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论著

灌注液中庆大霉素对白内障患者结膜囊细菌的作用

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摘要 目的: 分析白内障手术灌注液中庆大霉素对白内障患者结膜囊细菌的作用, 为制定围手术期眼内炎预防措施提供依据。方法: 采集 200 例白内障患者结膜囊拭子标本, 进行细菌培养鉴定和药物敏感试验, 观察检出细菌对 20 $\mu\text{g/mL}$ 、40 $\mu\text{g/mL}$ 、80 $\mu\text{g/mL}$ 庆大霉素和 2 $\mu\text{g/mL}$ 左氧氟沙星敏感率。结果: 结膜囊细菌培养阳性检出率为 62%, 其中以表皮葡萄球菌为主, 耐甲氧西林金黄色葡萄球菌(MRSA)检出率为 3.22%, 耐甲氧西林表皮葡萄球菌(MRSE)检出率为 28.2%; 全部检出细菌对 20 $\mu\text{g/mL}$ 、40 $\mu\text{g/mL}$ 、80 $\mu\text{g/mL}$ 庆大霉素和 2 $\mu\text{g/mL}$ 左氧氟沙星敏感率分别为 79.84%、95.16%、97.58%、78.23%, 中高浓度庆大霉素和左氧氟沙星比较, 差异有统计学意义(均 $P < 0.05$); MRSA 和 MRSE 对 20 $\mu\text{g/mL}$ 、40 $\mu\text{g/mL}$ 、80 $\mu\text{g/mL}$ 庆大霉素和 2 $\mu\text{g/mL}$ 左氧氟沙星敏感率分别为 69.23%、94.87%、100%、41.03%, 各浓度庆大霉素和左氧氟沙星比较, 差异有统计学意义(均 $P < 0.05$)。结论: 白内障患者结膜囊细菌对灌注液中庆大霉素具有较高的敏感度, 灌注液中加入适宜浓度庆大霉素, 作为白内障围手术期眼内炎预防的措施应继续加以推广。

关键词 灌注液; 庆大霉素; 白内障; 眼内炎; 左氧氟沙星

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Effect of gentamicin in irrigating solutions on bacteria in conjunctival sac of cataract patient

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Abstract **Objective:** To analyze the effect of gentamicin in cataract irrigating solutions on bacteria in conjunctival sac of cataract patient and to provide the evidence for endophthalmitis precaution in cataract perioperative period. **Methods:** Bacterial culture and drug sensitive test were performed for 200 samples from cataract patients' conjunctival sac. Susceptibility rates of detected pathogens against 20 $\mu\text{g/mL}$, 40 $\mu\text{g/mL}$, 80 $\mu\text{g/mL}$ gentamicin and 2 $\mu\text{g/mL}$ levofloxacin were observed. **Results:** Cultural positive rate of conjunctival sac was 62% (mainly *Staphylococcus epidermidis*, among them MRSA 3.22%, MRSE 28.2%). The sensitivity rates of all detected bacteria to 20 $\mu\text{g/mL}$, 40 $\mu\text{g/mL}$, 80 $\mu\text{g/mL}$ gentamicin and 2 $\mu\text{g/mL}$ levofloxacin were 79.84%, 95.16%, 97.58%, 78.23%, respectively. The difference between high and medium concentrations of gentamicin and levofloxacin was statistically significant (all $P < 0.05$). The sensitivity rates of MRSA and MRSE to 20 $\mu\text{g/mL}$, 40 $\mu\text{g/mL}$, 80 $\mu\text{g/mL}$ gentamicin and 2 $\mu\text{g/mL}$ levofloxacin were 69.23%, 94.87%, 100%, 41.03%, respectively. The difference between gentamicin in each concentration and levofloxacin was statistically significant (all $P < 0.05$). **Conclusion:** The bacteria in the conjunctival sac of patients with cataract have a high sensitivity to gentamicin in irrigating solutions. Gentamycin at appropriate concentration in irrigating solutions is a good measure for perioperative endophthalmitis prevention during cataract surgery.

