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TURBT 术后灌注不同剂量丝裂霉素对肿瘤复发的影响 *

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摘要 目的:探讨经尿道膀胱肿瘤电切术(Transurethral resection of bladder tumor, TURBT)术后灌注不同剂量丝裂霉素对非肌层浸润性膀胱肿瘤(Non-muscularized invasive bladder tumor, NIMBC)复发率的影响。**方法:**选择三原县医院 2013 年 1 月至 2016 年 12 月收治的 90 例 NIMBC 患者,根据入院先后顺序分为 A、B、C 三组,A 组 TURBT 后即刻给予 20 mg 丝裂霉素,B 组给予 30 mg 丝裂霉素,C 组给予 40 mg 丝裂霉素,对比三组患者术后不同时间点的复发率、平均复发时间、膀胱刺激综合征及其他不良反应。**结果:**三组术后不同时间点 NIMBC 复发率为 A 组 > B 组 > C 组。术后 12 个月、18 个月、24 个月时 A 组的复发率明显高于 C 组 ($P < 0.05$),其余时间点组间对比无统计学意义 ($P > 0.05$)。三组膀胱刺激综合征发生率 C 组 > B 组 > A 组,但组间对比无统计学意义 ($P > 0.05$)。三组患者均完成丝裂霉素灌注治疗,未出现因严重膀胱刺激征无法耐受而中断膀胱治疗者。本研究所有患者灌注后未发现骨髓抑制、肝肾功能异常者。**结论:**TURBT 术后即刻应用 40 mg 丝裂霉素,可显著降低患者的 NIMBC 复发率,通过术前、术后服用琥珀酸索利那新,可降低患者的膀胱刺激综合征,辅助患者完成 TURBT 术后丝裂霉素灌注化疗。

关键词:非肌层浸润性膀胱肿瘤;丝裂霉素;经尿道膀胱肿瘤电切术;复发率;膀胱刺激征

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The Influence of Different Doses of Mitomycin Perfusion on Tumor Recurrence After TURBT Surgery*

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ABSTRACT Objective: To investigate the effect of different doses of mitomycin perfusion after transurethral resection of bladder tumor (TURBT) on the recurrence rate of non-muscularized invasive bladder tumor (NIMBC). **Methods:** 90 cases with NIMBC from Jan. 2013 to Dec. 2016 in Sanyuan County hospital were chosen and who were divided into the A, B, C groups, the group A TURBT was immediately given 20 mg mitomycin, the group B was given 30 mg mitomycin, group C were given 40 mg mitomycin, the recurrence rate, mean recurrence time, bladder stimulation syndrome and other adverse reactions were compared among the three groups. **Results:** The recurrence rate of NIMBC at different postoperative time points in the three groups was group A > group B > group C. The recurrence rate of group A was significantly higher than that of group C at 12, 18 and 24 months after operation ($P < 0.05$), and there was no statistically significant difference between the groups at other time points ($P > 0.05$). The bladder stimulation syndrome incidence in three groups was group C > group B > group A, while which had no significant difference ($P > 0.05$). All patients in the three groups were completed the mitomycin perfusion therapy, and no patients were found to interrupt the bladder therapy due to severe bladder irritation intolerance. There were no bone marrow suppression or abnormal liver and kidney functions were found in all patients after perfusion. **Conclusion:** The TURBT immediately after the application of 40 mg mitomycin, which could significantly reduce the recurrence rate of NIMBC patients, by preoperative and postoperative use of succinyl solinaxine, and reduce the bladder stimulation syndrome of patients, assist patients to complete the infusion chemotherapy of TURBT after mitomycin.

Key words: Non-muscularized invasive bladder tumor (NIMBC); Mitomycin; Transurethral resection of bladder tumor (TURBT); Recurrence rate; Bladder stimulation syndrome

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前言

膀胱癌是发生于膀胱黏膜上的恶性肿瘤,其发病率位于泌尿生殖系统肿瘤第一位^[1-3]。男性膀胱癌的发病率是女性的3~4倍,其可发生于任何年龄,多发生于中年以后,且发病率随患者年龄增加而增加,高发年龄为50~70岁^[4-6],其中非肌层浸润性膀胱肿瘤(Non-muscularized invasive bladder tumor, NIMBC)约占膀胱癌的75%~85%,经尿道膀胱肿瘤电切术(Transurethral resection of bladder tumor, TURBT)与术后膀胱灌注化疗为NIMBC的主要治疗手段,术后复发率较高,即使采用TURBT联合膀胱灌注化疗,患者复发率也高达60%,临床效果不满意,因此为降低膀胱癌的复发率,泌尿外科医师需在手术方式、时机、膀胱灌注化疗药物选择、灌注剂量上进行探索^[7-9]。丝裂霉素是NIMBC患者术后常用的灌注化疗药物,但其术后仍存在一定的复发率。而有研究发现^[11,12],对于浅表膀胱癌术后加大丝裂霉素灌注剂量,可降低患者的复发率,但其在NIMBC术后患者中是否存在相同的作用,研究较少^[13,14]。因此,本研究分析了TURBT术后采用不同剂量丝裂霉素对NIMBC患者复发率

