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不同剂量头孢噻肟钠预防肺癌患者术后感染的疗效分析*

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摘要 目的:探讨不同剂量头孢噻肟钠对预防肺癌患者术后感染的临床疗效,为临床合理用药提供参考。**方法:**回顾性分析 2013 年 1 月-2015 年 8 月在本院行肺癌根治术的 90 例非小细胞肺癌患者的临床资料,按照头孢噻肟钠使用剂量的不同分为小剂量组(n=44)和大剂量组(n=46)。两组患者术前 30 min 均给予头孢噻肟钠静滴,其中小剂量组给予 2g 注射用头孢噻肟钠+0.9% NaCl 100 mL,当手术时间超过 3 h,术中再次给予同等剂量头孢噻肟钠静滴,术后 12 h 给予 2 g 头孢噻肟钠静滴,大剂量组用药方法同小剂量组,各阶段头孢噻肟钠用量改为 3 g。观察并比较两组患者术前、术后 3 d 血清超敏 C 反应蛋白(hs-CRP)、肿瘤坏死因子- α (TNF- α)、白蛋白(ALB)、白细胞计数(WBC)的变化情况,记录患者住院时间、切口愈合时间、术后感染及不良反应发生情况,统计两组病原菌清除率。**结果:**术后 3 d 两组患者血清 hs-CRP、TNF- α 、WBC 水平均较术前上升,血清 ALB 水平较术前下降,有统计学差异($P<0.05$),但两组间上述指标比较差异无统计学意义($P>0.05$)。小剂量组患者住院时间为(18.80 $\pm$ 2.50)d、手术切口愈合时间为(13.50 $\pm$ 1.05)d,大剂量组分别为(18.10 $\pm$ 2.35)d、(12.95 $\pm$ 2.05)d,两组比较差异无统计学意义($P>0.05$)。小剂量组与大剂量组术后感染率为 9.09%、10.87%,病原菌清除率为 83.33%、85.71%,两组患者感染率、病原菌清除率比较差异均无统计学意义($P>0.05$),且用药期间均未发生严重不良反应。**结论:**对围手术期肺癌患者给予小剂量头孢噻肟钠能达到与大剂量用药相同的预防术后感染效果,且安全有效,值得推广使用。

关键词:非小细胞肺癌;头孢噻肟钠;手术;感染;剂量

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Effect Analysis of Different Doses of Cefotaxime Sodium on the Prevention of Postoperative Infection in Lung Cancer Patients*

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ABSTRACT Objective: To explore the effect of different doses of Cefotaxime Sodium on the prevention of postoperative infection in lung cancer patients, so as to provide the basis for clinical rational use of drugs. **Methods:** The clinical data of 90 patients with non-small cell lung cancer underwent radical resection in our hospital from January 2013 to August 2015 were analyzed retrospectively. The patients were divided into low-dose group (n=44) and high-dose group (n=46) according to the using doses of Cefotaxime Sodium. The intravenous injection of Cefotaxime Sodium were given for both two groups, in which the low-dose group was injected with 2g Cefotaxime Sodium+0.9% NaCl 100 mL, when the surgery time was more than three hours, the patients were continuously given the same dose of Cefotaxime Sodium by intravenous injection during the surgery, finally the patients were given 2 g Cefotaxime Sodium by intravenous injection twelve hours after the surgery. The drug application methods of high-dose group was the same as the low-dose group, except change the usage to 3 g in each period of surgery. The changes of serum high sensitivity C reactive protein (hs-CRP), tumor necrosis factor- α (TNF- α), albumin (ALB), white blood cell count (WBC) were observed and compared in two groups before surgery and three days after surgery. The length of stay and surgical incision healing time, incidence rate of postoperative infection and adverse reactions in two groups were recorded, and the clearance rate of pathogenic bacteria in two groups were counted. **Results:** Three days after surgery, the serum hs-CRP, TNF- α and WBC in two groups were higher than before surgery, and the serum ALB was lower than before surgery ($P<0.05$), but the differences of above indexes in two groups after surgery had no statistical significance ($P>0.05$). The length of stay and surgical incision healing time in low-dose group were (18.80 $\pm$ 2.50) days and (13.50 $\pm$ 1.05) days respectively, which in high-dose group was (18.10 $\pm$ 2.35) days and (12.95 $\pm$ 2.05) days, there was no significant difference between the two groups ($P>0.05$). The incidence rate of postoperative infection between the two groups were 9.09%, 10.87%, and pathogenic bacteria clearance rate were 83.33%, 85.71%, there was no significant difference in infection rate and pathogenic bacteria clearance rate between the two groups ($P>0.05$), and there

