Infection after radical abdominal hysterectomy and pelvic lymphadenectomy: prevention of infection with a two-dose peri-operative antibiotic prophylaxis

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Surgical site-related infections occurred in 21% of 87 consecutive patients undergoing radical hysterectomy with pelvic lymphadenectomy (RHPL) without planned peri-operative prophylaxis. A prospective, randomized double-blind, placebo-controlled study was conducted in 68 consecutive RHPL patients. In the 32 available patients with two-dose cefuroxime and metronidazole prophylaxis no surgical site-related infections developed as opposed to a rate of 14% in the 28 patients in the placebo group (P < 0.05). In a prospective, randomized double-blind study two two-dose antibiotic prophylactic regimens were compared in 105 consecutive patients. Surgical site-related infections developed in one (2%) patient in the cefuroxime plus metronidazole group, and in six (12%) patients in the moxalactam group. This difference did not achieve statistical significance. The mean length of the postoperative hospital stay of the patients with scheduled surgical prophylaxis was significantly shorter (P < 0.01) than that of the patients operated on without surgical prophylaxis. A two-dose antibiotic regimen is recommended, because levels of antibiotics assayed in samples collected during the course of the operation indicated a rapid clearance of the antibiotics from the operative site, most likely due to the high volume of peri-operative blood loss.

KEYWORDS: antibiotic prophylaxis, radical hysterectomy, surgical site-related infections.

The use of peri-operative prophylactic antibiotics is justified if the incidence of postoperative infections at the operative site is high(1). The frequency of infections after vaginal hysterectomy, varying from 12 to 64%(2), has led to the peri-operative use of prophylactic antibiotics in patients undergoing this operation(3). The efficacy of antibiotic prophylaxis in reducing the frequency of postoperative infections in such patients has been established(2,4). In the 1970s estimates from studies compiling various complications after radical abdominal hysterectomy with bilateral pelvic lymphadenectomy (RHPL) showed that surgical site-related infections occurred in 11%(5,6) to 24%(7) of the RHPL patients. Recent prospective studies showed that a higher percentage of patients not given antibiotic prophylaxis developed infections(8-12). Although patients undergoing RHPL have commonly been given prophylactic antibiotics(13,14), controlled trials studying the efficacy of antibiotic prophylaxis in RHPL patients are scarce(2,13). In addition, findings from the rather small number of studies are conflicting.
Results of placebo-controlled clinical trials and one non-randomized study demonstrated a significant reduction in the incidence of infectious morbidity among RHPL patients with multi-dose antibiotic prophylaxis. However, in another prospective study and in one retrospective study no significant decrease in the infectious morbidity after RHPL with peri-operative prophylaxis was achieved. We report here the results of our studies in RHPL patients showing the benefit of antibiotic prophylaxis.

Both aerobic and anaerobic bacteria are involved in the occurrence of infections after major gynecological surgery. We conducted a study with cefuroxime, having activity against various aerobes, in combination with metronidazole which has activity purely against anaerobes, both agents having been used as effective prophylactic agents in hysterectomy patients. Although it has been suggested that prophylaxis need not to be effective against both aerobic and anaerobic flora to yield a reduction of the rate of infections after vaginal hysterectomy, the use of two antibiotics to cover both segments of the microflora was superior to either of the drugs alone or to a regimen with amoxycillin-clavulanic acid having a spectrum of activity against aerobes as well as against anaerobes. In order to study whether in RHPL patients the use of cefuroxime and metronidazole was more efficacious than a single agent, we compared the effect of the combination with that of moxalactam, providing coverage against most aerobes and anaerobes in the female genital tract.

Patients and methods

Patient population

The study involved a total of 287 patients treated consecutively in our department from January 1980 through 1989. Cancer of the cervix was diagnosed in 255 patients: nine had stage 1A, 196 stage 1B, 48 stage IIa, and two stage IIb. Malignancies of the corpus uteri were diagnosed in 32 patients: two had stage I and 20 stage II. The remaining 10 patients had a sarcoma of the uterus. Intracavitary radiotherapy was given to 203 patients one month before planned surgery.

Patients were admitted one or 2 days prior to their operation. Preoperatively a complete blood cell count with differential white blood cell count, a SMAC biochemical profile, blood clotting tests and microscopic examination of the urine with culture were done. A chest radiograph was performed. The length and the weight of the patients were measured to calculate the Quetelet index as indicator of obesity. The evening prior to surgery all patients received a saline enema for cleansing the gastro-intestinal tract. No preoperative douching was performed.

