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· 临床研究 ·

术前改善ICGR₁₅对肝癌术后并发症及近期肝功能的影响

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摘要

背景与目的: 肝切除术后肝功能失代偿是导致术后患者病死率升高的主要因素, 因此术前有效的评估肝功能显得尤为重要。吲哚菁绿 15 min 滞留率 (ICGR₁₅) 是临床常用的肝功能评估手段, 可快速、准确的评估肝脏储备功能, 术前ICGR₁₅与肝脏切除术后肝功能失代偿密切相关, ICGR₁₅<20%被认为是可耐受大块肝脏切除 (≥3个肝段) 的必要条件之一, 临床上常见部分患者ICGR₁₅介于20%~30%之间, 在给予护肝等对症治疗后ICGR₁₅可有改善。对于此类患者能否安全实施大块肝切除术后仍存争议, 本研究旨在探讨术前改善ICGR₁₅对肝癌患者术后并发症及术后近期肝功能的影响。

方法: 选取2015年5月—2017年10月收治的入院时ICGR₁₅为20%~30%, 术前对症治疗后ICGR₁₅均<20%肝癌患者32例 (观察组), 及45例入院时ICGR₁₅<20%的肝癌患者 (对照组), 两组均行开放肝癌切除术 (≥3个肝段)。比较两组患者术中与术后指标、出院时以及术后1、3、6个月总胆红素 (TBIL)、谷草转氨酶 (AST)、白蛋白 (ALB)、凝血酶原时间 (PT)、美国东部肿瘤协作组 (ECOG) 活动状态评分等指标。

结果: 两组入院时ICGR₁₅差异有统计学意义 ($P<0.05$), 其余术前一般资料与生化指标差异均无统计学意义 (均 $P>0.05$)。两组患者的切肝范围与其他术中指标差异均无统计学意义 (均 $P>0.05$)。两组均无围手术期死亡病例, 观察组与对照组术后并发症发生率分别为37.5% (12/32) 与31.1% (14/45), 差异无统计学意义 ($P>0.05$), 观察组患者住院时间、引流管拔出时间较对照组延长 (均 $P<0.05$)。观察组出院时及术后1、3、6个月的TBIL均明显高于对照组 ($P<0.05$); 观察组ALB水平与ECOG评分在出院至术后1个月均明显低于对照组 (均 $P<0.05$), 两者在随后时间与对照组差异均无统计学意义 (均 $P>0.05$); 两组其余生化指标在出院至术后6个月各时间点差异均无统计学意义 (均 $P>0.05$)。

结论: 术前ICGR₁₅ 20%~30%之间的患者, 经护肝治疗后ICGR₁₅好转后, 能安全耐受大块肝脏切除, 未明显增加术后并发症发生率。术后短期内TBIL水平较高, 并未对患者的生存质量造成不良影响, 但患者长期预后情况尚须进一步随访观察。

关键词

肝肿瘤; 肝功能不全; 肝切除术; 吲哚花青绿; 肝功能试验

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Influence of preoperative improvement of ICGR₁₅ on postoperative complications and short-term liver function in patients after hepatectomy for liver cancer

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Abstract

Background and Aims: Liver function decompensation is the main cause for the increased mortality in patients after liver resection. So, effective preoperative liver function assessment is of great importance. Indocyanine green retention rate at 15 minutes (ICGR₁₅) is a simple and accurate test to evaluate preoperative liver function and is widely used in clinical practice. ICGR₁₅ <20% is essential to major hepatectomy (≥3 segments). Patients with ICGR₁₅ value ranging from 20% to 30% are frequently encountered in clinical practice, and their ICGR₁₅ can be improved after symptomatic management such as hepatoprotective treatment. Whether the major hepatectomy can be safely performed in these patients remains controversial. Therefore, this study was to evaluate the effectiveness of preoperative ICGR₁₅ improvement on complications and liver function in patients after hepatectomy for liver cancer.

