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Preventive Effect of Oral Antimicrobial Agent, Levofloxacin, on Infection After Transurethral Resection of the Prostate

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Recently, oral antibiotics have been evaluated in place of parenteral antibiotics for prophylactic chemotherapy against infections after transurethral resection of the prostate (TURP). We studied the prophylactic effect of levofloxacin (LVFX) on infections following TURP in 98 patients with prostatic hypertrophy. The subjects were divided into a high-risk group (patients with preoperative urinary tract infection and/or diabetes mellitus) and a low-risk group. For postoperative acute-phase prophylaxis (within 7 days of surgery), 600 mg/day of LVFX was administered orally in the high-risk oral group (Group Ia) and 200~400 mg/day was given in the low-risk oral group (Group IIa). A parenteral antibacterial agent was initially administered for 2 days in the high-risk intravenous group (Group Ib) and the low-risk intravenous group (Group IIb), after which they subsequently received the oral LVFX regimens mentioned above. In the healing phase (from postoperative day 8 onwards), 100 mg of LVFX was administered orally before bedtime until the disappearance of pyuria (less than 10 WBC/HPF) in all groups.

The percentage of patients with acute phase infection was 9.1% in Group Ia (n = 11), 18.8% in Group Ib (n = 16), 15.4% in Group IIa (n = 39), and 12.5% in Group IIb (n = 32). The percentage of patients with healing phase infections was 20.0% in the high-risk group (Ia+Ib, n = 15) and 16.7% in the low-risk group (IIa+IIb, n = 48). Oral LVFX therapy was useful for the prevention of acute phase infections in both the high-risk group and the low-risk group. In addition, administration of a low dose of LVFX once before bedtime was safe and useful for prophylaxis in the healing phase after TURP.

Introduction

Recently, prophylactic oral antibacterial therapy has been evaluated for the prevention of infection after transurethral resection of the prostate (TURP)[1)~8)]. Such therapy should be effective and safe with the minimum dose of antibacterial agent and should be suitable for use when TURP is performed as day surgery in the future. Although the clinical benefit of prophylactic chemotherapy for prevention of post-TURP infections

has been shown by extensive studies, most such studies were performed in the acute postoperative period. However, pyuria can persist for 1～3 months after the acute postoperative stage of TURP[9)～11)]. In general, postoperative pyuria is thought to reflect healing condition of the surgical wound. There remains a risk of infection after the acute postoperative stage. In this healing period urinary tract infection (UTI) or epididymitis can occur[2)3)11)～14)] and the incidence of infection is reported to be 7～47%[4)9)～11)].

In the present study, we divided post-TURP infections into acute postoperative infections occurring within 7 days after surgery and healing phase infections occurring after 7 days. Furthermore, we divided patients into a high-risk group, which had preoperative UTI or conditions liable to infections, and a low-risk group without such risk factors[8)], and evaluated the prophylactic effect of oral antibacterial therapy for prevention of post-TURP infections, using a fluoroquinolone, levofloxacin (LVFX).

Subjects and Methods

Subjects

The subjects were patients with benign prostatic hypertrophy who underwent TURP at our department during the period from January 1994 to March 1997. The high-risk group and the low-risk group were each divided into two subgroups, one of which received oral LVFX alone and another received parenteral antibacterial agent for the first 2 days postoperatively as a control. Patients with urethral stenosis, bladder calculus, or prostatic cancer were excluded from the study because they required additional treatment, and so a total of 98 patients were enrolled. Consent was obtained orally from all patients to participate in the clinical study. The patients were assigned to the following groups: a high-risk oral LVFX group (Group Ia, n = 11), a high-risk intravenous antibiotic group (Group Ib, n = 16), a low-risk oral LVFX group (Group IIa, n = 39), and a low-risk intravenous antibiotic group (Group IIb, n = 32). The 27 patients in the high-risk groups comprised 20 patients with preoperative UTI (including 14 patients in whom urethral catheterization had been done for urinary retention) and 9 patients with diabetes mellitus (5 patients on oral drug therapy and 4 patients receiving insulin). Two patients had both preoperative UTI and diabetes mellitus.