的影响,以为降低NIMBC患者复发率选择合适剂量的灌注药物提供依据。

1 资料与方法

1.1 一般资料

选择三原县医院2013年1月至2016年12月收治的90例病理确诊为NIMBC且行TURBT术治疗的患者。纳入标准:术后病理证实为Ta、T1、Tis期膀胱癌;术后即刻接受丝裂霉素灌注治疗;有完整的随访治疗资料。排除TURBT术中严重并发症者、合并上尿路肿瘤者、术后诊断为膀胱非尿路上皮癌者、不能完成术后膀胱灌注治疗者。其中男68例,女22例,年龄41~75岁,平均 61.5 ± 5.6 岁,血尿时间为7~23d,平均血尿时间为 14.1 ± 2.3 d。根据入院先后顺序,分为A组(29例)、B组(30例)、C组(31例),其中2013年1月至2014年4月为A组,2014年5月至2015年9月为B组,2015年10月至2016年12月为C组。三组一般资料具有可比性($P>0.05$),见表1。本研究所有患者或家属知情同意,且经医院伦理委员会批准同意。

表1 三组患者一般资料对比
Table 1 Comparison of general data of three groups of patients

Groups	n	Gender		Average age(old)	Mean hematuria time (d)
		Male	Female		
Group A	29	23	6	61.4 ± 5.4	14.0 ± 2.1
Group B	30	21	9	62.1 ± 6.2	14.4 ± 2.5
Group C	31	24	7	61.9 ± 5.7	14.7 ± 2.8

1.2 方法

所有患者均行TURBT,取截石位及腰硬联合麻醉,经尿道电切镜行镜检,先认真观察膀胱肿瘤位置、大小、数目、形态、与输尿管开口及膀胱颈位置关系及橙染区膀胱粘膜分布,用电切环切除肿瘤及其基底部,切除范围为肿瘤及其周边1~2cm正常膀胱粘膜,深度达肌层。

B组术后即刻开始灌注丝裂霉素(海正辉瑞制药有限公司生产,规格:20mg,国药准字:H1999025),灌注前患者需排空尿液,采用F10硅胶导管经尿道置入膀胱内,将20mg丝裂霉素溶于40mL生理盐水中,缓慢注入药液,药物保留时间为2h,拔管前用注入10mL生理盐水冲洗导管,以防止流出残余药液腐蚀尿道口或阴囊皮肤组织。灌注后嘱患者按照左侧卧位、右侧卧位、仰卧位、俯卧位等变换体位,使药液均匀接触膀胱各处粘膜,于30min后将膀胱排空,1次/周,连续灌注8周,8周后每月1次,连续灌注10个月,总疗程为48周。B组将30mg丝裂霉素溶于40mL生理盐水中,C组将40mg丝裂霉素溶于40mL生理盐水中,两组其余操作与A组相同。

本研究三组患者术前6h、术后连续3d均服用琥珀酸索利那新,每次5mg,1次/d。

1.3 观察指标

(1)术后第1年,所有患者每3个月采用膀胱镜、泌尿系统B超随访1次,术后第2年,每6个月采用膀胱镜及泌尿系统

B超随访一次,所有患者均随访2年,对比三组术后3个月、6个月、9个月、12个月、18个月、24个月的复发率。复发率的判断定义:患者膀胱镜或泌尿系统B超下再次发现可疑肿瘤组织,取可疑病灶组织活检,证实为肿瘤细胞,则记为肿瘤复发,对比三组术后不同时间的复发率;(2)对比三组灌注时膀胱刺激征发生率,膀胱刺激征判别标准为通过患者自述灌注出现尿急、尿频或尿痛等症状,即可记为膀胱刺激征;(3)每次灌注化疗后3d复查患者的血常规及肝肾功能,对比三组患者其他不良反应。

1.4 统计学方法

采用SPSS21.0软件,计数资料用%表示,行 χ^2 检验,计量资料用 $\bar{x} \pm s$ 表示,行t检验, $P<0.05$ 为差异有统计学意义。

2 结果

2.1 复发率比较

三组术后不同时间点NIMBC复发率A组>B组>C组。术后12个月、18个月、24个月时A组的复发率明显高于C组($P<0.05$),其余时间点组间对比无统计学意义($P>0.05$),见表2。

2.2 灌注时膀胱刺激征发生率对比

A组5例发生膀胱刺激征,发生率为17.2%(5/29),B组8例发生膀胱刺激征,发生率为26.7%(8/30),C组12例发生膀胱刺激征,发生率为38.7%(12/31),三组发生率C组>B组

>A 组,组间对比无统计学意义($P>0.05$),见表 3。三组患者均中断膀胱治疗者。完成丝裂霉素灌注治疗,未出现因严重膀胱刺激征无法耐受而

表 2 两组患者不同时间点的复发率对比[例(%)]

Table 2 Comparison of recurrence rate between the two groups at different time points[n(%)]

Groups	n	After surgery for 3 months	After surgery for 6 months	After surgery for 9 months	After surgery for 12 months	After surgery for 18 months	After surgery for 24 months
Group A	29	0	1(3.4)	2(6.9)	5(17.2)*	6(20.7)*	7(24.1)*
Group B	30	0	0	1(3.3)	2(6.7)	2(6.7)	3(10.0)
Group C	31	0	0	0	0	1(3.2)	1(3.2)

Note: Compared with group A, * $P<0.05$.

