The Seoul Journal of Medicine
Vol. 26, No. 3:221-227, September 1985

Clinical Study of Prophylactic Antibiotics to Determine the Optimum Duration of Administration*

Jin-Pok Kim and Sun-Whe Kim

Department of Surgery, College of Medicine, Seoul National University, Seoul 110, Korea

= Abstract = To confirm the benefits of short term perioperative chemoprophylaxis a prospective randomized comparative study was performed. The patients admitted for elective gastroduodenal or biliary tract surgery had been enrolled. The patients were given two different antibiotic regimens; cefazolin (I) or combination of penicillin and gentamicin (II), for three different periods starting preoperatively; 1 day (group A), 3 days (group B) and 5 to 7 days (group C). The each group of patients was similar in terms of age, sex, weight, duration of operation, preoperative hospital days and distribution of disease and operation. The rate of infection was 5.1% (5/99) in group A, 7.7% (8/104) in group B and 6.9% (7/101) in group C. No significant difference was found between cefazolin alone (5.8%) and penicillin plus gentamicin (7.3%) in the rate of infection. This result suggests that there is no benefit from continuing antibiotic administration beyond the day of operation in preventing infectious complication after clean contaminated operation.

Key Words : ***Antibiotic prophylaxis, Decisive period, Clean contaminated surgery***

INTRODUCTION

The timing and duration of antibiotic administration to prevent postoperative infection has long been debated. Even still many published data contain inconclusive results, a principle almost established is that prophylaxis should be started preoperatively to be effective and continued only a brief postoperative period to be safe. This concept of early administration of short course antibiotics had been suggested by Miles (1957) and Burke (1961). The value of the concept had been confirmed in their pioneering experimental work and in numerous well controlled clinical trials. Despite this fact, use of antibiotics is still inappropriate in terms of duration of administration in many hospitals in different countries (Shapiro *et al.* 1979; Weiner *et al.* 1980). This is a clinical study to determine the duration of effective and economic use of prophylactic antibiotics.

MATERIALS AND METHODS

During 9-month period 382 patients who were admitted for elective gastroduodenal or biliary tract surgery at the Department of Surgery, Seoul National University Hospital, had been involved in this study. The following patients were excluded before assignment; immunosuppressed patients, chronic debilitated patients, patients with diabetes or renal failure, patients who received antibiotics within two weeks prior to surgery and pregnant or lactating women. The patients were given two distinct regimens; cefazolin alone or combination of penicillin and gentamicin. Antibiotic prophylaxis were started 1 hour prior to surgery. The patients in cefazolin group were given 0.5 gm dose every 6 hours intravenously. The patients in combination therapy group were given 2 to 4 million units (50,000 U/kg) of crystallin penicillin-G every 6 hour intravenously or 1 to 2 million units(25,000 U/kg)of procaine penicillin-G every 12 hours intramuscularly and 60-80 mg (1-2 mg/kg) of gentamicin every 8 hours intramuscularly. These antibiotics were administered for three distinct duration; 1 day, group A; 3 days, group B; 5 to 7 days, group C. Each group was divided into two subgroups according to the antibiotics administered; subgroup I for cefazolin alone and subgroup II for combina-

* Presented at the 14th International Congress of Chemotherapy, Kyoto, Japan, June 25, 1985.

tion of penicillin and gentamicin (A-I, A-II, B-I, B-II, C-I, C-II). The patients were evaluated for possibility of exclusion and assigned to one of 6 subgroups of protocol using random number chart in the day before operation. To prevent possible untoward effects, skin tests for antibiotics were performed. Operative field was prepared with 7.5% Betadine soap and Hygien alcohol. Before closing the wound, it was cleansed with saline only. If operative time was prolonged beyond 6 hours, another dose was given intraoperatively. Although the patients were assigned to one of 6 groups, the patients were excluded from the study if there were reactive skin test to the antibiotics, gross spillage of intestinal contents, infected bile, acute inflammation, pus drainage, unexpected operation or unprepared colonic resection. After operation, the patients were observed for the occurrence of untoward effects of antibiotics and infectious complications. Infection had been defined as gross pus drainage from wound or the presence of symptoms and signs, the most likely explanation of which was the evolution of abscess in the peritoneal cavity. Culture and sensitivity test were performed for all the specimens obtained.

