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宫颈冷刀锥切术治疗宫颈上皮内瘤变的疗效观察 及术后切缘阳性的危险因素分析*

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摘要 目的:探讨宫颈冷刀锥切术(CKC)治疗宫颈上皮内瘤变(CIN)的疗效,并分析术后切缘阳性的危险因素。**方法:**回顾性分析 2009 年 1 月至 2017 年 12 月在广州医科大学附属第三医院接受治疗的 509 例 CIN 患者的临床资料,其中行 CKC 治疗的患者 318 例记为 CKC 组,行宫颈环形电切术(LEEP)治疗的患者 191 例记为 LEEP 组,对比两组患者的手术指标、术后并发症发生率、切缘阳性率以及复发率,根据所有患者术后病理检查结果将其分为切缘阳性组和切缘阴性组,采用单因素和多因素 Logistic 回归分析方法分析 CIN 患者术后切缘阳性的危险因素。**结果:**CKC 组患者的手术时间、住院时间均长于 LEEP 组患者,术中出血量多于 LEEP 组患者,组间比较差异有统计学意义($P<0.05$)。CKC 组患者的术后并发症发生率、切缘阳性率、复发率均低于 LEEP 组患者,组间比较差异有统计学意义($P<0.05$)。单因素分析显示,切缘阳性组的手术方式、人类乳头状瘤病毒(HPV)感染、CIN 病变分级、有无宫颈上皮腺体受累与切缘阴性组比较差异有统计学意义($P<0.05$)。多因素 Logistic 回归分析显示,手术方式为 LEEP、HPV 感染呈阳性、CIN 病变分级为 III 级、有宫颈上皮腺体受累是 CIN 术后切缘阳性的危险因素($P<0.05$)。**结论:**采用 CKC 治疗 CIN 能够降低患者术后切缘阳性率和复发率,安全可靠。手术方式为 LEEP、HPV 感染呈阳性、CIN 病变分级为 III 级、有宫颈上皮腺体受累是 CIN 术后切缘阳性的危险因素,在治疗过程中应重视以上危险因素,并采取针对性措施以降低 CIN 术后切缘阳性的发生率。

关键词:宫颈上皮内瘤变;宫颈冷刀锥切术;宫颈环形电切术;疗效;切缘阳性;危险因素

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Observation of Curative Effect of Cold Knife Conization for Cervical Intraepithelial Neoplasia and Analysis of Risk Factors for Positive Margin after Operation*

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ABSTRACT Objective: To investigate the efficacy of cold knife conization (CKC) in the treatment of cervical intraepithelial neoplasia (CIN), and the risk factors of positive margin after operation. **Methods:** The clinical data of 509 patients with CIN who were treated in the Third Affiliated Hospital of Guangzhou Medical University from January 2008 to July 2017 were retrospectively analyzed. 318 patients treated with CKC were classified as CKC group, 191 patients treated with cervical circumferential electrotomy (LEEP) were recorded as LEEP group. The operative indexes, the incidence rate of postoperative complications, the positive rate of incision margin and the recurrence rate were compared between the two groups. The patients were divided into positive margin group and negative margin group according to the results of pathological examination after operation. The univariate and multivariate logistic regression analysis was used to analyze the risk factors of positive incision margin in patients with CIN. **Results:** The operation time and hospitalization time of CKC group were longer than those of LEEP group, the intraoperative bleeding volume was more than that in LEEP group, there were significant differences between groups ($P<0.05$). The postoperative complications, positive incision margins and recurrence rates in CKC group were lower than those in LEEP group, there were significant differences between groups ($P<0.05$). Univariate analysis showed that there were significant differences in surgical methods, human papillomavirus (HPV) infection, CIN grading, accumulative involvement of cervical epithelial glands between positive margin group and negative margin group ($P<0.05$). Multivariate logistic regression analysis showed that LEEP, positive HPV infection, grade III CIN lesions and accumulative involvement of glands in cervical epithelium were risk factors for positive incision margin after CIN ($P<0.05$). **Conclusions:** CKC treatment of CIN can reduce the positive rate of incision margin and recurrence rate, which is safe and reliable. The LEEP, HPV infection, CIN grade III and

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cervical epithelial gland involvement are the risk factors of positive incision margin after CIN. In the course of treatment, we should pay attention to the above risk factors and take appropriate measures to reduce the incidence of positive incision margin after CIN.