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was no obvious adverse reactions during treatment in two groups. **Conclusion:** Giving low-dose of Cefotaxime Sodium can achieve the same effect of preventing postoperative infection in lung cancer patients as the high-dose of Cefotaxime Sodium, which with good safety and efficacy, and it is worthy to promotion and application.

Key words: Non-small cell lung cancer; Cefotaxime Sodium; Surgery; Infection; Dose

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前言

肺癌的发病率及死亡率居全世界恶性肿瘤排行的首位,其中非小细胞癌占其总数的 85%-90%,目前早期手术治疗及化疗仍然是临床治疗与提高患者生存率的主要手段^[1-3]。由于肺癌手术创伤大,加之肺癌患者长期受到疾病的折磨,导致其营养状况差、自身免疫功能低下,因此,容易出现术后感染,影响患者的生活质量^[4-6],所以预防肺癌患者术后感染已成为临床研究的热点。头孢噻肟钠作为第三代半合成头孢菌素,是一类化学新药,具有较广的抗菌谱,临床上主要用于各种敏感菌的感染治疗,近年来越来越多的应用到癌症患者围手术期的抗感染治疗中^[7-9],但是具体使用剂量目前还未明确。随着头孢噻肟在临床的广泛使用,许多临床病原菌对头孢噻肟产生耐药性而导致临床治疗方案的失败,为避免抗菌药的过度使用而造成的耐药性问题,本研究通过分析不同剂量头孢噻肟钠对非小细胞肺癌患者术后感染的预防效果,为规范临床头孢噻肟钠的使用提供参考,现将结果报告如下。

1 资料与方法

1.1 临床资料

回顾性分析 2013 年 1 月 -2015 年 8 月在本院行肺癌根治术的 90 例非小细胞肺癌患者的临床资料,纳入标准:(1)所有患者均经 CT、MRI 检查并经病理学或细胞学确诊为非小细胞癌 I-III 期者;(2)中性粒细胞 $\geq 1.5 \times 10^9/L$,血小板 $\geq 100 \times 10^9/L$;(3)对本研究知情同意,且自愿接受肺癌根治术治疗者。排除标准:(1)明确为小细胞肺癌或混有小细胞肺癌者;(2)对头孢噻肟钠过敏者;(3)术前存在肺部感染或其他感染者;(4)不配合治疗者。其中男性 50 例,女性 40 例,年龄 35-72 岁,平均 (46.63 ± 8.50) 岁;病理学分类:鳞癌 40 例,腺癌 28 例,腺鳞癌 22 例;解剖学占位分类:中央型肺癌 51 例,周围型肺癌 39 例;TNM 分期:I 期 30 例,II 期 34 例,III 期 26 例。按照头孢噻肟钠使用剂量的不同分为小剂量组($n=44$)和大剂量组($n=46$)。两组患者一般资料比较,差别无统计学意义($P>0.05$),具有可比性,详见表 1。

表 1 两组患者一般资料比较[n(%)]

Table 1 Comparison of general data between the two groups[(%)]