Method of administration of antimicrobials

During the postoperative acute phase (the first 7 days including the day of operation), LVFX was administered orally at a dose of 600 mg/day for 7 days in Group Ia, while LVFX was given at 400 mg/day for 2 days and then at 200 mg/day for 5 days in Group IIa. In Group Ib and Group IIb (the control groups), parenteral penicillins or

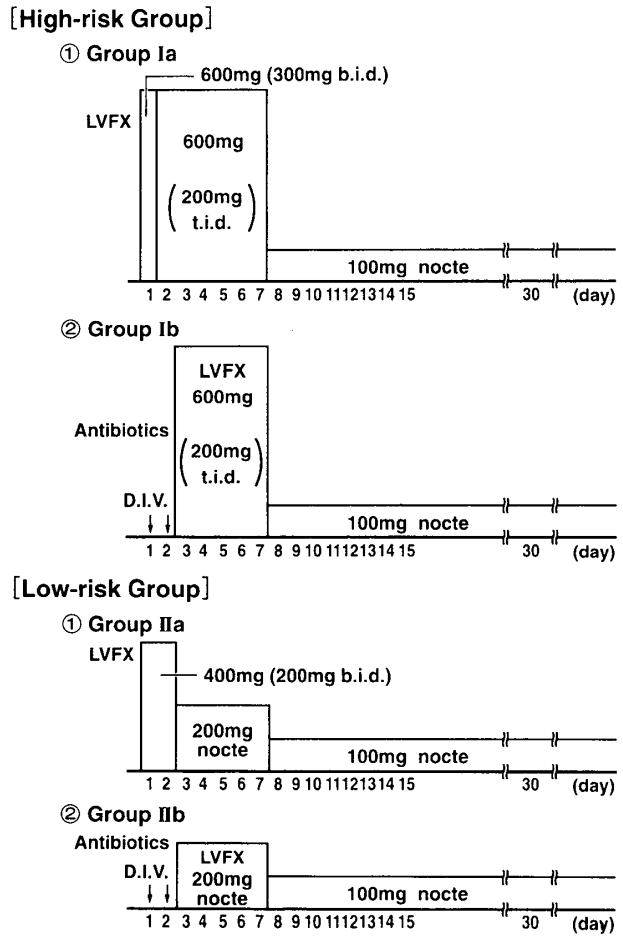

Fig. 1 Methods of administration of antimicrobials

Table 1 Patient profile

	High-risk group		Low-risk group	
	Ia	Ib	IIa	IIb
Patients	11	16	39	32
Age (years)	71.8 ± 6.3	73.6 ± 6.8	68.1 ± 7.5	66.8 ± 6.3
Body weight (kg)	59.5 ± 8.6	57.2 ± 8.9	63.6 ± 8.2	62.9 ± 9.3
Weight of resected prostate (g)	22.0 ± 8.6	21.1 ± 13.5	20.8 ± 16.1	20.9 ± 15.5
Time required for operation (min)	106 ± 31	99 ± 26	106 ± 25 *	87 ± 33 *
Duration of urethral catheterization (days)	3.5 ± 1.8	4.1 ± 2.0	3.2 ± 0.9	4.3 ± 3.2

* : $p < 0.01$, There were no significant differences except for the operating time between Group IIa and IIb.

cephems were administered for the first 2 days, and then they were given the respective oral LVFX regimens mentioned above from day 3 to day 7. During the healing phase (on and after day 8), LVFX (100 mg) was administered once before bedtime in all groups continuing until pyuria became 10 WBC/HPF or less (Fig. 1).

Definition of urinaly tract infection

The presence or absence of fever (38℃ or higher) and UTI were noted. Overt symptoms of infection or bacteriuria ($\geqq 10^4$ CFU/ml) was regarded as indicating UTI in addition to pyuria. During the acute postoperative phase, pyuria was observed in almost all patients along with some urgency symptoms, so the appearance of bacteriuria was regarded as important for the diagnosis of UTI. However, during the healing phase, UTI was diagnosed by the occurrence of symptoms such as pain on urination, pollakiuria, and a sensation of residual urine, as well as an increase of pyuria even when the bacterial count was less than 10^4 CFU/ml.

Urinary examination

Urine culture was done on the day after the operation, before discharge from hospital (4~5 days postoperatively), and once every 2 weeks during the healing phase (at the time of outpatient visits).

Statistical analysis

Statistical analysis was performed using Student's t-test and Fisher's exact test.