RESULTS

Three hundreds and eighty two patients were assigned to this study, but of these 78 patients were excluded due to gross spillage or acute inflammation, unexpected operation, reactive skin test and poor cooperation and then actually 304 patients were eligible (Table 1). No significant differences were noted between groups in terms of number of patients, age, sex, body weight, duration of operation and preoperative hospital day (Table 2). Gastroduodenal surgery had been performed on 197 patients and biliary tract surgery had been performed on 107 patients (Table 3 & 4).

Table 5 shows the infection rates in each subgroups. The overall infection rate was 6.6% (20/304). All the infection cases were wound infection except one which was subphrenic abscess developed after partial gastrectomy in group A-II. The infection rate of group A-I was the lowest as 3.8% and that of group C-II was the highest as 9.1%, but there was no statistical significance between them.

According to the duration of administration the infection rate of group A was 5.1% (5/99); group B,

Table 1. Reasons for exclusion of patients after assignment

Total number of patients	382
Poor cooperation	39
Gross spillage or acute inflammation	10
Unexpected operation	15
Reactive skin test	14
Actually studied patients	304

Table 2. Patient statistics

	A-I	A-II	B-I	B-II	C-I	C-II
No. of patients	52	47	56	48	46	55
Mean age (years)	49.3	50.5	50.3	50.2	49.5	52.1
Sex (M/F)	28/24	30/17	33/23	29/19	32/14	34/21
Average Weight(kg)	55.8	54.3	53.5	50.9	53.1	53.9
Preop. hospital day	5.1±3.4	5.2±2.7	5.3±2.9	6.0±3.5	5.7±3.4	6.1±3.4
Operation duration(min.)	143±33	139±38	150±52	149±41	156±36	157±54

Table 3. Disease distribution of each group

Disease	A-I	A-II	B-I	B-II	C-I	C-II	Total
Stomach cancer	25	23	30	22	27	32	159
Benign gastric ulcer	4	3	6	4	3	2	22
Duodenal ulcer	2	2	3	3	4	2	16
GB stone	13	11	14	10	9	12	69
CBD stone c̄/s̄ GB stone	7	8	3	8	3	7	36
Intrahepatic stone	-	-	-	1	-	-	1
GB cancer	1	-	-	-	-	-	1

Table 4. Distribution of operation of each group

Operation	A-I	A-II	B-I	B-II	C-I	C-II	Total
Op. including gastrectomy	25	24	30	24	29	32	164
Vagotomy + pyloroplasty	2	3	3	2	3	1	14
Gastrojejunostomy	4	1	6	3	2	3	19
Cholecystectomy	13	10	12	8	8	10	61
CBD exploration	8	9	5	8	4	7	41
Sphincteroplasty	-	-	-	1	-	-	2
Biliary-enterostomy	-	-	-	1	-	2	3

7.7% (8/104) and group C, 6.9% (7/101). No significant difference was found between them (Table 6). Comparing cefazolin group (A,B,C-I) with combination of penicillin and gentamicin (A,B,C-II), 9 out of 154 patients had infections in group I (5.8%) and 11 out of 150 patients had infections in group II (7.3%) (Table 7). Significant difference could not be found between them. The rate of postoperative infection in gastroduodenal surgery was 3.6% (7/197) and that in biliary tract surgery was 12.1% (13/107) (Table 6). There was significant difference between them ($p<0.05$). In this study infectious complications after clean contaminated surgery did not depend on the antibiotics selected and the duration of administration. It is suggested that postoperative infection may depend on the kinds of operation, duration of operation and skillfulness of operative techniques (Table 8).

Table 5. Postoperative infection in each group

Group	No. of patients	Infection(%)
A-I	52	2(3.8)
A-II	47	3*(6.4)
B-I	56	5(8.9)
B-II	48	3(6.3)
C-I	46	2(4.3)
C-II	55	5(9.1)
Total	304	20(6.6)

* One of these cases was subphrenic abscess

Table 6. Postoperative infection rate according to duration of administration

Area of Operation	Number of Infection/Total patients(%)			Total
	A(1 day)	B(3 days)	C(5-7 days)	
Stomach	1/59(1.7)	2/68(2.9)	4/70(5.7)	7/197(3.6)
Biliary	4/40(10.0)	6/36(16.7)	3/31(9.7)	13/107(12.1)
Total	5/99(5.1)	8/104(7.7)	7/101(6.9)	20/304(6.6)

Details of infection cases were shown in Table 9. The causative organisms were mostly enteric bac-