Methods: From May 2015 to October 2017, 32 liver cancer patients whose ICGR₁₅ values were between 20% and 30% on admission and were improved to less than 20% after symptomatic treatment before operation (observation group), and the other 45 liver cancer patients with the ICGR₁₅ <20% on admission (control group) were selected. All patients underwent open liver cancer resection (≥3 segments). The intra- and postoperative variables, and the total bilirubin (TBIL), aspartate aminotransferase (AST), albumin (Alb), and prothrombin time (PT) as well as the ECOG physical status scores were compared between the two groups of patients.

Results: Between the two groups of patients, except the ICGR₁₅ values on admission that were significantly different ($P < 0.05$), all other preoperative general data and biochemical indexes showed no statistical difference (all $P > 0.05$). There were no statistical differences in liver resection scopes and other intraoperative variables between the two groups of patients (all $P > 0.05$). No perioperative death occurred in both groups, and the incidence rates of postoperative complications were 37.5% (12/32) in observation group and 31.1% (14/45) in control group, which had no statistical difference ($P > 0.05$). The length of hospital stay and time to drainage tube removal were prolonged in observation group compared with control group (both $P < 0.05$). The levels of TBIL at hospital discharge or 1 month, and 3 and 6 months after operation were all significantly higher in observation group than those in control group (all $P < 0.05$). The levels of ALB and ECOG scores at hospital discharge or 1 month after operation were all significantly lower in observation group than those in control group (all $P < 0.05$), but both variables showed no significant differences between the two groups later (all $P > 0.05$). There were no significant differences in the remaining biochemical indexes between the two groups at each time point from the time of hospital discharge to 6 months after operation (all $P > 0.05$).

Conclusions: Patients with the preoperative ICGR₁₅ between 20% to 30% can tolerate major hepatectomy safely after improvement of ICGR₁₅ to less than 20% by hepatoprotective treatment, without increase of postoperative complications. Although the TBIL level is relatively high during a short period after operation, it does not exert harmful effect on patients' quality of life. However, the long-term results of the patients still need further observations.

Key words

Liver Neoplasms; Hepatic Insufficiency; Hepatectomy; Indocyanine Green; Liver Function Tests

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原发性肝癌是常见恶性肿瘤之一，其发病率在世界范围内占恶性肿瘤的第6位，病死率居第2位，我国每年新发病例占全球的一半以上^[1-3]。目前，手术切除是治疗原发性肝癌的主要手段，也是患者可能取得长期存活的最有效措施之一^[4-5]。随着肝脏外科技术的不断进步，专业的肝胆外科中心

可将病死率控制在0~3%，但非专业的肝胆外科中心术后严重并发症的发生率仍可达10%以上。据报道^[6-7]仍有5%~9%左右的患者术后会出现肝脏功能衰竭，因此如何有效的评估术前肝储备功能尤为重要。吲哚菁绿15 min滞留率(indocyanine green retention rate at 15 minutes, ICGR₁₅)检测是一种简

单、无创、可重复的肝功能评价方法,在各种急慢性肝病及肝脏外科的评估中证实具有重要意义^[8-9]。既往研究证实术前ICGR₁₅与肝脏切除术后并发症及病死率密切相关^[10-12],ICGR₁₅<20%被认为是可耐受大块肝脏切除(≥3个肝段)的必要条件之一,ICGR₁₅>20%可明显增加术后肝功能失代偿等严重并发症的发生率^[13]。临床上常见部分患者ICGR₁₅介于20%~30%之间,在给予护肝等对症治疗后ICGR₁₅可有改善。对于此类患者能否安全实施肝脏切除术后仍存争议,笔者观察了部分此类患者围手术期并发症情况并总结术后短期肝功能变化,报告如下。

1 资料与方法

1.1 一般资料

选取2015年5月—2017年10月我院行肝癌切除患者32例作为观察组,男26例,女6例;年龄36~71岁,平均(57.2±10.7)岁;HBV阳性者28例,HCV阳性者2例,合并Budd-Chiari综合征患者1例,无肝炎相关疾病背景者1例;术前AFP>400 ng/mL者21例,AFP≤400 ng/mL者11例。选取同期45例术前ICGR₁₅<20%的患者作为对照组。所有患者术后均有病理证实,术前无影像学胆道癌栓或门静脉癌栓证据,且未行TACE等其他治疗措施。