Operation

In the operating room the abdominal skin, the vagina and the perineum were prepared with a povidone-iodine preparation. A transurethral catheter connected to a closed urinary catheter drainage system was inserted and remained in place for 7 days. Less than 10% of the patients needed catheterization for a longer period. Thrombo-embolic prophylaxis was with 5% (w:v) dextran 40 (Pharmacia AB, Uppsala Sweden) in glucose 5% (w:v) saline during surgery and for 2–4 days thereafter. Thereafter all patients received acenocoumarol (Sintrom) for 6 weeks.

RHPL included removal of 2–4 cm of the vagina and removal of the parametrium to the pelvic wall. Pelvic node dissection was carried out from above the bifurcation of the common iliac arteries to the inferior epigastric vessels. The hypogastric nodes and the nodes in the obturator fossae were also dissected. Closed suction pelvic drainage system was used in each operation. The vagina was closed around an active-suction drain. Drains were left in place for 2–4 days. The operation time was recorded and the volume of blood loss during the operation was assessed. All operations were performed by the same three gynecologic oncologists together with various senior residents. The surgical technique was uniform throughout the whole study period.

Design of the study

In the years 1980 through 1983 the incidence of infections in 114 patients after RHPL without planned perioperative antibiotic prophylaxis (first study era) was determined prospectively.

In 1984 and through 1985 a prospective randomized, double-blind, placebo-controlled study was conducted to assess the value of peri-operative prophylaxis (second study era). In total 68 consecutive patients entered this study. After an informed consent was obtained patients were randomly allocated to receive two doses of 1500 mg of cefuroxime plus 500 mg metronidazole or placebo. The first dose was administered intravenously in the operating room 30 min before operation and the second dose just before closing the peritoneum (approximately 2.5 h operating time). Patients in the placebo group were
given intravenously a volume of saline according to the same schedule.

In the years 1986 through 1989 (third study era) the efficacy of this antibiotic prophylactic regimen was compared with the efficacy of 2000 mg of moxalactam, given intravenously 30 min prior to surgery and just before closing the peritoneum. This prospective randomized, double-blind study was conducted in 105 consecutive RHPL patients, randomly allocated to receive either cefuroxime plus metronidazole or moxalactam. Exclusion criteria included preoperative clinical evidence of ongoing infections, any history of antibiotic exposure in the previous 2 weeks and known sensitivity to cefuroxime, metronidazole or moxalactam. Patients requiring antibiotic prophylaxis for pulmonary infections, orthopedic protheses-associated infections, or endocarditis were also excluded from the study. Patients were withdrawn from analysis if the dose of one of the protocol antibiotics was violated.

Analysis of the infectious morbidity

In the post-operative period protocol-assigned data included complete blood cell counts on days 2, 6 and 12 after RHPL, as well as a SMAC biochemical profile. Oral temperature and other vital signs were monitored at least three times daily. Infections were diagnosed based on clinical evaluation by an observer not involved in the treatment of the patients. The criteria for surgical site-related infections as defined by Grossman et al. (22) were used with slight modifications.

These infections included infections of the abdominal wound, the vaginal cuff and the pelvic area. Abdominal wound infection was defined as the presence of significant erythema and induration with or without drainage of serous or purulent material or wound dehiscence with serous or purulent exudate. Mild erythema around the stab wounds and drain-sites was not included. A vaginal cuff abscess was defined as the presence of fever, pelvic pain, a collection of pus at the apex of the vaginal vault and when drainage of infected material was followed by clinical amelioration. Pelvic cellulitis was present in patients with temperature elevations and pelvic, lower abdominal or lower back pain and tenderness and vaginal induration without localized collection of pus on pelvic examination.

Bacteremia was diagnosed when the patient had a body temperature of 38.5°C or greater and chills or hypotension, and a micro-organism was isolated from collected blood cultures. Non-surgical site-related infections included postoperative urinary and respiratory tract infection and were defined according to the criteria given by Grossman et al. (22) and Garner et al. (23). Catheter-related bacteriuria was diagnosed when 10^5 micro-organisms per ml or more were cultured from two urine specimens collected postoperatively at days 5 and 7.