Table 2 Incidence of acute phase infections

	n	Fever	UTI	Total (Fever or UTI)	p
				patients (%)	
High-risk group					
Ia	11	0	1	1/11 (9.1)	NS
Ib	16	3	1	3/16 (18.8)	
Low-risk group					
IIa	39	6	0	6/39 (15.4)	NS
IIb	32	2	2	4/32 (12.5)	

NS: not significant by Fisher's exact test, The incidence of acute phase infections showed no significant differences between Group Ia and Ib, and between Group IIa and IIb.

Results

Clinical factors

The age, body weight, resected prostate weight, operating time, and postoperative urethral catheterization period were compared between the four groups (Table 1). There was a significant difference in the operating time between Groups IIa and IIb.

Postoperative acute phase infections

The number of patients with acute phase infections was 1 (9.1%) in Group Ia (n = 11), 3 (18.8 %) in Group Ib (n = 16), 6 (15.4%) in Group IIa (n = 39), and 4 (12.5%) in Group IIb (n = 32) (Table 2). In Group Ia, 1 patient had UTI. In Group Ib, 3 patients had fever and 1 patient had UTI. In Group IIa, 6 patients had fever and in Group IIb, 2 patients had fever and 2 patients had UTI. In 1

Table 3 Incidence of healing phase infections

	Infection	p
	patients (%)	
High-risk Group (Ia + Ib)	3/15 (20.0)	NS
Low-risk Group (IIa + IIb)	8/48 (16.7)	

NS: not significant by Fisher's exact test. The incidence of healing phase infections showed no significant differences between the high-risk group and low-risk group.

patient from Group Ib, both fever and UTI were observed.

Healing phase infections

The number of patients assessed for healing phase infections was 63 (Table 3). Fourteen patients were excluded because they received therapy that failed to conform to the study protocol owing to treatment of their acute phase infections. In addition, 8 patients were disqualified by protocol violations, 4 were lost to follow-up, 2 developed adverse reactions to LVFX (eczema in 1 and diarrhea in 1), and 3 required a change in therapy due to complications of TURP (postoperative hemorrhage in 2 and urethral stenosis in 1). Healing phase infections were observed in 3 patients (20.0%) from the high-risk groups (Ia +Ib) (n=15) and in 8 patients (16.7%) from the low-risk groups (IIa+IIb) (n=48), for a total of 11 out of 63 patients (17.5%). In Group I, 1 patient had prostatic bed infection and 2 had asymptomatic UTI in which bacteriuria was the only sign. In Group II, there were 6 cases of prostatic bed infection and 2 cases of asymptomatic UTI. Acute pyelonephritis or epididymitis was not observed in any group.

Bacterial isolation from urine

Fifteen bacterial and fungal strains were isolated from the urine postoperatively, when organisms isolated from different samples were counted separately. There were 6 strains of coagulase-negative Staphylococcus, 3 of *Staphylococcus aureus*, 4 of Enterococcus sp, 1 of *Pseudomonas cepacia*, and 1 of *Candida glabrata*.

Discussion

There has been much controversy about the usefulness of antibiotic prophylaxis after TURP. Many authors recommend antibiotic prophylaxis[15)~22)], but there are also many authors who have concluded that antibiotic prophylaxis is not necessary for patients without preoperative UTI[23)~26)]. In a review summarizing the results of various researchers, Grabe[13)] reported that bacteremia had occurred at a frequency of 10~32% after TURP and that UTI had occurred at a frequency of 6~70% when prophylaxis had not been given. The recent European Collaborative Study Group investigation of 764 TURP patients also concluded that antibiotic prophylaxis was useful even for patients without bacteriuria[22)].

It has been pointed out that a patient's general condition, the performance of the operation, and the nature of postoperative care were all factors that influenced the occurrence of infections after TURP[13)16)20)26)27)]. Risk factors of post-TURP infection are summerized in Fig. 2.

Taking these various factors into consideration, we agree with the view that antibiotic prophylaxis is necessary after TURP. We also recommend the use of an antibacterial agent at the smallest dose that is effective and safe. We divided the post-TURP course into two phases, the postoperative acute phase and the healing phase and studied the infections occurring in each phase. The postoperative acute phase was defined as the time when the influence of risk factors present before or during surgery was reflected, that was, 1 week after the day of the operation. This acute phase almost corresponds to the period of hospital stay after TURP in our facility. The healing phase was defined as the period for which pyuria (an indicator of the healing of the wound in the prostatic bed) was present from day 8 onwards (Fig. 2).