1.2 术前评估

主要采用ICGR₁₅、Child-Pugh评分结合生化检查进行肝功能评估。两组患者术前Child-Pugh评分均为A级,结合影像学检查计算残肝体积不低于标准肝体积的45%;观察组术前ICGR₁₅介于20%~30%,平均(26.6±3.2)%;给予护肝治疗后复查ICGR₁₅,<20%后实施手术。术前HBV DNA>300 IU者均口服抗病毒药物治疗。

使用日本光电工业株式会社生产的DDG-3300K分析仪及其配套分析软件检测ICGR₁₅,按0.5 mg/kg剂量,将ICG(辽宁省丹东医创药业有限责任公司)用灭菌用水配成50 mg/L溶液,从右侧肘正中静脉内均匀快速注入,测定ICGR₁₅。

1.3 治疗

两组患者均为同一观察组医师施术,采取开放肝脏肿瘤切除术。术后常规治疗措施两组患者一致。

1.4 数据收集

观察两组患者术后相关并发症的发生率;同时统计患者住院时间、引流管拔出时间、出院时肝功能相关生化指标总胆红素(total bilirubin, TBIL)、天门冬氨酸氨基转移酶(aspartate transaminase, AST)、白蛋白(albumin, ALB)、凝血酶原时间(prothrombin time, PT);术后第1、3、6个月入院复查,并对肝功能相关生化指标(TBIL、AST、ALB、PT)、美国东部肿瘤协作组(Eastern Cooperative Oncology Group, ECOG)活动状态评分等相关数据进行统计。

1.5 统计学处理

应用SPSS 17.0软件进行分析,计量资料以均数±标准差($\bar{x} \pm s$)表示,两组间均数的比较使用 t 检验,组间率的比较采用 χ^2 检验, $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组入院时一般资料与术中情况

两组患者入院时ICGR₁₅差异有统计学意义($P<0.05$),其余资料及肝功能指标差异均无统计学意义(均 $P>0.05$)。观察组患者中行左半肝(肝II/III/IV段)切除19例,右半肝(肝V/VI/VII/VIII段)切除术6例,肝中叶(肝IV/V/VIII段)切除4例,不规则切除3例;对照组患者中行左半肝(肝II/III/IV段)切除22例,右半肝(肝V/VI/VII/VIII段)切除术10例,肝中叶(肝IV/V/VIII段)切除9例,不规则切除4例。两组各项术中指标差异均无统计学意义(均 $P>0.05$)(表1)。

2.2 两组围手术期情况比较

两组患者均无围手术期死亡病例;观察组与对照组术后并发症发生率分别为37.5%(12/32)与31.1%(14/45),差异无统计学意义($P>0.05$)。观察组患者平均住院时间、拔管时间及出院时ECOG评分等情况均较对照组差(均 $P<0.05$);出院时肝功能相关指标显示研究组TBIL及ALB较对照组差(均 $P<0.05$),两组AST及PT差异无统计学意义(均 $P>0.05$)(表2)。

2.3 两组患者术后随访复查情况

两组第1、3、6个月复查情况显示,术后1个月观察组患者TBIL较对照组高,ALB水平研究组较

对照组低 (均 $P < 0.05$), AST、PT 两组差异均无统计学意义 (均 $P > 0.05$)。术后 3、6 个月观察组 TBIL 水平均较对照组高 (均 $P < 0.05$), 余肝功能指标两组差异均无统计学意义 (均 $P > 0.05$)。术后 1 个月 ECOG 评分结果显示观察组较对照组低 ($P < 0.05$), 术后 3、6 个月 ECOG 评分两组差异均无统计学意义 (均 $P > 0.05$) (表 3)。

表 1 两组患者入院时一般资料与术中指标比较

Table 1 Comparison of the general data on admission and intraoperative variables between the two groups of patients