Fever of unknown origin was defined in patients with a body temperature of 38°C or higher occurring more than 24 h following surgery on at least two occasions with 12-h interval, without any sign of a general or local infection. Such patients underwent detailed evaluation including physical examination, complete blood count with differential white blood cell count and urine culture. A chest radiograph was also obtained. Blood culture was performed for fever over 38.5°C. After discharge patients were seen 2–3 weeks after they had left the hospital and at regular intervals of 3 months in the first year after surgery.

Bacteriological methods

Clinical specimens from any presumed site of infection were collected for culture. Aerobic and anaerobic cultures were performed according to standard methods(20). Blood samples were cultured in conventional aerobic and anaerobic media. Urine specimens were cultured quantitatively and qualitatively. The susceptibility of aerobic bacteria to various antibiotics, including those used for prophylaxis, was determined by standard disk diffusion method(20). The susceptibility of anaerobic bacteria to cefuroxime, metronidazole and moxalactam was determined by the broth-disk method(25). Breakpoints tested were at 32 mg l^-1 for cefuroxime, at 16 mg l^-1 for metronidazole and at 32 mg l^-1 for moxalactam.

Assay for antibiotics

In order to assay the levels of prophylactic antibiotics, blood and hemolymph at the operative site were collected.

Cefuroxime and metronidazole were assayed in samples from 16 patients and moxalactam in samples from 18 patients. Blood samples were collected just prior to (control) and 1 h after the administration of the antibiotics. Additional blood samples were taken when the peritoneum was closed and 6 h after surgery. During the course of RHPL hemolymph was collected from the pelvic lymph node areas, from the vaginal cuff and from the subcutaneous area just before suturing the abdominal skin. Samples were dispatched without delay after their collection to the laboratory of the Department of Hospital Pharmacy. Serum was separated and stored at −20°C until assayed by reversed-phase high-pressure liquid
chromatography (HPLC) techniques. After deproteinization 0.1 ml aliquots were injected into a Nucleosil 5 C-18 column. The mobile phase and measurement by uv absorption were appropriate for the antibiotics. All concentrations were calculated from peak heights. Spiked serum standards were used and treated identically to the patient specimens. Standard curves over the required ranges were found to be reasonably linear with \( r = 0.999 \). The minimum quantifiable drug concentrations were approximately 1 mg l\(^{-1} \). The mean extraction recovery from specimens for cefuroxime and moxalactam was about 99.9% and for metronidazole 97.1%.

Statistics

Differences in rates of infection between placebo and antibiotic groups were tested for significance by the chi-square test or by Fisher's exact test when appropriate. Comparisons of means (duration of operation, estimated blood loss during surgery) were analyzed by the Student's \( t \)-test. Patient age and Quetelet index comparisons were done using the unpaired Wilcoxon rank sum test. A \( P \) value of \( < 0.05 \) was considered as significant.

Results

In the first study era from 1980 through 1983 114 patients were admitted for RHPL. Of these 27 (24%) were, for various reasons, given prophylactic perioperative antibiotics. Therefore 87 patients were enrolled in the study to assess the incidence of infection after RHPL (Table 1). Among these patients 18 (21%) developed 25 surgical site-related infections (Table 1).

Table 1. The rate of infection in 87 radical abdominal hysterectomy patients operated on without antibiotics peri-operatively

<table>
<thead>
<tr>
<th>Infection</th>
<th>No. of (%) patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical site-related</td>
<td></td>
</tr>
<tr>
<td>Vaginal cuff</td>
<td>13 (15)</td>
</tr>
<tr>
<td>Pelvic cellulitis</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Abdominal wound</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>18 (21)</td>
</tr>
<tr>
<td>Non-surgical site</td>
<td></td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Upper urinary tract</td>
<td>0 --</td>
</tr>
<tr>
<td>Catheter-related bacteriuria</td>
<td>44 (50)</td>
</tr>
<tr>
<td>Total</td>
<td>46 (53)</td>
</tr>
<tr>
<td>Fever of unknown origin</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5 (6)</td>
</tr>
</tbody>
</table>

Three had both abdominal wound and vaginal cuff infections. One developed a secondary bacteremia. Another patient had abdominal wound infection as well as post-surgical pneumonia. The predominant non-surgical site infection was catheter-related bacteriuria, occurring in 46 (53%) patients, usually at the end of the first week postoperatively. Fever without any sign of a general or local infection was noted in five (6%) patients for a total of 23 days.