Key words irrigating solutions; gentamicin; cataract; endophthalmitis; levofloxacin

革兰染色阳性球菌是白内障术后眼内炎主要致病菌, 其中又以表皮葡萄球菌为多^[1]。有效杀灭经手术切口进入眼内细菌是减少白内障手术后眼内炎发生的重要措施。目前常规应用的措施是围手术期滴用广谱抗菌素眼药水, 以左氧氟沙星滴眼液最常用^[2]。左氧氟沙星采用滴眼方式给药, 前房内药物浓度可维持约 2 $\mu\text{g/mL}$ ^[3]。葡萄球菌属细菌对左氧氟沙星耐药率呈增高趋势^[4]。耐甲氧西林金黄色葡萄球菌(methicillin resistant *staphylococcus aureus*, MRSA)和耐甲氧西林表皮葡萄球菌(methicillin resistant

staphylococcus epidermidis, MRSE)临床检出率超过 30%, 针对 MRSE 和 MRSA, 左氧氟沙星的抑制 90% 细菌生长的最低药物浓度(MIC_{90})范围为 8~56 $\mu\text{g/mL}$ ^[5]。因此, 单纯采用手术后滴用左氧氟沙星滴眼液作为预防措施, 白内障术后眼内炎发生的风险增加。白内障手术灌注液中加入庆大霉素曾经是预防术后眼内炎发生重要预防措施, 分析不同浓度庆大霉素对白内障患者结膜囊检出细菌敏感率可以为白内障术后眼内炎防控措施的选择提供科学依据。

1 对象与方法

1.1 研究对象 本研究纳入了天津医科大学眼科

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医院白内障科 2019 年 3 月 1 日到 2019 年 5 月 31 日白内障患者共计 200 例 200 眼,男 89 例,女 111 例,年龄(63.5±7.8)岁。所行术式均为白内障超声乳化吸除术+人工晶状体植入术,全部入组患者均植入人工晶体且手术中均无特殊并发症发生。排除标准:睑缘疾病患者、泪道不通患者、1 个月内行第 2 只眼手术患者第 2 只眼。

1.2 试剂和仪器 羊血琼脂平皿和药敏板由天津金章生物有限公司提供。细菌鉴定采用法国梅里埃全自动细菌鉴定系统(VITEK 2Compact)。质控菌株为金黄色葡萄球菌 ATCC29213,由中国食品药品检定研究院提供。所用试剂盒均在有效期内,所有病原学试验均严格参照仪器和试剂说明书进行。

1.3 方法

1.3.1 细菌培养和鉴定 无菌棉拭子生理盐水浸湿,由内眼睑开始从内到外旋转轻拭下方结膜囊和下睑结膜表面,避免接触睫毛和睑缘。标本采集后立即接种于增菌液中 37℃培养箱中培养 24 h 后转种羊血琼脂平皿培养基中,血平皿放置 37℃培养箱中培养 24 h 观察,如无菌落生长,再放置 6 d 观察仍无菌落生长报告阴性,如有菌落生长进行细菌鉴定和药敏试验。MRSA 检测参考 2019 年美国临床实验室标准化协会(Clinical and Laboratory Standards Institute, CLSI)的规定,采用头孢西丁药敏试纸检测,如果抑菌环≤21 mm 判定为 MRSA,如果抑菌环≥22 mm 则判定为甲氧西林敏感金黄色葡萄球菌(methicillin sensitive staphylococcus aureus, MSSA)。MRSE 检测参考 2019 年美国 CLSI 的规定,采用头孢西丁药敏试纸检测,如果抑菌环≤24 mm 判定为 MRSE,如果抑菌环≥25 mm 则判定为甲氧西林敏感表皮葡萄球菌(methicillin sensitive staphylococcus epidermidis, MSSE)。