项目	观察组(n=32)	对照组(n=45)	P
年龄(岁, $\bar{x} \pm s$)	57.2±10.7	52.1±9.8	>0.05
性别[n(%)]			
男	26(81.3)	35(77.8)	>0.05
女	6(18.7)	10(22.2)	
肝病背景[n(%)]	30(93.8)	39(86.7)	>0.05
AFP [ng/mL, n(%)]			
≤400	11(34.4)	16(35.6)	>0.05
>400	21(65.6)	29(64.4)	
ICG ₁₅ (%, $\bar{x} \pm s$)	26.6±3.2	12.4±4.1	<0.05
TBIL(μmol/L, $\bar{x} \pm s$)	11.2±2.1	12.7±1.0	>0.05
ALB(g/L, $\bar{x} \pm s$)	42.0±4.7	39.0±3.8	>0.05
AST(U/L, $\bar{x} \pm s$)	29.3±7.1	23.2±4.5	>0.05
PT(s, $\bar{x} \pm s$)	12.6±2.2	11.5±1.3	>0.05
ECOG 评分($\bar{x} \pm s$)	0.8±0.2	0.7±0.3	>0.05
肿瘤数目[n(%)]			
单发	25(78.1)	33(73.3)	>0.05
多发	7(21.9)	12(26.7)	
肝切除范围[n(%)]			
3个肝段	23(71.9)	31(68.9)	>0.05
>3个肝段	9(28.1)	14(31.1)	
肿瘤直径(cm, $\bar{x} \pm s$)	8.7±3.2	6.9±2.4	>0.05
入肝血流阻断[n(%)]			
全肝	12(37.5)	10(22.2)	>0.05
选择性	16(50)	27(60.0)	
未阻断	4(12.5)	8(17.8)	
出血量(mL, $\bar{x} \pm s$)	358±77	213±59	>0.05
术中输血[n(%)]			
有	5(18.5)	9(20.0)	>0.05
无	27(84.3)	36(80.0)	

表 2 两组患者围手术期指标比较

Table 2 Comparison of the perioperative variables between the two groups of patients

指标	观察组(n=32)	对照组(n=45)	P
并发症[n(%)]			
腹水	1(3.1)	3(6.7)	>0.05
胸腔积液	2(6.3)	1(2.2)	
腹腔感染	2(6.3)	1(2.2)	
肺部感染	1(3.1)	1(2.2)	
切口感染	2(6.3)	2(4.4)	
胆瘘	2(6.3)	1(2.2)	
消化道出血	1(3.1)	2(4.4)	
腹腔出血	1(3.1)	2(4.4)	
切口裂开	0(0.0)	1(2.2)	
肝功能指标($\bar{x} \pm s$)			
TBIL(μmol/L)	31.4±7.3	21.5±3.3	<0.05
ALB(g/L)	33.3±5.1	35.0±3.2	<0.05
AST(U/L)	54.5±9.1	44.0±4.7	>0.05
PT(s)	13.5±1.2	12.1±2.4	>0.05
住院时间(d, $\bar{x} \pm s$)	17.4±3.8	14.1±3.0	<0.05
拔管时间(d, $\bar{x} \pm s$)	9.4±1.6	7.7±2.1	<0.05
ECOG 评分($\bar{x} \pm s$)	1.3±0.2	2.1±0.4	<0.05

表 3 两组患者术后复查指标比较 ($\bar{x} \pm s$)

Table 3 Comparison of the variables at reexaminations between the two groups of patients ($\bar{x} \pm s$)

指标	观察组(n=32)	对照组(n=45)	P
术后 1 个月			
TBIL(μmol/L)	32.2±4.6	25.6±3.8	<0.05
AST(U/L)	50.1±2.2	45.0±6.4	>0.05
ALB(g/L)	33.5±7.8	35.6±4.6	<0.05
PT(s)	14.7±1.8	12.8±2.0	>0.05
ECOG 评分	0.9±0.3	1.9±0.4	<0.05
术后 3 个月			
TBIL(μmol/L)	31.8±3.7	22.5±2.7	<0.05
AST(U/L)	36.6±3.7	33.0±8.9	>0.05
ALB(g/L)	34.4±1.8	35.8±2.6	>0.05
PT(s)	13.7±2.9	13.1±1.3	>0.05
ECOG 评分	1.5±0.4	1.6±0.2	>0.05
术后 6 个月			
TBIL(μmol/L)	29.8±3.2	19.9±2.6	<0.05
AST(U/L)	34.7±5.1	32.5±3.9	>0.05
ALB(g/L)	35.1±2.8	36.7±3.3	>0.05
PT(s)	13.4±2.8	12.9±31.0	>0.05
ECOG 评分	1.3±0.3	1.5±0.1	>0.05