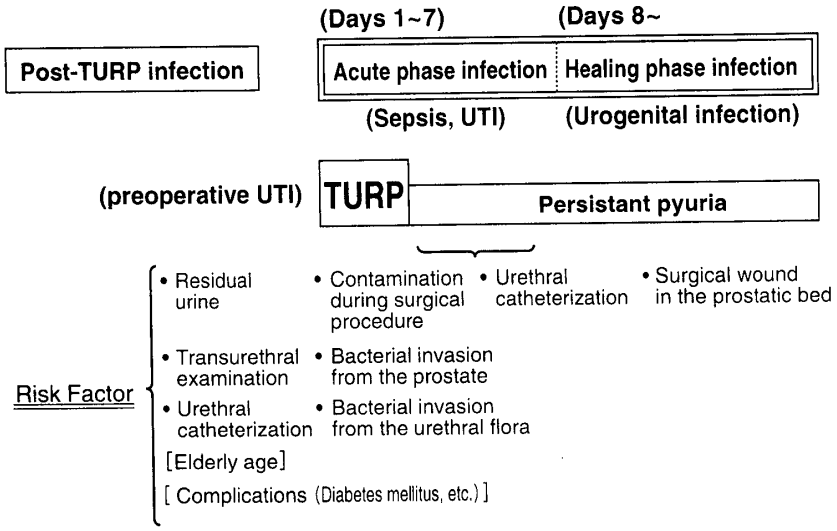

Fig. 2 Post-TURP infection and risk factors

As a result of recent advances in the development of antibacterial agents, oral agents with a strong broad-spectrum antibacterial action have become available, which achieve high levels in the prostate tissues and in the urine. The benefit of prophylactic oral antibacterial therapy for prevention of postoperative infections has been demonstrated by recent clinical studies. Grabe et al[2] used oral ciprofloxacin (CPFX) to assess the usefulness of prophylactic antibacterial chemotherapy for post-TURP infections. They administered CPFX (short course; 500 mg of CPFX orally every 12 hr for 3～4 days, prolonged course; 8～9 days) to patients with and/or without preoperative bacteriuria. They detected post-TURP bacteriuria in 34.8 and 8.8% respectively after the short and prolonged courses of prophylaxis in the group with preoperative bacteriuria and in 3.4 and 2.5% respectively in the group without preoperative bacteriuria. In the control group without prophylactic antibacterial therapy, post-TURP bacteriuria occurred in 81.6 and 19.4% respectively in the group with and without preoperative bacteriuria. Based on these results, they reported that oral CPFX was a useful prophylaxis of postoperative bacterial infections. Adolfsson et al[3] administered 160/800 mg/day of trimethoprim-sulfamethoxazole (TMP-SMX) or 400 mg/day of norfloxacin (NFLX) to patients with preoperative bacteriuria for 6 days from the evening before surgery and assessed the elimination of bacteria at 10～20 days postoperatively. Bacterial eradication was achieved in 57/73 (78.1%) patients treated with TMP-SMX and in 72/92 (78.3%) patients treated with NFLX, and upper UTI or septicemia was not observed in any of the patients. They reported that NFLX showed little toxicity and was clinically beneficial. Hall et al[7] and Murdoch et al[1] also reported that prophylactic therapy with oral antibacterial agents was useful for prevention of post-TURP infections based on studies using fleroxacin and ciprofloxacin, respectively. It has also been reported that therapy using oral antibacterial agents was as effective as treatment with parenteral antibacterial agents[5][6], so that post-TURP therapy using only oral antibacterial agents was likely to be more widely employed in the future.

LVFX is a fluoroquinolone and is the optical S-(−) isomer of ofloxacin. LVFX shows potent and broad antibacterial activity. LVFX rapidly achieves a high tissue concentration without accumulation and is largely excreted unchanged in the urine. The present study showed that oral ad-

ministration of LVFX in the postoperative acute phase was useful; there was no significant difference in prophylactic effect between oral antibacterial therapy and intravenous therapy in both the high-risk and low-risk groups.