The 27 patients given antibiotics, but not for surgical prophylaxis, demonstrated significantly less infectious morbidity (\( P < 0.01, \chi^2 \) test) and a significantly lower frequency of surgical site-related infections (\( P < 0.01; \) Fisher's exact, one-tailed) than the 87 patients without antibiotics (data not shown). Cultures from abdominal wound pus showed growth of *Staphylococcus aureus*, group B streptococci, *Escherichia coli* or *Staphylococcus epidermis* often together with anaerobic species belonging to *Bacteroides* or *Peptostreptococcus* species. The majority of vaginal cuff infections was caused by *E. coli*, various other Gram-negative rods, *Staph. aureus*, group B streptococci or enterococci in combination with various anaerobes, mainly *Bacteroides, Fusobacterium, Eubacterium* and *Peptostreptococcus* species. Bacteriuria associated with the indwelling catheter was mainly due to *E. coli* or various other Gram-negative rods.

In the second study era (1984 through 1985) 60 of 68 consecutive patients enrolled in the double-blind, placebo-controlled study, were available for analysis. From the excluded patients, six were given prophylaxis because they were at risk for endocarditis or respiratory tract infection. One patient did not receive appropriately the planned antibiotics for surgical prophylaxis and one patient was known to be allergic for cephalosporins. Characteristics of the 28 controls and 32 patients with peri-operative prophylaxis were not different, except for the number of patients with cervical cancer stage IIa (Table 2). The rate of surgical site-related infections in patients with two-dose peri-operative prophylaxis with cefuroxime and metronidazole was significantly lower (\( P < 0.05; \) Fisher's exact; one-tailed) than in the placebo-group (Table 3). The onset of these infections was not associated with a particular stage or localization of the cancer (\( P = 0.12; \) Fisher's exact; one-tailed). Cultures from pus of the infected sites showed growth of *S. aureus*, group B streptococci, *E. coli*, or enterococci together with *Bacteroides fragilis*, other *Bacteroides* species or *Eubacterium lentum* and *Peptostreptococcus* species. The aerobic isolates from these infections, except enterococci, were susceptible to cefuroxime. The anaerobes, except some *Peptostreptococcus* species
showed susceptibility to metronidazole. The frequency of non-surgical site-related infections in both patient groups was not different (Table 3). The most pronounced non-surgical site-related infection was catheter-related bacteriuria, mainly due to *E. coli*.

In the third study era (1986 through 1989) the efficacy of two-dose peri-operative prophylaxis with either cefuroxime plus metronidazole or moxalactam was compared in 105 consecutive patients. Evaluation was done in 95 patients; four patients were treated for prophylaxis of endocarditis or for respiratory tract infections and five patients had no appropriate administration of the scheduled antibiotics. One patient had antibiotics for treatment of urinary tract infection just prior to surgery.

### Table 2. Comparison of patient and treatment characteristics between the placebo group and the group with peri-operative prophylaxis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo</th>
<th>Cefuroxime + Metronidazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>28</td>
<td>32</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>50 (+14)*</td>
<td>46 (+15)</td>
</tr>
<tr>
<td>Quetelet index</td>
<td>25.6 (+3.7)</td>
<td>24.4 (+4.3)</td>
</tr>
<tr>
<td>Cervical cancer stage Ia</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Ib</td>
<td>17</td>
<td>25</td>
</tr>
<tr>
<td>IIa</td>
<td>8†</td>
<td>1</td>
</tr>
<tr>
<td>Endometrial cancer stage II</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Sarcoma uteri</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Radium application</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Mean operation time (min)</td>
<td>200 (+35)</td>
<td>199 (+29)</td>
</tr>
<tr>
<td>Mean blood loss (l)</td>
<td>1.9 (+0.9)</td>
<td>1.5 (+0.8)</td>
</tr>
</tbody>
</table>

*In parenthesis standard deviation.
†Placebo versus antibiotic group *P* < 0.02 (Fisher’s exact, two-tailed).