Table 7. Postoperative infection rate according to antibiotics

Area of Operation	Number of Infection/Total patients(%)		Total
	A,B,C-I	A,B,C-II	
Stomach	4/104(3.8)	3/93(3.2)	7/197(3.6)
Biliary	5/ 50(10.0)	8/57(14.0)	13/107(12.1)
Total	9/154(5.8)	11/150(7.3)	20/304(6.6)

Table 8. Comparison between total case and infection case

	Total case	Infection case
Mean age (years)	50.3	53.0
Preoperative hospital day	5.6	7.3
Duration of operation(min.)	148	166
Area of operation		
Stomach	197	7(3.6%)
Biliary	107	13(12.1%)

Table 9. Details of Infection cases

No.	Group	Sex Age	Preop. hospital day	Op. Duration (min)	Diagnosis	Operation	Organisms
1	A-I	M/44	14	160	CBD stone	Cholecystectomy & choledochostomy	*E. coli*
2	A-I	M/49	2	95	GB stone	Cholecystectomy	-
3	A-II	M/46	3	145	GB stone	Cholecystectomy	*E. coli*
4	A-II	M/47	5	150	GB stone	Cholecystectomy	*E. coli*
*5	B-I	M/71	5	160	Stomach cancer	Subtotal gastrectomy	Enterococci *Proteus mirabilis*
6	B-I	F/46	5	150	GB & CBD stone	Cholecystectomy & Choledochostomy	-
7	B-I	M/37	5	135	Stomach cancer	Subtotal gastrectomy	*Staphylococcus aureus* *Pseudomonas fluorescence*
8	B-I	M/46	5	360	Stomach cancer	Total gastrectomy	Enterococci *Staphylococcus epidermidis*
9	B-I	F/53	12	210	CBD stone	Sphincteroplasty	Enterococci
10	B-I	F/61	9	140	CBD stone	Cholecystectomy	*E. coli*
11	B-II	M/54	13	165	GB stone	Cholecystectomy & choledochostomy	*E. coli* *Proteus morganii*
12	B-II	M/68	10	120	CBD stone	Cholecystectomy & choledochostomy	*E. coli*
13	B-II	M/41	8	220	Intrahepatic stone	Choledochojejunostomy	-
14	C-I	F/44	2	170	Stomach cancer	Subtotal gastrectomy	-
15	C-I	M/57	6	150	Stomach cancer	Subtotal gastrectomy	-
16	C-II	M/74	13	60	GB & CBD stone	Cholecystectomy & choledochostomy	*E. coli* *Proteus morganii*
17	C-II	M/61	7	190	Stomach cancer	Subtotal gastrectomy	*E. coli*
18	C-II	F/44	7	210	GB stone	Cholecystectomy & choledochostomy	*Klebsiella pneumoniae*
19	C-II	M/51	13	160	CBD stone	Cholecystectomy	*E. coli*
20	C-II	M/66	4	170	Stomach cancer	Subtotal gastrectomy	*Staphylococcus epidermidis*

* 5; Subphrenic abscess

teria. Infection was rarely caused by microorganisms from operative environment, patient's skin or surgeon's hand, but was mainly caused by intestinal and biliary contents.

DISCUSSION

There are three major principles in the prophylactic use of antibiotics. First, prophylactic antibiotics should be administered when postoperative infection rate would be relatively high or the consequence of infection might be serious. Second, antibiotics should be effective against major anticipated contaminating bacterial species. Agents of lowest toxicity and cost to the patients should be selected. Third, prophylaxis should be started before operation and continued only a brief period.

Surgical procedures are classified into four categories; clean surgery, clean contaminated surgery, contaminated surgery and dirty surgery. There is no need for prophylaxis in the operation classified as clean surgery, except when the prosthetic materials or devices are involved. High risk of infection justifies antibiotic prophylaxis in clean contaminated and contaminated surgery such as gastric and biliary tract surgery. Cruse (1975) reported 7.5% of overall wound infection rate in 9,370 clean contaminated wounds, 10% wound infection rate after partial gastric resection, 6.9% after cholecystectomy and 17.1% after choledochotomy. There is few bacteria in the upper gastrointestinal tract due to gastric acidity and motility. So antibiotic prophylaxis may not be recommended in patients with simple duodenal ulcer. If gastric acidity is reduced or motility is impaired for some reasons, the number of bacteria increase with risk of infection. Then prophylaxis is indicated in the patients with gastric ulcer, malignancy and ulcer with hemorrhage or obstruction. All the patients with duodenal ulcer in this study had complications such as hemorrhage or obstruction.