It is known that pyuria continues for a relatively long time during the healing phase after TURP[9)~11)]. Pyuria is regarded as a local reaction to the process of healing and it does not necessarily indicate infection. Thus, there have been arguments over the use of prophylactic therapy during this period. However, elderly patients with various complications may be at risk of postoperative urinary tract infections. In the present study, the incidence of healing phase infection was compared between the high-risk and low-risk groups during low-dose of LVFX prophylaxis, and no difference between two groups was found (20.0 and 16.7% respectively). In Japan, the incidence of urinary tract infection during the healing phase is reported to be 7～47%[4)9)~11)], although there have been only a few studies performed and the incidence differs depending on the type of antibiotic therapy and the observation period. The incidence observed in our study was fairly low and there was no pyelonephritis or epididymitis. If infection of a parenchymatous organ occurs, intravenous chemotherapy is often needed. Therefore, if administration of LVFX at a small dose during the healing phase has a prophylactic effect, as was shown in our study, there may be great advantages from both clinical and economic viewpoint.

The necessity for prophylactic therapy after TURP will continue to be further discussed in the future. We consider that there is no need for postoperative antibacterial therapy if the following requirements are met: the patient does not have preoperative UTI or a systemic disease that may compromise immune function, such as diabetes mellitus; TURP is performed aseptically in a short time without complications; the prostatic adenoma is removed completely; the urethral catheter is kept clean and removed at an early stage; and urinary obstruction is improved with no residual urine. If one of the above criteria is not met, low-dose prophylactic therapy with a safe oral antibacterial agent such as LVFX may be useful.

References

1) **Murdoch DA, Badenoch DF, Gathalian ER**: Oral ciprofloxacin as prophylaxis in transurethral resection of the prostate. Br J Urol **60**: 153–156, 1987
2) **Grabe M, Forsgren A, Björk T et al**: Controlled trial of a short and a prolonged course with ciprofloxacin in patients undergoing transurethral prostatic surgery. Eur J Clin Microbiol **6**: 11–17, 1887
3) **Adolfsson J, Köhler C, Falck L**: Norfloxacin versus trimethoprim-sulfamethoxazole: A study in patients with known bacteriuria undergoing transurethral resection of the prostate. Scand J Urol Nephrol **23**: 255–259, 1989
4) **Ueda S, Matsuoka K, Yamashita T et al**: Antibiotic prophylaxis with an oral antibacterial agent in patients undergoing TUR-P. Nishinihon J Urol **51**: 1183–1187, 1989 (in Japanese)
5) **Klimberg IW, Childs SJ, Madore RJ et al**: A multicenter comparison of oral lomefloxacin versus parenteral cefotaxime as prophylactic agents in transurethral surgery. Am J Med **92** (Suppl 4 A) : 121–125, 1992
6) **Crawford ED, Berger NS, Davis MA et al**: Prevention of urinary tract infection and bacteriuria following transurethral surgery: Oral lomefloxacin compared to parenteral cefotaxime. J Urol **147**: 1053–1055, 1992
7) **Hall JC, Christiansen KJ, England P et al**: Antibiotic prophylaxis for patients undergoing transurethral resection of the prostate. Urology **47**: 852–856, 1996
8) **Goya N, Toma H, Ito H et al**: Investigation of prophylactic oral antibacterial therapy after transurethral prostatectomy. J Tokyo Wom Med Coll **66**: 90–94, 1996 (in Japanese)
9) **Sagawa S, Takaha M, Sonoda T et al**: Chemotherapy after prostatectomy—Effects of long term administation of Pivmecillinam (PMPC). Acta Urol Jpn **30**: 423–430, 1984 (in Japanese)
10) **Murakami S, Igarashi T, Hara S et al**: Long-

term chemotherapy for treatment of persistent pyuria in patients undergoing transurethal prostatectomy. Rinsho Hinyokika **43**: 977–979, 1989 (in Japanese)