General data		Low-dose group (n=44)	High-dose group (n=46)	χ^2	P
Gender	Male	26(59.09)	24(52.17)	0.436	0.509
	Female	18(40.91)	22(47.83)		
Age (years)	>60	31(70.45)	35(76.09)	0.365	0.546
	≤ 60	13(29.55)	11(23.91)		
Pathological classification	Squamous cell carcinoma	19(43.18)	21(45.65)	0.056	0.814
	Adenocarcinoma	15(34.09)	13(28.26)	0.357	0.550
	Adeno squamous cell carcinoma	10(22.73)	12(26.09)	0.137	0.711
Classification of space occupying lesions	Central type	27(61.36)	24(52.17)	0.773	0.379
	Peripheral type	17(38.64)	22(47.83)		
TNM staging	Stage I	12(27.27)	18(39.13)	1.423	0.233
	Stage II	16(36.36)	18(39.13)	0.073	0.787
	Stage III	16(36.36)	10(21.74)	2.341	0.126
Preoperative chemotherapy	Yes	2(4.55)	3(6.52)	0.167	0.682
	No	42(95.45)	43(93.48)		
Hypertension	Yes	19(43.18)	22(47.83)	0.196	0.658
	No	25(56.82)	24(52.17)		
Diabetes mellitus	Yes	13(29.55)	18(39.13)	0.915	0.339
	No	31(70.45)	28(60.87)		

1.2 治疗方法

两组患者术前 30 min 均给予头孢噻肟钠静滴,其中小剂量组给予 2 g 注射用头孢噻肟钠(重庆科瑞制药集团有限公司,国药准字:H50021418,规格:1.0g)+0.9% NaCl 100 mL,当手术时间超过 3 h,术中再次给予同等剂量头孢噻肟钠静滴,术后 12 h 给予 2 g 头孢噻肟钠静滴。大剂量组用药方法同小剂量组,各阶段头孢噻肟钠用量改为 3 g,预防性给药时间控制在 24 h 内。

1.3 感染诊断标准

肺部感染^[10]:患者出现咳嗽、痰粘稠,肺部湿罗音,并有下列情况之一:(1)发热,体温 $\geq 38^{\circ}\text{C}$;(2)白细胞总数 $\geq 10\times 10^9/\text{L}$ 和(或)嗜中性粒细胞 $\geq 1.5\times 10^9/\text{L}$;(3)X 线显示肺部有炎性浸润性病变。手术切口感染^[11]:患者具备下述任意症状并经病原学培养为阳性:(1)手术切口出现红肿、疼痛,脓性分泌物;(2)体温 $\geq 38^{\circ}\text{C}$,存在压痛感;(3)深部切口出现脓性分泌物。术后感染率=(肺部感染人数+手术切口感染人数)/总人数 $\times 100\%$ 。

1.4 病原菌培养

清晨洗漱后使用生理盐水、双氧水依次漱口后取深咳痰液在培养皿中培养。培养合格后接种至血琼脂平皿,温度为 35°C ,培养 24 h,然后培养于沙堡培养基,温度保持不变,培养 4 h,再培养于乳糖培养基平板上,观察细菌在培养皿中的生长状况,对培养阳性且为优势菌种者进行分离与生化鉴定。实验操作、实验质量控制及结果判定均严格按照美国临床实验室标准化委员会(national clinical committee laboratory standardization, NCCLS)的规定进行。

1.5 观察指标

于术前、术后 3 d 空腹抽取患者肘静脉血 5 mL,低温离心 15 min,离心速度为 3000 r/min,吸取上清液即得血清,采用免疫比浊法(试剂盒由上海太阳生物技术公司提供)检测血清超敏 C 反应蛋白(high sensitivity C reactive protein, hs-CRP)水平,采用酶联免疫吸附试验(enzyme linked immunosorbent assay, ELISA)测定肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)水平,试剂盒由上海森雄科技实业有限公司提供,所有操作均严格按照试剂盒说明书进行。观察白蛋白(albumin, ALB)、白细胞计数(white blood cell count, WBC)变化情况,患者住院时间、切口愈合时间,术后感染及不良反应发生情况。观察病原菌清除情况(金黄色葡萄球菌,铜绿假单胞菌,肺炎克雷伯菌,鲍氏不动杆菌等),清除率=该病原菌清除数/总菌株数 $\times 100\%$ 。

