COMPARISON OF TWO SYSTEMIC ANTIBIOTICS FOR THE PREVENTION OF COMPLICATIONS IN ELECTIVE COLORECTAL SURGERY

CONFRONTO DI DUE ANTIBIOTICI NELLA PROFILASSI SISTEMICA PER LA PREVENZIONE DI COMPLICAZIONI NELLA CHIRURGIA ELETTIVA COLO-RETTALE

Antonelli MM¹, Antonelli W²

¹ Pharmaceutical Service, Hospital of Macerata, Italy
² Division of Surgery, Hospital of Macerata, Italy


Key words: antibiotic systemic prophylaxis, elective colorectal surgery

Parole chiave: profilassi antibiotica sistemica, chirurgia colorettale elettiva

Abstract

The surgical site infections are the third most frequent hospital-acquired infection and 3/4 of the deaths occurred in patients with surgical site infections are to relate to them. Antibiotic prophylaxis is crucial in the prevention of surgical site infections, in particular types of surgical operations such as the colon, an organ with high bacterial load. The use of antibiotics, to be effective, needs to be specific for the type of surgical operation, pharmaceutical form, dose, timing of administration appropriate to spectrum of activity targeted to most frequently encountered bacteria. The inappropriate use of antibiotics in the prophylaxis of surgical site infection leads to the ineffectiveness of the administration with an increased incidence of infections and a rise in costs, because it increases the days of hospitalization and working days lost to sickness. It also increases the risk of iatrogenesis, the side effects of the drugs administered. Moreover, the inappropriate use of antibiotics in the prophylaxis increments the selection of resistant
strains. In a prospective randomized trial on 77 patients undergoing elective colorectal surgery, cefoxitin and cephalothin were given as systemic antibiotic prophylaxis. Cefoxitin is a betalactamase stable cephalosporin-cephamycin, especially effective against gram-negative organisms and Bacteroides species which are likely to be present in postoperative infections after large bowel surgery. These organisms were frequently shown to be resistant to the antibiotics used in systemic prophylaxis as cefalothin or ampicillin. All patients received low residue diet and preoperative standard bowel preparation with saline enema and oral laxatives for 3 days before surgery excluding the patients undergoing colo-sigmoidostomy closure operations. Two groups of 40 and 37 randomized patients were studied. Cefoxitin group: the 40 patients received cefoxitin (2 gm) intravenously 30 minutes preoperatively, an additional dose of 2 gm during surgery (over two hours) and then 2 gm 8h postoperatively for 48 hours. Cephalothin group: the 37 patients received cefalothin (2 gm) intravenously 2 hours preoperatively, 2 gm during surgery, and 2 gm every 6 hours postoperatively for 2 days. Postoperative sepsis occurred in 2/40 (5 %) of those given cefoxitin compared to 9/37 (24.3 %) of those given cephalothin. The reduction in the infection rate in the group treated by cefoxitin was statistically significant (p<0.02). Specific drug toxicity was not evidenced except for transient skin rashes in two patients of both groups. In the patients with infectious complications, aerobic and anaerobic bacteria were present in most cases. B. fragilis, C. perfringens, E. coli, S. epidermidis, K. Penuomoniae, Bacterioides, Peptococcus, Corynebacterium, P. morganii, C. perfringens and B. melaninogenicus.