### Table 3. The incidence of infection after RHPL in 28 patients in the placebo group and in 32 patients in the cefuroxime plus metronidazole group

| Infection                     | Placebo | Cefuroxime + Metronidazole | *P*
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical site-related</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal cuff</td>
<td>3 (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic cellulitis</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal wound</td>
<td>1 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4 (14)</td>
<td>0</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Non-surgical site-related</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>1 (4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Upper urinary tract</td>
<td>0</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Catheter-related bacteriuria</td>
<td>14 (50)</td>
<td>19 (59)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>15 (54)</td>
<td>20 (62)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Fever of unknown origin</td>
<td>1 (11)</td>
<td>1 (3)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Comparison of patient characteristics yielded no difference between both groups (Table 4). In one (2%) patient in the cefuroxime plus metronidazole group a vaginal cuff abscess developed. Six (12%) patients in the moxalactam group had surgical-site related infections. The rate of infection in both treatment groups was not significantly different (*P* = 0.12; Fisher’s exact; two-tailed). The micro-organisms encountered in pus were viridans streptococci, *Staph. epidermidis*, enterococci or *Enterobacter* species together with *B. fragilis*, *Bacteroides disiens*, *Bacteroides bivius* or *Eubacterium* species. Most aerobic and anaerobic isolates showed intermediate susceptibility to moxalactam or were resistant to moxalactam. Patients with moxalactam prophylaxis had less often catheter-related bacteriuria and urinary tract infection (*P* < 0.02; *χ²* test) than patients with cefuroxime and metronidazole prophylaxis (Table 5).

The length of postoperative hospitalization of patients with surgical site-related infections, being 24±14 days, was significantly longer than that of patients having non-surgical site infections (*P* < 0.05;
Table 5. The incidence of infection after RHPL in 45 patients in the cefuroxime plus metronidazole group and in 50 patients in the moxalactam group

<table>
<thead>
<tr>
<th>Infection</th>
<th>No. (%) of patients</th>
<th>Cefuroxime + Metronidazole</th>
<th>Moxalactam</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical site-related</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal cuff</td>
<td>1 (2)</td>
<td>5 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic cellulitis</td>
<td>0</td>
<td>2 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal wound</td>
<td>0</td>
<td>1 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1 (2)</td>
<td>6 (12)</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Non-surgical site-related</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper urinary tract</td>
<td>2 (4)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter-related bacteriuria</td>
<td>35 (77)</td>
<td>29 (58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>37 (82)</td>
<td>29 (58)</td>
<td>&lt; 0.04</td>
<td></td>
</tr>
<tr>
<td>Fever of unknown origin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4 (9)</td>
<td>2 (4)</td>
<td>n.s.</td>
<td></td>
</tr>
</tbody>
</table>

Table 6. Serum and hemolymph levels of antibiotics peri-operatively during RHPL and post-operatively. Antibiotics were given intravenously 0.5 h before surgery and at 2.5 h after the start of surgery

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Mean (±SD) level (mg l⁻¹) at indicated time (h) after the start of surgery in:</th>
<th>subcutaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefuroxime</td>
<td>0.5 h 48 (27)</td>
<td>1.5 h 9 (8)</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>0.5 h 13 (5)</td>
<td>1.5 h 8 (4)</td>
</tr>
<tr>
<td>Moxalactam</td>
<td>0.5 h 92 (21)</td>
<td>1.5 h 18 (19)</td>
</tr>
</tbody>
</table>

Data from:
*16 patients given cefuroxime (dose 1.5 g) plus metronidazole (dose 0.5 g).
†18 patients given moxalactam (dose 2 g).

Assays for the antibiotics showed that the mean serum level 1 h after administration of cefuroxime was 48±27 mg l⁻¹ (Table 6). Serum levels of metronidazole in these samples ranged from 7 to 28 mg l⁻¹ with a mean of 13 mg l⁻¹. Mean serum concentration of moxalactam was 92 mg l⁻¹, ranging from 15 to 199 mg l⁻¹. During operation serum concentrations of cefuroxime and moxalactam decreased significantly. The mean level of metronidazole remained high (Table 6). Levels of cefuroxime and moxalactam in hemolymph collected from the pelvic node areas and from the vaginal cuff area were more or less similar to serum levels after an operating time of 2.5 h. Half an hour after the second dose, the mean levels of cefuroxime and metronidazole in hemolymph from the abdominal wound tissues raised again, whereas the mean level of moxalactam showed only a slight increase (Table 6). Six hours after surgery mean serum levels of the antibiotics, except of metronidazole, had decreased significantly.