Key words: Cervical intraepithelial neoplasia; Cold knife conization of cervix; Circular electrotomy of cervix; Curative effect; Positive rate of incision margin; Risk factors

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前言

宫颈上皮内瘤变 (Cervical intraepithelial neoplasia, CIN) 是与宫颈浸润癌密切相关的一组子宫颈病变, 现又被称为子宫颈鳞状上皮内病变 (cervical squamous intraepithelial lesion, SIL), 包括低级别 CIN (CIN 病变 I 级) 和高级别 CIN (CIN 病变 II、III 级), 说明宫颈癌是一个连续发展的过程^[1,2]。患者处于 CIN 时, 往往表现为白带增多、带血、宫颈肥大、充血、糜烂等不典型症状, 但高级别 CIN 进展为宫颈浸润癌的风险约为 30%, 因此, 尽早地诊断和治疗 CIN 对于降低宫颈癌的发生率有重要作用^[3,4]。目前, 对于高级别 CIN 的治疗以手术切除为主, 其主要原则是切除异常的上皮细胞组织, 避免过度损伤正常的宫颈组织, 目前临床上应用最为广泛的两种切除术为宫颈冷刀锥切术 (Cold knife conization of cervix, CKC) 和宫颈环形电切术 (Circumferential electrotomy of cervix, LEEP)^[5,6]。有报道显示, 手术切除后切缘的病理学检查呈阳性是 CIN 患者复发的主要原因, 因此手术切除后切缘阳性率的高低是评价手术效果好坏的重要标准^[7-9]。本研究探讨了 CKC、LEEP 治疗 CIN 的疗效, 并分析了 CIN 患者术后切缘阳性的危险因素, 以期为 CIN 的手术治疗及避免术后切缘阳性的发生提供参考, 现汇报如下。

1 资料与方法

1.1 临床资料

回顾性分析 2009 年 1 月至 2017 年 12 月在广州医科大学附属第三医院治疗的 509 例 CIN 患者的临床资料, 纳入标准: ① 患者经细胞学检查、阴道镜检查及镜下活检、人类乳头状瘤病毒 (Human papillomavirus, HPV) 检测异常而行阴道镜下活检病理检查等手段确诊为 CIN II 级或 CIN III 级; ② 患者均具有手术治疗的指征; ③ 患者病历资料齐全; ④ 患者对研究内容知情同意且签署同意书。排除标准: ① 严重的心肝肾功能不全者; ② 凝血功能异常者; ③ 精神状态异常者。将入选患者按手术方式的不同分为 CKC 组 318 例和 LEEP 组 191 例, 其中 CKC 组患者年龄 32~59 岁, 平均年龄 (45.18±10.23) 岁; 绝经情况: 绝经 170 例, 未绝经 148 例; CIN 病变分级: II 级 102 例, III 级 216 例。LEEP 组患者年龄 31~60 岁, 平均年龄 (46.14±11.83) 岁; 绝经情况: 绝经 104 例, 未绝经 87 例; CIN 病变分级: II 级 50 例, III 级 141 例。两组患者一般资料比较差异无统计学意义 ($P>0.05$)。本研究经我院伦理委员会批准予以进行。

1.2 手术方法

CKC 组患者术中取截石位, 行椎管硬膜外麻醉, 以三瓣式无菌窥阴器对患者的宫颈部位进行暴露, 采用钳夹将宫颈牵拉, 并采用碘实验对患者的病变范围进行明确标记, 标记完成后在患者的宫颈病变外 0.5 cm 处取环形切口, 切割深度约

2.5-3 cm, 切口为内收状, 椎尖位于宫颈口内, 切除完成后进行创面电凝止血, 宫颈成形或荷包缝合, 完成手术操作。术后取切除的样本, 标识宫颈 12 点后, 分成 12 刀切片进行病理学检查。LEEP 组患者术中取截石位, 以三瓣式无菌窥阴器对患者的宫颈部位进行暴露, 采用钳夹将宫颈牵拉, 采用碘实验对患者的病变范围进行明确标记, 并采用 LEEP 刀从病灶外缘 3~5 mm 进刀做一切口, 切割深度为 15~20 mm, 且不超过宫颈内口, 之后进行创面电凝止血。不同的病变范围应选择适合的三角形或环形刀头, 如果病变范围大, 可以分次进行补切。术后取切除的样本标识后进行病理学检查。

1.3 观察指标

对比 CKC 组、LEEP 组患者的手术时间、术中出血量、住院时间以及术后并发症发生率、切缘阳性率、复发率, 并根据患者术后病理检查结果将其分为切缘阳性组和切缘阴性组, 并分析 CIN 患者术后切缘阳性的危险因素。