3 讨论

近年来, 随着肝癌手术方法和治疗理念的更新, 肝癌切除术后的病死率已大幅降低, 手术的

适应证也有一定程度的扩大^[14-15]。最近的一项Meta分析^[16]表明,部分巴塞罗那C期的患者行手术切除仍较经皮肝动脉栓塞治疗效果为好。但由于我国大部分患者合并有肝炎及肝硬化病史,术后发生肝功能失代偿甚至肝衰竭的可能性大大增加,因此如何术前有效的评估肝脏功能极为重要。ICGR₁₅是目前国内临床应用最为广泛的方法之一。2011年肝功能评估专家共识^[17]指出:Child评分为A级的患者,ICGR₁₅<30%是施行手术的必要条件之一。亚洲学者广为接受的Makuuchi^[18]标准也认为,对于术前胆红素正常的患者,预计行3个肝段以上的切除时,ICGR₁₅<20%是必要条件,并有部分学者据此研究出更为复杂的公式^[19-20]。既往研究^[21-22]认为,ICGR₁₅是肝癌切除术后的独立危险因素,ICGR₁₅超出20%的患者行肝切除,术后并发症及病死率均会明显上升,并且在肝脏介入及射频消融治疗的评估也取得类似的结果^[23-24]。

但ICGR₁₅的结果受影响因素较多,与胆汁排泄功能、肝脏血流灌注状况、有效肝细胞数量等因素关系密切,本研究也发现,经术前护肝等对症治疗后,ICGR₁₅可有明显好转,可能跟肝细胞血流灌注改善和胆汁排泄通常有关^[9, 25]。研究组患者行大块肝切除术后,短期内患者肝功能相关指标较对照组恢复较慢,住院时间、引流管拔出时间等较对照组延长,但术后并发症发生率无明显增高,提示ICGR₁₅术前对肝切术后的风险评价仍有一定局限性,故部分学者^[26-28]认为ICGR₁₅并非完全意义的客观指标,应联合其他的评估手段,更能准确的个体化评估患者。

对两组患者进行短期随访结果发现,观察组患者术后TBIL较对照组高,其余相关指标均无明显差异,结果提示胆汁排泄能力与ICGR₁₅关系密切。既往有学者^[29-30]也发现,任何原因导致的胆汁排泄障碍均可导致ICG代谢速率延缓。观察组患者术前经术前利胆、降酶治疗后,肝细胞泌胆功能一度好转,但经手术损伤后肝细胞增生能力下降导致有效肝细胞数目下降,无法短时间内完全代偿,从而可致术后较高TBIL水平。而其余肝功能相关指标如AST、ALB、PT等,经围手术期应用护肝药物、输注血浆、ALB等均可快速纠正,两组患者间均无统计学差异(均 $P>0.05$)。ECOG评分显示,术后第1个月复查时,观察组患者评分较高,第3个月及第6个月两组均无明显差异(均 $P>$

0.05)。可能与患者术后早期肝功能异常导致纳差、乏力、消瘦等临床症状相关,也与患者术后早期心理负担较重对生活质量的有关。

综上所述,对于术前ICGR₁₅评分>20%, <30%的患者,经对症治疗后好转,并未明显增加术后并发症发生率。但术后肝功能恢复较慢,短期内患者一般状况也较差,但并未对患者长期生存质量造成不良影响。因此,对于该类患者,经充分围手术期准备后,仍可安全耐受手术。但本研究纳入病例较少,且随访时间较短,因此尚须扩大样本量并增加随访时间,了解此类患者长期预后情况。

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