1.3.2 药敏试验 采用最低抑菌浓度法,庆大霉素判断试验结果采用 20 μg/mL、40 μg/mL、80 μg/mL 3 个浓度分别统计;左氧氟沙星采用眼科患者常用滴眼方式房水中可达到的平均药物浓度(2 μg/mL)进行判读并统计。观察全部检出细菌对上述 4 种条件下的抗菌素敏感率。

1.4 统计学方法 采用 SPSS19.0 统计软件进行分析,计数资料采用 χ^2 检验进行比较。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 结膜囊细菌检查情况 全部 200 例样本中,细菌培养阳性 124 例,细菌检出率为 62%,主要以表皮葡萄球菌为主,见表 1。

表 1 结膜囊细菌检出情况

Tab 1 Detection of bacteria in conjunctival SAC

细菌名称	株数	百分比/%
表皮葡萄球菌	93	75.00
金黄色葡萄球菌	17	13.70
微球菌	4	3.23
粪肠球菌	4	3.23
中间葡萄球菌	2	1.61
其他	4	3.23
总计	124	100.00

2.2 MRSA、MRSE 检出情况 全部菌株中,MRSA 检出率为 3.23%(4/124),MRSE 检出率为 28.23%(35/124)。耐药菌株合计 39 株,检出率为 31.45%(39/124)。

2.3 全部检出菌株对抗菌素敏感情况 检出细菌对 40 μg/mL 庆大霉素和 80 μg/mL 庆大霉素敏感率较高,且优于 2 μg/mL 左氧氟沙星,见表 2。

表 2 全部检出菌对抗菌素敏感率比较

Tab 2 Comparison of sensitivity of the bacteria to antibiotics

组别	抗菌素	敏感率/%	与④组比较	
			χ^2	P
①	20 μg/mL 庆大霉素	79.84(99/124)	0.097	0.755
②	40 μg/mL 庆大霉素	95.16(118/124)	15.415	0.000
③	80 μg/mL 庆大霉素	97.58(121/124)	21.842	0.000
④	2 μg/mL 左氧氟沙星	78.23(97/124)	-	-

注:各组间比较 $\chi^2=35.048$, $P=0.000$;②、③组与④组比较,差异具有统计学意义

2.4 MRSA 和 MRSE 对抗菌素敏感情况 检出的 MRSA 和 MRSE 对 40 μg/mL 庆大霉素和 80 μg/mL 庆大霉素敏感率较高,且优于 2 μg/mL 左氧氟沙星,见表 3。

表 3 MRSA 和 MRSE 对抗菌素敏感率比较

Tab 3 Comparison of susceptibility of MRSA and MRSE to antibiotics

组别	抗菌素	敏感率/%	与④组比较	
			χ^2	P
①	20 μg/mL 庆大霉素	69.23(27/39)	6.271	0.012
②	40 μg/mL 庆大霉素	94.87(37/39)	25.961	0.000
③	80 μg/mL 庆大霉素	100.00(39/39)	32.618	0.000
④	2 μg/mL 左氧氟沙星	41.03(16/39)	-	-

注:各组间比较 $\chi^2=47.441$, $P=0.000$;①、②、③组与④组比较,差异具有统计学意义

3 讨论

白内障手术术后眼内炎致病菌主要来源于患者术眼结膜囊^[6]。文献报道采用 PCR 方法检测白内障术后前房水,细菌阳性检出率超过 30%,且检出

细菌大部分同结膜囊内检出细菌同源^[7-8]。进入内眼细菌可以被体内吞噬清除机制清除,当进入眼内细菌数较多或体内清除机制不能有效清除的时候可以致眼内炎发生^[9-10]。本研究中结膜囊细菌检出率为62%,其中革兰阳性球菌为主,与文献报道一致。