Several studies have showed the increased incidence of positive bile culture and infectious complication in patients over age 70 or patients with acute cholecystitis, obstructive jaundice or common bile duct stone (Keighley 1975). Gunn (1976) reported that the patients who have three or more of seven following risk criteria have 50% positive rate of bile culture and need prophylactic antibiotics; age over 50, history of jaundice, empyema in gallbladder, abnormal liver function, nonfunctioning in oral GB, common bile duct dilatation and common bile duct stricture or stone. Patients in this study had not been specified and selected according to the risk factors like above.

Cefazolin was selected in this study because it is known to be safe, broad in spectrum and effective against anticipated organisms based on the data of bacteriology and sensitivity test during recent three years in this hospital. Penicillin and gentamicin were compared because they are lower in cost and have been commonly used in this country. Single agent prophylaxis is considered to be more convinient and safe.

Sufficient evidence to justify prophylactic use of antibiotics for prevention of postoperative infection had not been presented until Miles and Burke performed laboratory studies that provided scientific basis for the prophylaxis (Miles *et al.* 1957; Burke 1961; Edlich *et al.* 1973). The rationale they suggested is that the use of prophylactic antibiotics is a means of reducing the risk of infection during surgical procedure by supplementing the patient's natural resistance. The supplementary antibiotics must be available to act in coordination with the host defence mechanisms when bacteria arrive in the tissue. They defined the effective "decisive period" of prophylaxis and suggested that effective prophylaxis requires preoperative administration and antibiotics begun as late as 3 to 4 hours after skin incision fails to reduce postoperative infection (Fig. 1). Numerous subsequent clinical studies (Bernard & Cole 1964; Polk *et al.* 1969; Pollock *et al.* 1972; chetlin *et al.* 1973; Ketcham 1974; Keighley *et al.* 1975; Griffiths *et al.* 1976; Gunn 1976; Leigh *et al.* 1976; Stone *et al.* 1976 & 1979; Strachan *et al.* 1977) have supported this experimental observation. Polk and Lopez-Mayor (1969) performed the first prospective controlled randomized double blind study that confirmed the benefit of this concept.

Even though many clinical studies have demonstrated the efficacy of preoperative administration, the studies concerning the adequate duration of administration are rare. Published trials record a range of duration from one dose to 14 days, but many of them had given antibiotics for 24 hours or less. Clinical studies comparing two different durations have shown that the shorter duration has been as effective as the longer duration and that the prolonged administration beyond 1 or 2 days adds nothing to prevention and may carry the dangers such as evolution of resistant strains of bacteria (Stone *et al.* 1979; Strachan *et al.* 1977). A few trials of single dose antibiotic prophylaxis have been reported (Griffiths *et al.* 1976; Leigh *et al.* 1976; Pollock *et al.* 1972; Strachan *et al.* 1977). Leigh (1976) reduced wound infection after appendectomy by giving single intramuscular dose of lincocin after wound closure. Griffiths (1976) found that one dose of a combination of an aminoglycoside with incomycin effectively reduced sepsis after gastrointestinal sugery. When single and multiple doses were compared, no difference in efficacy was found in cefazolin prophylaxis for cholecystectomy (Strachan *et al.* 1977).

Still many surgeons, however, are used to start prophylaxis postoperatively and prefer to continue for several days or even throughout the hospital days (Shapiro *et al.* 1979; Weiner *et al.* 1980). The reasons for prolonged continuance are because it is thought to be able to compensate poor operative technique or insufficient antisepsis and because they have old habits of dependency on the antibiotics and false sense of security. Surgeons should make sure that prophylactic antibiotics cannot replace skillful surgical techiques such as preservation of blood supply, meticulous hemostasis, removal of necrotic tissue or foreign body and closing wound not remaining dead space.