1.6 统计学方法

使用 SPSS19.0 进行统计分析, TNF- α 、WBC 水平等计量资料用均数 $\pm$ 标准差($\bar{x}\pm s$)表示,比较采用 t 检验;感染率、病原菌清除率等计数资料用百分率(%)表示,采用 χ^2 检验,检验标准设置为 $\alpha=0.05$ 。

2 结果

2.1 两组患者血清炎症指标比较

两组患者术前、术后 3 d 血清 hs-CRP、TNF- α 、ALB、WBC 水平比较,差异均无统计学意义($P>0.05$);两组患者术后 3 d 血清 hs-CRP、TNF- α 、WBC 水平均较术前上升($P<0.05$),血清 ALB 水平较术前下降,有统计学差异($P<0.05$),见表 2。

表 2 两组患者血清炎症指标比较($\bar{x}\pm s$)

Table 2 Comparison of serum inflammatory markers between the two groups($\bar{x}\pm s$)

Groups	n	hs-CRP (mg/L)		TNF- α ($\mu\text{g/L}$)		WBC ($\times 10^9/\text{L}$)		ALB (g/L)	
		Before surgery	Three days after surgery	Before surgery	Three days after surgery	Before surgery	Three days after surgery	Before surgery	Three days after surgery
Low-dose group	44	8.15 $\pm$ 1.90	9.50 $\pm$ 3.12*	0.75 $\pm$ 0.13	0.91 $\pm$ 0.10*	6.55 $\pm$ 1.50	9.20 $\pm$ 0.71*	40.58 $\pm$ 4.80	30.55 $\pm$ 5.21*
High-dose group	46	8.05 $\pm$ 2.05	9.65 $\pm$ 3.51*	0.74 $\pm$ 0.09	0.88 $\pm$ 0.13*	6.40 $\pm$ 1.66	9.10 $\pm$ 0.56*	41.20 $\pm$ 5.35	31.04 $\pm$ 6.12*
t		0.240	-0.214	0.426	1.223	0.449	0.744	-0.578	-0.408
P		0.811	0.831	0.671	0.225	0.654	0.459	0.565	0.684

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

2.2 两组患者住院时间、手术切口愈合时间比较

小剂量组住院时间、手术切口愈合时间分别为(18.80 $\pm$ 2.50)d、(13.50 $\pm$ 1.05)d,大剂量组分别为(18.10 $\pm$ 2.35)d、(12.95 $\pm$ 2.05)d,两组比较差异均无统计学意义($P>0.05$)。

2.3 两组患者术后感染率与不良反应发生率比较

小剂量组术后感染 4 例,感染率为 9.09%,大剂量组术后感染 5 例,感染率为 10.87%,两组比较差异无统计学意义($P>0.05$)。两组患者使用头孢噻肟钠时均未发生严重不良反应。

2.4 两组患者病原菌清除率比较

小剂量组和大剂量组病原菌的清除率分别为 83.33%和 85.71%,两组比较差异无统计学意义($P>0.05$),见表 3。

3 讨论

国外研究发现肺癌患者术后发生医院感染比例达 5.8-25%,我国相关研究显示肺癌患者术后感染率达 10.4-17.9%^[12-14]。本研究中行肺癌根治术的 90 例非小细胞肺癌患者,共出现术后感染 9 例,感染率为 10.00%,与以上研究结果基本一致。此外,所有肺癌手术患者术后 hs-CRP、TNF- α 、WBC 均较治疗前明显上升,提示术后患者存在不同程度的炎症反应,说明对于需要进行手术治疗的肺癌患者应该给予相应的抗菌药物预防术后感染的发生。研究认为:使用抗生素的时间一般在术前 30 min 至 2 h 以内,以便抗生素药物浓度在术中达到峰值,实现抑菌的目的,同时为了避免抗生素不合理使用,术前、术后使用抗生素覆盖时间应该控制在 24 h 以内^[15-17]。