Abstract

Le infezioni del sito chirurgico rappresentano la terza infezione ospedaliera per frequenza e che circa i 3/4 dei decessi occorsi in pazienti con infezioni del sito chirurgico sono da correlarsi alle stesse. Il ricorso alla profilassi antibiotica ha un ruolo determinante nella prevenzione delle infezioni del sito chirurgico, particolarmente per alcuni tipi di interventi come quelli del colon, dove è presente una alta carica batterica. L’utilizzo di antibiotici, perché sia efficace, occorre che sia indicato per il tipo di intervento, con forma farmaceutica, dosi e tempi di somministrazione adeguati e spettro d’azione mirato ai germi più frequentemente riscontrati. L’inappropriatazza dell’uso degli antibiotici nella profilassi dell’infezione del sito chirurgico comporta l’inefficacia della somministrazione con aumentata incidenza di infezioni e relativo incremento dei costi conseguenti all’aumento di giornate di degenza ed alle giornate lavorative per malattia, oltre che la iatrogenesi correlata agli effetti indesiderati dei farmaci somministrati. L’uso non appropriato degli antibiotici comporta in ambiente nosocomiale la selezione di ceppi resistenti che rende più difficoltoso l’approccio terapeutico alle infezioni batteriche. In uno studio longitudinale randomizzato condotto su 77 pazienti sottoposti a chirurgia elettiva coloretale sono state somministrate cefossitina o cefalotina come profilassi antibiotica sistemica. Cefoxitina è una cefalosporina resistente alle betalattamasi, particolarmente efficace contro i batteri gram-negativi e le specie Bacteroides che possono essere presenti in caso di infezioni post-operatorie dopo l’intervento del grosso intestino. Questi organismi mostrano spesso di essere resistenti agli antibiotici utilizzati nella profilassi sistemica come cefalotina o ampicillina. Tutti i pazienti hanno ricevuto una dieta a basso residuo e una preparazione intestinale preoperatoria standard con clistere salino e lassativi per via orale per 3 giorni prima dell’intervento chirurgico esclusi i pazienti sottoposti a operazione di chiusura colo-sigmoidostomia. Due gruppi di 40 e 37 pazienti randomizzati sono stati studiati. Il gruppo trattato con Cefoxitina: 40 pazienti hanno ricevuto cefoxitina (2 grammi) per via endovenosa 30 minuti prima dell’intervento, una dose supplementare di 2 grammi durante l’intervento chirurgico (oltre due ore) e poi 2 gr 8h dopo l’intervento per 48 ore. Il gruppo trattato con Cefalotina: dei 37 pazienti hanno ricevuto cefalotina (2 grammi) per via endovenosa due ore prima dell’intervento, 2 gr durante l’intervento chirurgico, e 2 gr ogni 6 ore dopo l’intervento per 2 giorni. Le complicanze settiche si sono riscontrate in 2/40 (5%) del gruppo trattato con cefoxitina, contro 9/37 (24.3%) del gruppo trattato con cefalotina. La riduzione delle complicanze settiche post-operatorie nel gruppo trattato con cefoxitina è risultata statisticamente significativa (p<0.02). Non si sono riscontrati effetti collaterali di rilievo, fatta eccezione per transitori rashes cutanei in due pazienti di entrambi i gruppi. Nei pazienti con complicanze infettive da batteri aerobici ed anaerobici abbiamo isolato le seguenti specie B. fragilis, C. perfringens, E. coli, S. epidermidis, K. Penuomoniae, Bacterioides, Peptococcus, Corynebacterium, P. morganii, C. perfringens e B. melaninogenicus.
Background
Colorectal surgery is accompanied by a high risk of developing postoperative surgical sepsis with related complications (e.g. abdominal and perineal wounds, septicemia, peritonitis, anastomotic leakage, dehiscence and fistula) (1, 2). The organisms responsible for these infections are usually of intestinal origin (3, 4, 5). Postoperative sepsis can be reduced by preventing wound contamination during surgery by:

a) careful surgical technique;
b) mechanical preparation (but the latter does not seem to reduce the concentration of colonic microflora) (6, 7). Sepsis in colonic surgery can be lowered by the preoperative reduction of intestinal flora by a non-absorbable oral antibiotic bowel preparation (8, 9, 10) or by pre-and perioperative use of systemic antibiotics to decrease the bacterial flora in the intestinal lumen providing adequate antimicrobial blood and tissue levels at the time of operative contamination (11, 12).

Cefoxitin is a betalactamase stable cephalosporin-cephamycin, especially effective against gram-negative organisms and Bacteroides species which are likely to be present in postoperative infections after large bowel surgery. These organisms were frequently shown to be resistant to the antibiotics used in systemic prophylaxis as cephalothin or ampicillin. The aim of this study was to compare cefoxitin with cephalothin in the prophylaxis of elective colorectal surgery.

Material and Methods
Seventy-seven consecutive patients admitted to the Surgery Unit of the Hospital of Macerata for elective colorectal surgery from May 2011 to November 2012 entered the study. The patients were randomly allocated to one of the two treatment groups according to a sealed envelope system. Criteria for exclusion were antimicrobial treatment during the 3 weeks preceding the operation and known allergy to the drugs. All patients received low residue diet and preoperative standard bowel preparation with saline enema and oral laxatives for 3 days before surgery excluding the patients undergoing colo-sigmoidostomy closure operations.

Two groups of 40 and 37 randomized patients were studied. Cefoxitin group: the 40 patients received cefoxitin (2 gr) intravenously 30 minutes preoperatively, an additional dose of 2 gr during surgery (over two hours) and then 2 gr 8h postoperatively for 48 hours. Cephalothin group: the 37 patients received cephalothin (2 gr) intravenously 2 hours preoperatively, 2 gr during surgery, and 2 gr every 6 hours postoperatively for 2 days (according to the protocol recommended by Kjellgren and Sellstrom) (12). Wound sepsis was assessed on the third, sixth and ninth postoperative day and then at the first and second outpatient visit 4 and 6 weeks later. Wounds were graded as follows:

1) satisfactory healing (some erythema allowed);
2) with purulent discharge or dehiscence.

If a postoperative pyrexia of more than 38 °C was recorded, blood and pus samples and also wound swabs when necessary, were cultured for aerobic and anaerobic bacteria by standard procedures.