1.4 统计学方法

采用 SPSS 20.0 软件进行数据统计分析, 计量资料、计数资料分别以 ($\bar{x} \pm s$)、[n(%)] 表示, 组间比较分别采用 t 检验、 χ^2 检验, 采用单因素与多因素 Logistic 回归分析方法分析 CIN 患者术后切缘阳性的危险因素, 当 $P<0.05$ 时表示差异有统计学意义。

2 结果

2.1 CKC 组与 LEEP 组患者手术指标比较

CKC 组患者的手术时间、住院时间均长于 LEEP 组患者, 术中出血量多于 LEEP 组患者, 组间比较差异有统计学意义 ($P<0.05$), 见表 1。

2.2 CKC 组与 LEEP 组患者术后并发症发生率、切缘阳性率、复发率比较

CKC 组患者的术后并发症发生率、切缘阳性率、复发率均低于 LEEP 组患者, 组间比较差异有统计学意义 ($P<0.05$), 见表 2。

2.3 CIN 患者术后切缘阳性影响因素的单因素分析

509 例患者中切缘阳性患者共 71 例 (切缘阳性组), 切缘阳性率为 13.95%, 切缘阴性患者 438 例 (切缘阴性组)。经单因素分析显示, 切缘阳性组手术方式、HPV 感染、CIN 病变分级、有无宫颈上皮腺体受累与切缘阴性组比较差异有统计学意义 ($P<0.05$), 而两组年龄、手术时间、术中出血量、碘不着色区最大径线、绝经情况比较差异无统计学意义 ($P>0.05$), 见表 3。

2.4 CIN 患者术后切缘阳性影响因素的多因素 Logistic 回归分析

以术后是否发生切缘阳性为因变量, 将上述具有统计学差异的指标包括手术方式、HPV 感染、CIN 病变分级、有无宫颈上皮腺体受累作为自变量, 经多因素 Logistic 回归分析显示, 手术方式为 LEEP、HPV 感染呈阳性、CIN 病变分级为 III 级、有

宫颈上皮腺体受累是 CIN 患者术后切缘阳性的危险因素 ($P<0.05$), 见表 4。

表 1 CKC 组与 LEEP 组患者手术指标比较($\bar{x}\pm s$)

Table 1 Comparison of operative indexes between CKC group and LEEP group($\bar{x}\pm s$)

Groups	n	Operation time(min)	Intraoperative bleeding volume(mL)	Hospitalization time(d)
CKC group	318	37.01± 10.89	53.38± 14.82	7.67± 2.14
LEEP group	191	29.64± 8.38	36.90± 12.11	5.84± 1.92
t	-	8.326	14.440	9.703
P	-	0.000	0.000	0.000

表 2 CKC 组与 LEEP 组患者术后并发症发生率、切缘阳性率、复发率比较[n(%)]

Table 2 Comparisons of the incidence rate of postoperative complications, positive rate of incision margin and recurrence rate between CKC group and LEEP group [n (%)]

Groups	n	Incidence rate of postoperative complications	Positive rate of incision margin	Recurrence rate
CKC group	318	11(3.46)	28(8.81)	7(2.20)
LEEP group	191	18(9.42)	43(22.51)	15(7.85)
χ^2	-	8.326	18.681	9.218
P	-	0.005	0.000	0.002

表 3 CIN 患者术后切缘阳性影响因素的单因素分析

Table 3 Univariate analysis of influencing factors of positive incision margin in CIN patients

Factors		Positive margin group (n=71)	Negative margin group (n=438)	t/ χ^2	P
Age (years)		46.39± 10.30	45.40± 10.35	0.880	0.379
Menopausal status n(%)	Menopause	36(50.70)	238(54.34)	0.122	0.727
	Non-menopause	35(49.30)	200(45.66)		
Operative methods n(%)	CKC	28(39.44)	290(66.21)	18.681	0.000
	LEEP	43(60.56)	148(33.79)		
Operation time(min)		35.18± 11.28	34.09± 11.09	0.766	0.444
Intraoperative bleeding volume (mL)		49.37± 17.23	46.85± 16.22	1.204	0.229
Maximum diameter of iodine-free zone(cm)	<1	21(29.58)	139(31.74)	0.179	0.915
	1~2	32(45.07)	196(44.75)		
	>2	18(25.35)	103(23.52)		
HPV infection n(%)	Positive	59(83.10)	198(45.21)	35.094	0.000
	Negative	12(16.90)	240(54.79)		
Classification of CIN lesions n(%)	Grade II	28(39.44)	124(28.31)	19.840	0.000
	Grade III	43(60.56)	314(71.69)		
Accumulation of glands in cervical epithelium n(%)	Yes	48(67.61)	201(45.89)	11.529	0.001
	No	23(32.39)	237(54.11)		

