=4.700$		$\chi^2=19.880$
P			$P<0.001$		$P<0.001$

2.2 胆囊结石数量、直径比较

治疗前两组患者胆囊结石平均数量、直径比较无统计学意

义($P>0.05$), 治疗后观察组和对照组患者胆囊结石数量、直径

均降低, 观察组结石数量、直径均低于对照组($P<0.05$)。见表 2。

表 2 两组患者治疗前后胆囊结石数量、直径比较($\bar{x} \pm s$)Table 2 Comparison of the number and diameter of gallstones between the two groups before and after treatment($\bar{x} \pm s$)

Groups	Number of cases	Number of stones (individual)		t	P	Stone diameter		t	P
		Before treatment	After treatment			Before treatment	After treatment		
Control group	50	10.20± 2.41	9.18± 2.82	1.948	0.054	2.64± 1.05	1.26± 0.36	8.791	<0.001
Observation group	50	10.28± 2.39	5.16± 2.35	10.801	<0.001	2.63± 1.02	0.78± 0.29	12.336	<0.001
t		0.167	7.744			0.048	7.342		
P		0.868	<0.001			0.962	<0.001		

2.3 TNF 和 IL-1 水平比较

治疗前, 两组患者血清 IL-1 和 TNF 水平无明显差异($P>0.05$),

治疗 4 周后两组患者血清 TNF 和 IL-1 水平均明显降低($P<0.05$),

且观察组低于对照组($P<0.05$)。见表 3。

表 3 两组患者治疗前后 TNF 和 IL-1 水平比较($\bar{x} \pm s$)Table 3 Comparison of TNF and IL-1 levels between two groups before and after treatment($\bar{x} \pm s$)

Groups	number of cases	TNF (ng/mg)		t	P	IL-1 (μg/mg)		t	P
		Before treatment	After treatment			Before treatment	After treatment		
control group	50	26.31± 4.36	22.19± 5.02	4.190	<0.001	103.09± 3.38	89.59± 7.39	11.747	<0.001
Observation group	50	25.47± 4.92	15.28± 4.28	11.049	<0.001	104.27± 3.57	63.38± 8.27	32.099	<0.001
t		0.470	7.407			1.697	16.711		
P		0.479	<0.001			0.093	<0.001		

2.4 CCK-A 水平比较

治疗前两组患者血清 CCK-A 水平无明显差异($P>0.05$),

治疗后观察组和对照组患者血清 CCK-A 水平均明显升高, 且

观察组高于对照组($P<0.05$)。见表 4。

表 4 两组患者治疗前后 CCK-A 水平比较($\bar{x} \pm s$)Table 4 Comparison of CCK-A level between two groups before and after treatment($\bar{x} \pm s$)

Groups	number of cases	CCK-A (ng/mL)		t	P
		before treatment	after treatment		
control group	50	104.27± 12.39	115.39± 10.39	4.863	<0.001
Observation group	50	102.47± 11.93	121.36± 10.47	8.415	<0.001
t		0.740	2.862		
P		0.461	0.005		

2.5 安全性评价及不良反应

治疗前后两组患者血常规、尿常规、便常规、肝肾功能、心电图均无明显改变。治疗过程中观察组发生腹胀 1 例、恶心呕吐 2 例、腹泻 1 例, 不良反应发生率为 8.00%; 对照组发生腹胀 1 例、恶心呕吐 1 例、腹泻 1 例, 不良反应发生率为 6.00%, 差异比较无统计学意义。

3 讨论

胆囊结石是肝胆外科常见的疾病, 女性患病率高于男性, 其发病与生活、饮食习惯、雌激素的使用等因素有关^[11,12]。腹腔镜

镜保胆取石术保留了胆囊, 对患者损伤较小, 减少了胆总管损伤带来的手术并发症, 明显提高了患者术后的生活质量, 成为临床的主要治疗方案之一^[13,14]。但是对于结石数量较多且体积较大的患者单纯手术的治疗效果并不理想, 因此药物治疗辅助镜下取石的治疗方案越来越受到重视。有研究检测到^[15,16], 依泽替米贝能够上调低密度脂蛋白受体和甾醇调控元件结合蛋白 2 的表达, 进一步促进肝细胞摄取低密度脂蛋白胆固醇。作为一种新型的降脂药物, 依泽替米贝可抑制小肠对胆固醇的吸收, 从而减少胆汁中胆固醇含量, 达到使结石溶解甚至消失的目的^[17,18]。

本研究结果显示,观察组患者总有效率在治疗后优于对照组,且观察组结石数目和直径均明显低于对照组,说明依泽替米贝辅助腹腔镜微创治疗可有效减少胆固醇结石患者的结石数量和直径,缓解患者症状。胆囊结石患者胆汁中的胆固醇含量达到过饱和状态后从胆汁中析出,从而形成胆固醇结石。小肠是人体吸收胆固醇的重要部位,依泽替米贝能够与小肠刷状缘膜小囊泡上的膜蛋白结合,抑制对外源性胆固醇在小肠部位的吸收,从而降低患者血清、肝脏及胆汁中胆固醇含量,使胆囊结石形成的几率减小,已形成的结石可被溶解甚至消失^[19,20]。

CCK-A 是一种由小肠粘膜分泌的激素,可促进胆囊的收缩和排空,CCK-A 水平升高表明胆囊排空能力增强,可有效的防止胆囊内残渣残留,从而起到预防和改善胆囊结石的效果,可以作为监测术后患者胆囊功能、预测胆囊结石复发率的重要指标^[21,22]。本研究结果显示,治疗后观察组血清 CCK-A 含量明显高于对照组,说明依泽替米贝可提高患者血清 CCK-A 水平,促进胆囊收缩。依泽替米贝抑制胆固醇的吸收可能与其作用于小肠中段的尼曼-匹克 C1 型类似蛋白 1 有关,有研究发现,尼曼-匹克 C1 型类似蛋白 1 基因敲出的小鼠不服用依泽替米贝和正常小鼠服用依泽替米贝后胆固醇的吸收率基本相同^[23,24]。同时,有研究发现慢性胆囊炎患者的胆囊排空率明显低于正常人,慢性胆囊炎患者胆囊壁增厚、胆囊组织纤维化形成,CCK-A 受体水平减少,说明炎症反应与胆囊的收缩排空功能密切相关^[25,26]。故本研究进一步对两组患者血清炎症因子 TNF 和 IL-1 水平进行了检测,结果显示治疗后观察组患者 TNF 和 IL-1 水平明显低于对照组,说明依泽替米贝能够有效抑制患者胆囊内的炎症反应,从而恢复胆囊收缩排空功能。依泽替米贝通过其消除自由基的作用,降低患者血清 TNF、IL-1 水平,从而抑制炎症反应,恢复胆囊正常的收缩功能,胆囊收缩可排除残渣、排空胆汁,达到减少胆囊内胆固醇淤积的效果^[27-29]。李彩虹等人研究表明^[30]依泽替米贝联合阿托伐他汀治疗非酒精性脂肪肝合并冠心病患者可明显降低血脂,改善肝功能,可能与其调控脂质代谢,降低血清炎症因子水平有关,与本研究结果相符。

综上所述,依泽替米贝辅助腹腔镜微创治疗联合治疗胆囊结石,可降低患者血清炎症因子水平,促进 CCK-A 表达,抑制胆囊炎症,恢复胆囊生理功能,缓解患者痛苦,有较好的临床效果。

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