Results
40 out of the 77 patients undergoing elective colorectal surgery received systemic prophylaxis with cefoxitin and 37 with cephalothin. The two groups were similar with respect to age, sex and type of surgery (Table 1). There were slightly fewer patients with fecal residue in the colon at the time of surgery in the cefoxitin group as compared to the cephalothin group (Table 1). The incidence of sepsis and related complications in the two groups is shown in Table 2. The incidence of overall postoperative sepsis was significantly lower (p<0.02).

The incidence of abdominal and perineal wound infections was respectively 0/30 and 1/6 in the cefoxitin group and 3/30 and 2/4 in the cephalothin group. Clinical evidence of anastomotic leakage was observed in only one patient treated with cephalothin. Fistula occurred in only one patient treated with cefoxitin and in one treated with cephalothin. Prolonged hospitalization (5-10 days) was necessary for all patients with septic complications. In the patients with infectious complications, aerobic and anaerobic bacteria were present in most cases. B. fragilis was isolated from the infected abdominal and perineal wounds of all 5 patients of the cephalothin group. The same strain was isolated together with C. perfringens and E. coli in one patient, with E. coli and S. epidermidis in 3, with K. pneumoniae in one. In cases of peritonitis, the species Bacterioides was isolated together with Peptococcus in one patient and with Corynebacterium in...
Comparison of two systemic antibiotics for the prevention of complications in elective colorectal surgery

another one; in cases of fistula K. pneumoniae and P. morganii were isolated; in cases of anastomotic leakage Bacterioides and C. perfringens were isolated.

In the cefoxitin group, B. melaninogenicus, C. perfringens and K. penuoniae were isolated from infected perineal wounds and E. coli, S. epidermidis and B. melaninogenicus from fistulas.

Discussion and Conclusions

In the last decade a number of prospective and controlled studies have demonstrated that the prophylactic use of systemic antibiotics decreasing the colonic bacterial flora and providing adequate antimicrobial blood and tissue levels at the time of operative contamination, significantly reduces the high rate and morbidity of septic complications in colorectal surgery (13, 14). It was established that the origin of infection is above all endogenous with prevalence of anaerobic bacteria (Bacterioides fragilis, and Escherichia coli), particularly of those resistant to the usual antibiotics (15). Consequently the intestinal systemic prophylaxis should include antimicrobials specifically directed against aerobic and anaerobic colonic microflora.

Table 1 - Clinical details of patients in the study

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Cefoxitin</th>
<th>Cephalothin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age and Sex</td>
<td>Male/female</td>
<td>20/20</td>
</tr>
<tr>
<td></td>
<td>Mean ages (± S.E.)</td>
<td>66.6 ± 14</td>
</tr>
<tr>
<td>Operation</td>
<td>Right hemicolectomy</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Left hemicolectomy</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Anterior resection</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Abdominoperineal resection</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Colo-sigmoidostomy closure</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Colotomy with excision of polyps</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>37</td>
</tr>
<tr>
<td>Fecal residue at operation</td>
<td>Gross</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2 - Incidence of sepsis and related complications

<table>
<thead>
<tr>
<th></th>
<th>Cefoxitin</th>
<th>Cephalothin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall wound infection</td>
<td>2/40</td>
<td>9/37</td>
</tr>
<tr>
<td>Abdominal</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Perineal wound</td>
<td>1/16</td>
<td>2/4</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Septicemia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anastomotic leak</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dehiscence</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Fistula</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Wide-spectrum antibiotics against aerobic and anaerobic organisms of the colon, endowed with high affinity to intestinal tissue and biological liquids where bacterial contamination is possible and with good resistance to inactivating enzymes, were therefore used.

In these prospective trials, cefoxitin, a beta-lactamase stable cephalosporin-cephamycin, was used because it is more effective on anaerobic and Bacterioides species, especially Bacterioides fragilis (organisms most likely found in postoperative infections after large bowel surgery) than the older cephalosporin antibiotics such as cephalothin and cephaloridin (16, 17, 18). In addition, cefoxitin reaches high concentrations in the peritoneal liquid and is characterized by low toxicity and adverse reactions (19). Our study clearly shows a more significant reduction in postoperative wound infections in the group of patients receiving cefoxitin than in the group of patients receiving cephalothin (p<0.02). The significant differences in the results obtained with the two drugs indicate that the wide spectrum of cefoxitin action against Bacterioides fragilis and other anaerobes and beta-lactamase producing organisms, all of which are frequently resistant to cephalothin, results in an enhanced prophylactic activity (20). Consequently, patients undergoing colorectal surgery were protected against severe postoperative infectious complications. We conclude that cefoxitin used during the perioperative and postoperative period is a safe, simple, effective method of reducing post-operative sepsis.
References


Corresponding Author: Marco Matteo Antonelli
Pharmaceutical Service, Hospital of Macerata, Italy
E-mail: info@preventionandresearch.com

Autore di riferimento: Marco Matteo Antonelli
Divisione di Chirurgia, Ospedale di Macerata
E-mail: info@preventionandresearch.com