Discussion

The data obtained from our three prospective studies encompassing 287 RHPL patients, demonstrated a total rate of surgical site-related infections of 21% in RHPL patients operated on without antibiotic prophylaxis. These were predominantly vaginal cuff abscesses requiring antimicrobial therapy or surgical intervention and abdominal purulent wound breakdowns. Overall, febrile morbidity was not used as the index for the frequency of infection, since fever from non-infectious causes is included and neither the severity nor the site of the presumed infection is indicated. Results of a previous prospective randomized

Table 5. Prophylaxis in radical hysterectomy

Table 6. Serum and hemolymph levels of antibiotics peri-operatively during RHPL and post-operatively. Antibiotics were given intravenously 0.5 h before surgery and at 2.5 h after the start of surgery

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<td>Moxalactam</td>
<td>0.5 h 92 (21)</td>
<td>1.5 h 18 (19)</td>
</tr>
</tbody>
</table>

Data from:
*16 patients given cefuroxime (dose 1.5 g) plus metronidazole (dose 0.5 g).
†18 patients given moxalactam (dose 2 g).
study in 64 RHPL patients demonstrated that single-
dose doxycycline as surgical prophylaxis reduced sig-
nificantly the 'febrile index', but that the frequency of
surgical site-related infections, 27% in the control
group and 18% in the prophylactic study group was
not significantly reduced(10).

In our study a significantly lower frequency of surgic-
al site-related infections in the cefuroxime plus
metronidazole group as opposed to the placebo group
was found. Our third study showed that there was no
difference in the frequency of postsurgical infections
between RHPL patients with cefuroxime plus met-
ronidarole prophylaxis or RHPL patients with
moxalactam prophylaxis. Indirect evidence of the
efficacy of the surgical antibiotic prophylaxis was ob-
tained by the finding that the length of hospital stay
of patients with scheduled prophylaxis was significa-
cantly reduced.

In extended hysterectomy for endometrial cancer,
surgical prophylaxis with five doses of cefamandole(26)
or other cephalosporins for 5-7 days(27) has been
reported to reduce the rate of surgical site-related in-
fecions. In RHPL patients the prevention of surgical
site-related infections has been assessed in five con-
trolled studies available in the literature(8-12).

In total, 126 patients without prophylactic anti-
biotics and 116 antibiotic recipients were involved. In-
fecions related to the surgical site occurred in 43 (34%)
control patients as opposed to 13 (11%) patients with
antibiotic prophylaxis (P < 0.005; χ² test). These com-
piled findings provide evidence for the efficacy of
antibiotic prophylaxis in RHPL patients.

Our surveys comprised 127 patients with a two-
dose peri-operative prophylaxis with either
cefuroxime plus metronidazole or moxalactam. The
rate of surgical site-related infections was reduced sig-
nificantly (P < 0.005; χ² test) to 5.5%, as opposed to
19% in 115 patients without peri-operative antibiotics.

Among the various studies, however, the data re-
garding the efficacy of antimicrobial prophylaxis in
RHPL patients are conflicting(8-12,15,16). A number of
reasons may be responsible for the divergent results.
Analysis shows that the design of the studies, the
criteria used to define the occurrence of infections, the
antibiotics used, the dosages of the antibiotics used
and the length of the period that antibiotics were ad-
mministered, were rather different. In addition, factors
interrelated in the studies, such as hours of surgery
and blood loss during operation, differed markedly.
Mean operating time ranged from 2.6(16) to 6.1(12) and
estimated mean blood loss ranged from 0.5(16) to
2.4±1.7 l(9). In our study the mean operation time for
RHPL was 3.3±0.3 h and mean estimated blood loss
was 1.7±0.9 l.

A relatively short operation time along with a
moderate blood loss is thought to contribute to a low
incidence of infection at the operative site(16). This
assumption was derived from data collected retro-
spectively and was not confirmed by findings in a
prospective study(9). Bendvold & Kjorsjad(16) con-
cluded that surgical prophylaxis in RHPL patients
with cervical cancer Stage IB is not indicated. In our
study, surgical-related infections occurred in 11 (14%)
of 79 patients with cervical cancer Stage IB and in
seven (25%) of 28 patients with cervical cancer Stage
IIA (P > 0.05; χ² test) undergoing RHPL without anti-
biotic prophylaxis, indicating that the onset of infec-
tions at the surgical site is not related to the cervical
tumor stage.

In order to establish the efficacy of antibiotic
prophylaxis following RHPL the length of the follow-
up period after surgery is relevant. Without approp-
riate follow-up period two of the seven infected cases
among antibiotic recipients would have been missed
in our study. The mean interval between surgery and
the development of surgical site-related infection was
8±3 days in patients operated on without antibiotics
and 17±10 days in antibiotic recipients.