表 3 灌注时膀胱刺激征发生率对比[例(%)]

Table 3 Comparison of the incidence of bladder irritation during perfusion[n(%)]

Groups	n	Urgent urination	Frequency of urination	Odynuria	Bladder irritation
Group A	29	2	2	1	5(17.2 %)
Group B	30	3	2	3	8(26.7 %)
Group C	31	5	3	4	12(38.7 %)

2.3 其他不良反应对比

本研究所有患者灌注后未发现骨髓抑制、肝肾功能异常者。

3 讨论

膀胱肿瘤复发率较高主要是由于术前膀胱镜检查时肿瘤分期被低估,癌细胞已沿膀胱壁内的淋巴管扩散,术中不能完整切除肿瘤组织,导致肿瘤组织会有残留;术中肿瘤细胞脱落种植于肿瘤黏膜上;致癌因素仍然存在,膀胱粘膜上皮继续受到致癌物刺激发生癌变等^[15-17]。TURBT 结合膀胱灌注治疗是非肌层浸润性膀胱肿瘤的主要治疗方法,由于非肌层浸润性膀胱肿瘤组织细胞间粘附的分子存在缺失,会使得肿瘤细胞间结构松散,导致肿瘤细胞容易脱漏,增加了经尿道膀胱电切术后肿瘤的复发率^[18,19]。术后即刻灌注化疗药物可迅速进入膀胱壁,在膀胱组织中达到有效的药物浓度,使得癌细胞凋亡,抑制肿瘤细胞逃脱,有助于降低术后肿瘤的复发^[20,21]。其中丝裂霉素均是常用的分子量 >200 的灌注化疗药物^[22,23],本文分析了不同剂量丝裂霉素对 TURBT 术后 NIMBC 复发的影响。

本文结果表明,三组术后不同时间点 NIMBC 复发率 A 组 >B 组 >C 组。表明 TURBT 术后加大丝裂霉素的灌注剂量,可降低患者 NIMBC 的复发率。主要是由于丝裂霉素的疗效存在剂量依赖性^[24,26],因此加大药物剂量,可降低患者的 NIMBC 复发率。术后 12 个月、18 个月、24 个月时 A 组的复发率明显高于 C 组,表明 TURBT 术后应用 40 mg 丝裂霉素灌注较 20 mg 丝裂霉素可显著降低 NIMBC 复发率,主要是由于应用大剂量丝裂霉素,可更有效的杀灭术后残留的肿瘤细胞。

本研究中所有患者灌注后未发现骨髓抑制、肝肾功能异常者。主要是由于丝裂霉素的分子量较大,很少被膀胱粘膜吸收,而进行膀胱灌注几乎不会对患者产生骨髓抑制,也不会产生肝肾功能障碍^[27,28],其主要不良反应为对膀胱粘膜产生刺激,引起膀胱刺激征。

本研究结果发现三组膀胱刺激征发生率 C 组 >B 组 >A

组,表明应用 40 mg 丝裂霉素灌注的膀胱刺激征发生率较 20 mg 丝裂霉素高,主要是由于丝裂霉素化疗会刺激膀胱壁的传入神经,导致穿出神经末梢的乙酰胆碱释放,引起膀胱平滑肌的不自主收缩,引起膀胱刺激征^[8],而随着丝裂霉素灌注剂量的增大,其对膀胱粘膜的刺激越大,本研究所有患者在术前及术后均服用了琥珀酸索利那新,其是一种新型的乙酰胆碱 M 受体阻断剂,其可对 M3 受体进行特异性阻断,从而改善患者的膀胱刺激征^[29,30]。本研究三组患者均完成丝裂霉素灌注治疗,未出现因严重膀胱刺激征无法耐受而中断膀胱治疗者,表明临床中可尝试使用大剂量丝裂霉素用于 TURBT 术后灌注,预防 NIMBC 复发。

综上所述,TURBT 术后即刻应用 40 mg 丝裂霉素,可显著降低患者的 NIMBC 复发率,通过术前、术后服用琥珀酸索利那新,可降低患者的膀胱刺激综合征,辅助患者完成 TURBT 术后丝裂霉素灌注化疗。本研究的病例资料较少,且随访时间较短,有待扩大样本量,延长随访时间进行深入研究。

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