In summary, a prospective randomized clinical study was performed on 304 clean contaminated operations to determine the optimum duration of prophylaxis and the following conclusions were obtained. (1) Rate of postoperative infection did not depend on the duration of administration and the kinds of antibiotics selected in this study, but the type of operation could affect the rate of infection. (2) In clean contaminated operation, one day admi-

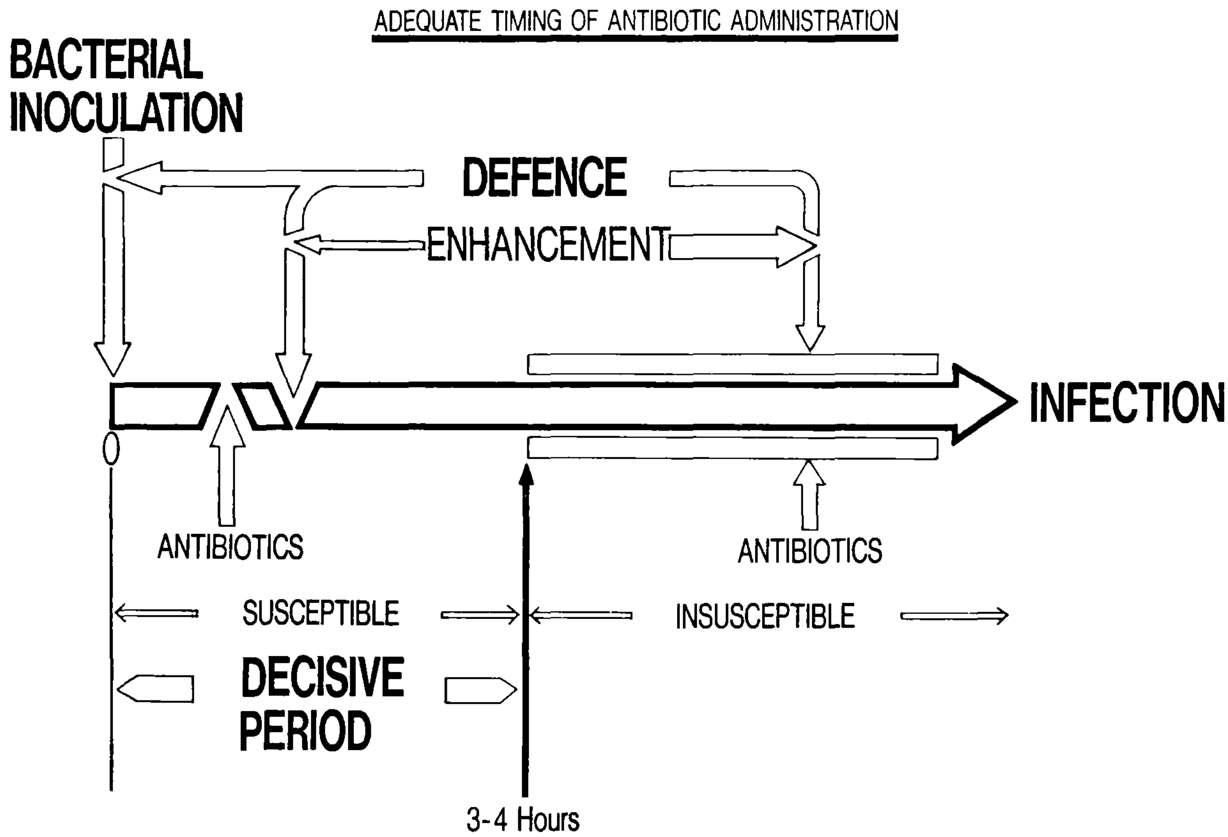

Fig. 1. The effectiveness of defense against bacteria depends largely on natural resistance. The resistance is reduced by the abnormal physiology enhanced by anesthesia, shock, trauma or operation. Infection can be prevented by supplementing the host defense, but only if the supplement is delivered during the early susceptible "decisive period."

nistration starting preoperatively was sufficient to prevent postoperative infection and no further benefit was obtained from prolonged prophylaxis.

REFERENCES

Berger SA, Nagar H, Weitzman S. Prophylactic antibiotics in surgical procedure. Surg. Gynecol. Obstet. 1978, 146:469-475

Bernard HR, Cole WR. The prophylaxis of surgical infection; The effect of antimicrobial drugs on the incidence of infection following potentially contaminated operations. Surgery 1964, 56:151-157

Burke JF. The effective period of preventive antibiotic action in experimental incisions and dermal lesions. Surgery 1961, 50:161-168

Chetlin SH, Elliot DW. Preoperative antibiotics in biliary surgery. Arch. Surg. 1973, 107:319-323

Cruse PJF. Incidence of wound infection on the surgical services. Surg. Clin. North Am. 1975, 55:1269-1275

Edlich R, Smith OT, Edgerton MT. Resistance of the surgical wound to antimicrobial prophylaxis and its mechanisms of development. Am. J. Surg. 1973, 126:583-591