表 4 CIN 患者术后切缘阳性影响因素的多因素 Logistic 回归分析

Table 4 Multivariate Logistic regression analysis of influencing factors of positive incision margin in CIN patients

Factors	β	SE	Wald χ^2	OR	95%CI	P
The operative method was LEEP	1.457	1.325	2.734	1.049	1.011~1.056	0.011
HPV infection was positive	1.489	1.333	2.789	1.092	0.984~1.275	0.010
CIN lesions were classified as grade III	1.562	1.403	3.098	2.071	1.761~2.342	0.000
Cervical epithelial gland involvement	1.513	1.582	2.893	1.831	1.679~2.234	0.007

3 讨论

近些年随着人们物质生活水平的提高、女性社会工作压力的增加以及不良生活习惯的加剧, CIN 的发病率呈逐年升高趋势, 对女性生命健康和生活质量带来较大危害^[10,11]。目前为了尽量保持患者生殖器官的完整性和生育功能, 在 CIN 的手术治疗过程中多采用保守的手术切除治疗^[12,13]。临床上常用的手术切除治疗方法有 CKC、LEEP, 但两者的优劣尚不清楚。在本研究中, CKC 组患者的手术时间、住院时间均长于 LEEP 组患者, 术中出血量多于 LEEP 组患者, 而术后并发症发生率、切缘阳性率、复发率均低于 LEEP 组患者, 说明两者在 CIN 的治疗中各具优势。CKC 可避免切除子宫, 保证了生殖器官的完整性, 但其存在着手术时间长、出血量多、术后康复时间长等不足^[14-16]; 而 LEEP 是采用高频电刀的超高频电波产生高热的一种手术方式, 其实现了对病变组织的切除和电凝止血, 具有手术时间短、术中出血量少、术后恢复快等优点^[17-19], 但由于切割深度浅, LEEP 也存在着切除不彻底的情况, 从而易造成术后切缘阳性的发生, 增加了患者术后复发的风险。同时 CKC 虽然手术过程相对复杂, 但患者术后的切缘阳性率能够控制在较低水平, 手术切除效果相比于 LEEP 更低^[20,21], 这可能与 CKC 的切除面积更大、深度更深以及对病变组织的切除更为彻底有关^[22]。

本研究结果显示, 509 例患者中, 术后有 71 例患者病理检查为切缘阳性。单因素分析显示, 切缘阳性组患者手术方式、HPV 感染、CIN 病变分级、有无宫颈上皮腺体受累与切缘阴性组患者比较差异有统计学意义($P < 0.05$), 而两组患者的年龄、手术时间、术中出血量、碘不着色区最大径线、绝经情况比较差异无统计学意义($P > 0.05$)。进一步经多因素 Logistic 回归分析显示, 手术方式为 LEEP、HPV 感染呈阳性、CIN 病变分级为 III 级、有宫颈上皮腺体受累是 CIN 术后切缘阳性的危险因素($P < 0.05$)。LEEP 的切除深度较浅, 可能会造成部分异常组织未切除干净而残留, 由此导致患者术后切缘阳性率升高^[23,24]。HPV 感染与 CIN 的发生有一定的关联, 分子生物学及流行病学研究表明 HPV 有致癌性^[25]; 多项临床报道也显示, HPV 的高表达是造成患者出现 CIN 及其他宫颈处癌变的高危因素^[26,27]; 因此 HPV 感染呈阳性的 CIN 患者更易发生术后切缘阳性。处于 CIN III 级病变的患者病灶组织累及情况严重, 从而将导致患者术后切缘阳性的风险明显提高^[28,29]。宫颈上皮腺体受累是患者病灶组织中细胞转移扩散的标志, 表明宫颈处的内瘤变细胞有较强的活性, 此时患者应做宫颈或子宫的完整切除, 才能避免 CIN 的复发^[30]。

综上所述, CKC 治疗 CIN 能够降低患者术后并发症发生率、切缘阳性率和复发率。LEEP 术式、HPV 感染呈阳性、III 级 CIN 病变、有宫颈上皮腺体受累是 CIN 患者术后切缘阳性的危险因素, 在手术治疗过程中应对上述因素高度重视, 并采取针对性措施, 以降低术后切缘阳性率。

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