The incidence of non-surgical site-related infections
and fever of unknown origin was not affected by surgi-
cal prophylaxis. There is a difference of opinion about
the clinical significance of bacteriuria as a cause of in-
fecious morbidity after gynecological surgery and as
to whether it can be prevented by peri-operative anti-
biotic prophylaxis(1,28). Non-symptomatic catheter-
related bacteriuria was most predominant with an
incidence of more than 50%. Surprisingly, RHPL
patients with short-term peri-operative prophylaxis,
irrespective of the antibiotics used, clearly showed a
significantly higher (0.01 < P < 0.02; χ² test) rate of
catheter-related bacteriuria than patients operated on
without antibiotics. Although a short-course prophylaxis was applied, alteration of the bacterial flora as a cause for the higher frequency of the bac-
teriuria in antibiotic recipients has to be considered(29).
It is tempting to speculate that cefuroxime and
moxalactam affect the autochthonous bacteria resid-
ing in the distal urethra(30), enabling Gram-negative
uropathogens to spread more easily along the external
surface of the catheter. In the present study the
occurrence of non-symptomatic bacteriuria did not
prolong the hospital stay.

Failure of prophylaxis may be due to micro-
organisms resistant to the antibiotics used or to too
low antibiotic levels at the operative site. It is un-
known whether the pathogens involved in surgical in-
fec tions in hysterectomy patients reside in the aerobic
or the anaerobic segment of the urogenital flora(29).
Several studies on the efficacy of antibiotic prophylaxis in hysterectomy were conducted with regimens active against pathogens in both segments\(^{19,31}\). For RHPL patients no optimum prophylactic regimen has been established. Cultures from specimens of infected surgical-related sites demonstrated the well known polymicrobial nature of these infections. Susceptibility testing of the isolates from surgical infected sites revealed that they were rather resistant to moxalactam, although moxalactam as a single agent provides coverage against most aerobes and anaerobes in the female genital tract\(^{20}\), and was effective in decreasing the rate of postoperative infections. The combination of cefuroxime with a rather broad spectrum of activity against the aerobic part of the flora and metronidazole acting on the anaerobes, covering both segments of the microflora\(^{17}\), showed a high efficacy as surgical prophylaxis in RHPL patients. Cefotixin\(^{9}\), mezlocillin\(^{11}\) and cefaperazone combined with sulbactam\(^{12}\), active against aerobes as well as anaerobes, reduced also significantly the rate of postoperative infections in RHPL patients. So far, studies in RHPL with antibiotics active against either aerobes or anaerobes are not available. Therefore antibiotics acting on pathogens of both segments of the microflora are still recommended in RHPL patients.

Assays for the antibiotics showed that after one dose, mean serum levels 1 and 3 h after administration were normal for cefuroxime\(^{32}\), metronidazole\(^{33}\) and moxalactam\(^{34}\). At the operative site however, antibiotics, except metronidazole, were rapidly cleared and were present at low levels when MIC-values of microorganisms causing infections after RHPL are considered\(^{2,20,37}\). In RHPL patients low tissue levels of antibiotics in comparison to serum levels have been found at the operative site, when large volumes of fluids by the use of closed suction drainage were evacuated\(^{35,36}\). In our patients closed suction drainage was started just after closure of the abdominal wound. This part of the study shows that it is necessary to administer peri-operatively a second dose of cefuroxime or moxalactam in RHPL patients to obtain levels of cefuroxime or moxalactam at which most micro-organisms encountered in surgical site-related infections are thought to be susceptible\(^{20,37}\).

The appropriate duration of antibiotic prophylaxis in RHPL patients is unknown. In other prospective studies such patients received single\(^{6}\), three\(^{11,12}\) or 12-dose\(^{9,10}\) antibiotic prophylaxis. In vaginal hysterectomy a single peri-operative dose was equivalent to three doses\(^{18,38-40}\). Recently, Orr et al.\(^{41}\) evaluating retrospectively the efficacy of cefoxitin prophylaxis in RHPL patients, found that a single-dose prophylaxis was as efficacious as a three-dose regimen.

In conclusion, our data show that antibiotic prophylaxis is indicated in patients undergoing RHPL. Analysis of the current literature shows divergent results in the small number of clinical trials with rather small patient populations. A two-dose peri-operative regimen with appropriate antibiotics effectively reduced the frequency of surgical site-related infections.

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