Griffiths DA, Simpson RA, Shorey BA, Speller DCE, Williams NB. Single dose preoperative antibiotic prophylaxis in gastrointestinal surgery. Lancet 1976, 2:325-328

Gunn AA. Antibiotic in biliary surgery. Br. J. Surg. 1976, 63:627-630

Keighley MRB, Drysdale RB, Quaraish AH. Antibiotic treatment of biliary sepsis. Surg. Clin. North Am. 1975, 55:1379-1390

Ketcham AS. Systemic prophylactic antibiotics in surgical patients. JAMA 1974, 229.1638-1639

Leigh DA, Pease R, Henderson H, Simmons K, Russ R. Prophylactic lincomycin in the prevention of wound infection following appendectomy. Br. J. Surg. 1976, 63:973-977

Miles AA, Miles EM, Burke J. The value and duration of defense reaction of the skin to the primary lodgement of bacteria. Br. J. Exp. Pathol. 1957, 38:79-96

Polk HC Jr, Lopez-Mayor JF. Postoperative wound infection; A prospective study of determinant factors and prevention. Surgery 1969, 66:97-103

Pollock AV, Tindal DS. The effect of a single dose parenteral antibiotic in the prevention of wound infection. Br. J. Surg. 1972, 59:98-99

Shapiro M, Townsend TR, Rosner B, Kass EH. Use of antimicrobial drugs in general hospital. N. Engl. J. Med. 1979, 301:351-355

Stone HH, Hooper CA, Kolb LD, Geheber CE, Dawkins EJ. Antibiotic prophylaxis in gastric, biliary and colonic surgery. Ann. Surg. 1976, 184:443-452

Stone HH, Haney BB, Kolb LD, Geheber CE, Hooper CA. Prophylactic and preventive antibiotic therapy; Timing, duration and economics. Ann. Surg. 1979, 189:691-699

Strachan CJ, Black J, Powis SJ, Waterworth TA, Wise R, Wilkinson AR, Burdon DW, Severn M, Mitra B, Norcott H. Prophylactic use of cefazolin against wound sepsis after cholecystectomy. Br. Med. J. 1977, 1:1254-1256

Weiner JP, Gibson G, Munster AM. Use of prophylactic antibiotics in surgical procedure; Peer review guidelines as a method for quality assurance. Am. J. Surg. 1980, 139;348-351

= 국문초록 =

예방적 항생제의 적정 투여기간 결정을 위한 임상적 연구

서울대학교 의과대학 외과학교실

김진복 · 김선회

Clean-contaminated surgery에 있어서 수술 후 감염성 합병증을 예방하기 위한 항생제의 적정한 투여기간을 결정하기 위하여, 위십이지장수술 또는 담도계수술을 받기 위해 서울대학교병원 일반외과에 입원한 304명을 대상으로 전향성 임상연구를 시행하였다. 투여 항생제에 따라 I군(cefazolin 단독투여)과 II군(penicillin과 gentamicin의 복합투여), 수술 1시간 전부터 시작하여 수술 후 투여되는 기간에 따라 A군(1일간), B군(3일간), C군(5~7일간)으로 분류하여 모두 6개의 소군으로 분류하고 (A-I, A-II, B-I, B-II, C-I, C-II) 이를 수술 전날 난수표를 이용하여 임의로 결정, 투여 지시하였다. 각 소군에 속한 환자들은 연령, 성별, 체중, 수술시간, 수술전 입원기간과 진단 또는 수술종류의 분포에 있어서 유의한 차이가 없었다.

전체 대상의 감염율은 6.6% (20/304)였다. 가장 감염율이 낮은 군은 A-I으로 3.8%, 가장 높은 군은 C-II로 9.1%였으나 의미있는 차이는 아니었다. 투여기간에 따라 1일간 투여한 A군이 5.1% (5/99), 3일간 투여한 B군이 7.7% (8/104), 5~7일간 투여한 C군이 6.9% (7/101)로서 투여기간에 따라 유의한 차이는 없었다. Cefazolin을 단독투여한 군의 감염율이 5.8%, penicillin과 gentamicin을 복합투여한 군의 감염율이 7.3%로서 투여 항생제에 따른 감염율에도 의미있는 차이는 없었다. 즉 저자의 임상연구 결과, clean contaminated surgery의 감염성 합병증을 예방하기 위한 항생제의 투여는 수술 시작부터 1일간으로 충분하며 그 이상 기간의 투여는 도움을 주지 못하는 것을 알 수 있었다.