11) **Fujita K, Matsushima H, Munakata A**: Pyuria after transurethral prostatectomy: A long follow-up study on ofloxacin. Chemotherapy **39**: 989–991, 1991 (in Japanese)
12) **Melchior J, Valk WL, Foret JD et al**: Transurethal prostatectomy and epididymitis. J Urol **112**: 647–650, 1974
13) **Grabe M**: Antimicrobial agents in transurethral prostatic resection. J Urol **138**: 245–252, 1987
14) **Sherman CP, Silverman SH, Johnson M et al**: Single dose, oral antibiotic cover for transurethral prostatectomy. Br J Urol **62**: 434–438, 1988
15) **Gaudin HJ, Zide HA, Thompson GJ**: Use of sulfanilamide after transurethral prostatectomy. JAMA **110**: 1887–1890, 1938
16) **Nielsen OS, Maigaad S, Frimodt-Møller M et al**: Prophylactic antibiotics in transurethral prostatectomy. J Urol **126**: 60–62, 1981
17) **Allan WR, Kumar A**: Prophylactic mezlocillin for transurethral prostatectomy. Br J Urol **57**: 46–49, 1985
18) **Prokocimer P, Quazza M, Gibert C et al**: Short-term prophylactic antibiotics in patients undergoing prostatectomy: Report of a double-blind randomized trial with 2 intravenous doses of cefotaxime. J Urol **135**: 60–64, 1986
19) **Charton M, Vallancien G, Veillon B et al**: Antibiotic prophylaxis of urinary tract infection after transurethral resection of the prostate. J Urol **138**: 87–89, 1987
20) **Raz R, Almog D, Elhanan G et al**: The use of ceftriaxone in the prevention of urinary tract infection in patients undergoing transurethral resection of the prostate (TUR-P). Infection **22**: 347–349, 1994
21) **Rossetti SR, Boccafoschi C, Pellegrini A et al**: Aztreonam monotherapy as prophylaxis in transurethral resection of the prostate. A multicenter study. Rev Infect Dis **13** (Suppl 7) : S626–S628, 1991
22) **European Study Group (Hargreave TB, Botto H, Rikken GHJM et al)** : European collaborative study on antibiotic prophylaxis for transurethral resection of the prostate. Eur Urol **23**: 437–443, 1993
23) **Qvist N, Christiansen HM, Ehlers D**: Prophylactic antibiotics in transurethral prostatectomy. Urol Res **12**: 275–277, 1984
24) **Ferrie BG, Scott R**: Prophylactic cefuroxime in transurethral resection. Urol Res **12**: 279–281, 1984
25) **Houle AM, Mokhless I, Sarto N et al**: Perioperative antibiotic prophylaxis for transurethral resection of the prostate: Is it justifiable? J Urol **142**: 317–319, 1989
26) **Christensen MM**: Antimicrobial prophylaxis in transurethral resection of the prostate. Scand J Urol Nephrol **25**: 169–174, 1991
27) **Symes JM, Hardy DG, Sutherns K et al**: Factors reducing the rate of infection after transurethral surgery. Br J Urol **44**: 582–586, 1972

経尿道的前立腺切除術後の感染症に対する経口抗菌剤 Levofloxacin 予防的投与の効果の検討

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われわれは前立腺肥大症患者98例を，リスク群（術前尿路感染症を有する患者および糖尿病患者）と非リスク群とに分け，経尿道的前立腺切除術（TURP）後感染症に対する経口剤の予防的効果を検討した．術後急性期（手術日を含め7日以内）の化学療法は，リスク経口群（Ia群）ではlevofloxacin（LVFX）600 mg/日を7日間，非リスク経口群（IIa群）ではLVFX 400 mg/日を2日間およびLVFX 200 mg/日を5日間投与した．対照として，リスク点滴静注群（Ib群）および非リスク点滴静注群（IIb群）では2日間のみ抗生剤の点滴静注を行い，3日から7日までは経口群（IaおよびIIa群）と同様とした．また創傷治癒期（術後7日目以降）には，4群ともにLVFX 100 mgを就寝前に1回服用させ，膿尿が白血球10コ/high power field以下になるまで継続した．感染症については，38.0℃以上の発熱および尿路性器感染症の有無を検討した．

急性期感染症を示した症例は，Ia群（n＝11）：9.1%，Ib群（n＝16）：18.8%，IIa群（n＝39）：15.4%，IIb群（n＝32）：12.5%であった．創傷治癒期感染症は，検討できた63例のうち，リスク群（Ia＋Ib群，n＝15）：20.0%，非リスク群（IIa＋IIb群，n＝48）：16.7%であった．

術後急性期における経口抗菌剤LVFXによる化学療法は，リスク症例，非リスク症例ともに，注射用抗生物質を併用した群に比べ感染症発症頻度に有意差を認めず，有用であった．また創傷治癒期においても，LVFXの少量就寝前1回投与法は，安全で有用であると考えられた．