本研究使用的头孢噻肟钠属第三代头孢菌素类抗生素,通过抑制细菌细胞壁的合成达到抑制细菌的目的,对大肠埃希

表 3 两组患者病原菌清除率比较(%)

Table 3 Comparison of pathogenic bacteria clearance rate between the two groups(%)

Pathogenic bacteria	Low-dose group			High-dose group		
	Total number	Clear number	Clearance rate	Total number	Clear number	Clearance rate
Staphylococcus aureus	2	1	50.00	3	2	66.67
Pseudomonas aeruginosa	2	2	100.00	2	2	100.00
Klebsiella pneumoniae	1	1	100.00	1	1	100.00
Acinetobacter baumannii	1	1	100.00	1	1	100.00
Totals	6	5	83.33	7	6	85.71

菌、奇异变形杆菌、克雷伯菌属和沙门菌属等革兰阴性菌有较大活性,对普通变形杆菌和枸橼酸杆菌属亦有良好作用^[18-20]。作为广谱抗生素,临床上主要用于包括创伤及术后感染在内的各种敏感菌的感染治疗^[21,22]。为了合理使用头孢噻肟钠,避免抗生素泛滥使用,本研究回顾性调查了不同剂量头孢噻肟钠预防肺癌术后感染患者的相关资料,结果发现术前、术后 24 h 内预防性给药每次使用 2 g 头孢噻肟钠静滴,总剂量不超过 6g 的小剂量组,与每次使用 3 g 头孢噻肟钠静滴,术后总剂量不超过 9 g 的大剂量组相比,两组患者术后 hs-CRP、TNF- α 、ALB、WBC 均无明显差异 ($P<0.05$),同时,小剂量组患者住院时间为 (18.80 ± 2.50) d、手术切口愈合时间为 (13.50 ± 1.05) d,大剂量组分别为 (18.10 ± 2.35) d、 (12.95 ± 2.05) d,两组比较差别无统计学意义 ($P<0.05$),小剂量组术后感染发生率为 9.09%,大剂量组术后感染发生率为 10.87%,两组发生术后感染率无统计学差异 ($P<0.05$),提示小剂量头孢噻肟钠即可达到与大剂量头孢噻肟钠的预防肺癌患者术后感染的效果,也不影响患者的疾病恢复,这与相关研究结果一致^[23]。而值得注意的是,本研究中病原学检测显示,肺癌患者术后感染的主要病原菌为革兰阳性菌(如金黄色葡萄球菌)与革兰阴性菌(如铜绿假单胞菌),而头孢噻肟钠对需氧菌和部分厌氧菌均具有抑制作用,其中对呼吸道的病原菌作用更加显著,能够穿透呼吸道组织及分泌物,阻滞细菌内蛋白质的合成,进而阻断细胞壁的形成,从而抑制其增殖^[24,25]。本研究小剂量组和大剂量组病原菌的清除率分别为 83.33%和 85.71%,说明不同计量的头孢噻肟钠的杀菌作用显著,但并未发现两组病原菌清除率的有统计学差异 ($P>0.05$),因此,推荐对围手术期肺癌患者给予小剂量头孢噻肟钠进行抗感染治疗,避免由于抗生素的过量应用,引起病原菌的耐药性^[26-28]。同时,治疗过程中应准确评估患者营养状况,给予恰当的营养支持治疗,并重视患者住院期间的口腔护理,减少口腔细菌滋生及细菌下行引起肺部感染,同时做好病房消毒和护理过程中的手卫生,进一步降低肺癌患者术后感染发生的风险^[29,30]。

综上所述,不同剂量头孢噻肟钠对预防肺癌患者术后感染疗效相当,为避免抗生素过量应用,临床上可采用小剂量头孢噻肟钠进行肺癌患者术后感染的预防,符合抗菌药物用药原则,且无严重不良反应。

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