为保障白内障围手术期安全,进一步降低眼内炎发生率,围手术期抗菌素应用必不可少。因为血房水屏障作用,全身应用抗菌素到达内眼浓度有限,所以局部应用抗菌素眼科更常见,使用方式包括滴眼、结膜下注射、前房注射、玻璃体腔注射等方式。常用抗菌素包括喹诺酮类、氨基糖苷类、糖肽类、头孢类^[11]。万古霉素是治疗多重耐药菌中革兰阳性球菌的重要抗菌素,为减少我国耐万古霉素菌株产生的概率,不建议眼部常规局部应用万古霉素,通常用于治疗确诊革兰阳性菌株导致眼内炎^[12]。另外,头孢类抗菌素中的头孢唑林钠作为部分特殊眼科手术患者预防性全身使用,头孢呋辛白内障术后前房注射偶有报道^[13]。

左氧氟沙星滴眼剂属于喹诺酮类,是眼科常用抗菌素之一,具有良好的角膜穿透性。文献报道采用不同滴用模式,前房水内左氧氟沙星峰浓度可以达到2 $\mu\text{g/mL}$ ^[14]。本研究中,以2 $\mu\text{g/mL}$ 作为标准判断左氧氟沙星对结膜囊常见菌群敏感性,敏感率为78.23%,与20 $\mu\text{g/mL}$ 庆大霉素对检出菌的敏感率相当;但针对MRSA和MRSE的敏感率仅为41.03%,低于20 $\mu\text{g/mL}$ 庆大霉素对检出菌的敏感率。因此单独使用左氧氟沙星作为白内障围手术期眼内炎预防措施,仍然存在一定安全隐患。

庆大霉素是一种浓度依赖性抗菌素,对葡萄球菌属细菌具有良好杀菌作用,本研究中40 $\mu\text{g/mL}$ 庆大霉素对检出菌的敏感率为95.16%,80 $\mu\text{g/mL}$ 庆大霉素对检出菌的敏感率为97.58%,优于2 $\mu\text{g/mL}$ 左氧氟沙星对检出菌敏感率,差异有统计学意义。针对MRSA和MRSE,40 $\mu\text{g/mL}$ 和80 $\mu\text{g/mL}$ 庆大霉素的敏感率均优于2 $\mu\text{g/mL}$ 左氧氟沙星,差异有统计学意义。结果显示白内障灌注液中加入适宜浓度庆大霉素可减少术后眼内炎发生的可能性。

庆大霉素杀菌效果同峰值浓度与最低抑菌浓度比值($C_{\text{max}}/\text{MIC}$)相关^[15]。白内障手术灌注液中加入80 $\mu\text{g/mL}$ 为眼科机构采用^[16],该浓度对大多数结膜囊内检出细菌的 $C_{\text{max}}/\text{MIC}$ 大于8,提示具有良好的杀菌效果。国内眼科机构也曾经广泛采用,但2015年版《抗菌药物临床应用指导原则》提示氨基糖苷类抗菌素不可用于眼内或结膜下给药,因可能引起黄斑坏死^[17]。庆大霉素结膜下注射如果误入内眼可

能导致视网膜损伤,导致在临床使用逐步减少。结膜下注射庆大霉素的常规剂量为20 mg,如果误入内眼,按照眼球平均容积计算眼内庆大霉素浓度可能超过1 000 $\mu\text{g/mL}$,该浓度会导致视网膜栓塞和视网膜坏死。为减轻庆大霉素的不良反应,全身应用庆大霉素应避免 C_{max} 大于12 $\mu\text{g/mL}$ 。局部用药对全身影响不明显,白内障手术灌注液中加入浓度为80 $\mu\text{g/mL}$ 庆大霉素可以对白内障患者结膜囊内检出的细菌具有明显的杀菌作用,但对全身无明显不良反应。

综上,灌注液中庆大霉素对白内障患者结膜囊细菌具有良好的杀菌作用,可能减少术后眼内炎发生。鉴于目前庆大霉素在眼科应用中的情况,有必要进一步评估该药物在白内障患者围手术期应用的意义,为预防白内障术后眼内炎发生提供经济有效的措施。

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