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A Prospective Randomized Comparison of a Single Antibiotic (Moxalactam) Versus Combination Therapy (Gentamicin and Clindamycin) in Penetrating Abdominal Trauma

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From July 1 to December 31, 1983, 50 consecutive patients undergoing abdominal exploration for penetrating abdominal trauma from stab and gunshot wounds were prospectively randomized to receive postinjury, preoperative antibiotic coverage with moxalactam (2 g intravenously every 12 hours) or a combination of gentamicin (3 to 5 mg/kg/day in three equal doses administered every eight hours) and clindamycin (600 mg intravenously every six hours). No intraabdominal abscesses or wound infections developed, and no direct evidence of toxicity of the antibiotic regimens developed in either group. In the study group, moxalactam therapy was an effective alternative to the combination antibiotic regimen. The subsequently documented incidence of moxalactam-induced bleeding episodes precludes its use as a primary preventive antibiotic; however, other less toxic cephalosporins may demonstrate similar effectiveness. (Henry Ford Hosp Med J 1988;36:52-5)

Intraabdominal and wound infections are major sources of morbidity and mortality in patients sustaining penetrating abdominal injury. In the pre-antibiotic era, penetrating abdominal injury with hollow viscus injury was almost universally fatal. Today, with modern techniques of transport, resuscitation, and postoperative management, the early deaths from hemorrhagic shock have been partly supplanted by late deaths from multiple system organ failure caused by intraabdominal infection (1-6). Controversy remains regarding the optimal regimen of perioperative antibiotics, and cost has become an increasingly important consideration in therapy for these patients. To obtain the wide spectrum of coverage necessary for abdominal injuries, multiple drug regimens traditionally have been recommended (2,7,8). Treatment with one antibiotic has been found to be effective in comparison to multidrug regimens (9-15). Agents recommended are usually of the newer generation cephalosporin type due to their wide spectra including both anaerobes and aerobes (16-18). Some studies have found multiple drug regimens to be superior to treatment with one antibiotic therapy of cefamandole or cefoxitin but not of moxalactam (19,20).

In an effort to further clarify the role of single antibiotic therapy in abdominal trauma, a moxalactam regimen was prospectively compared to the more traditional two-drug combination including an aminoglycoside.

Materials and Methods

Fifty patients consecutively admitted for penetrating abdominal trauma to the Trauma Surgery Service from July 1 to December 31, 1983, were entered into a prospective randomized study. Informed consent regarding the nature of the study was obtained. The study, consent, and randomization were approved by the hospital's research review committee.

Patients were randomized according to a predetermined sequence of regimen choices. Special packaging of the antibiotics concealed the identity of the selected regimen to the managing physicians; once the patient was entered into the study, the antibiotic regimen was revealed to the treating physicians. Antibiotic therapy prior to injury was cause for exclusion from the study. Group 1 included 25 patients who received gentamicin (3 to 5 mg/kg/day in three equal doses administered every eight hours) and clindamycin (600 mg intravenously every six hours). Group 2 included 25 patients who received moxalactam (2 g intravenously every 12 hours); these patients also received phytonadione (10 mg intramuscularly each week) as part of the protocol. Antibiotics were given according to the randomization schedule as soon as the decision to explore the abdomen was made. No other antimicrobials were given during the initial management period. Treatment was continued a minimum of three days for patients without injury to hollow viscus. Patients who were found to have hollow viscus injury at celiotomy received antibiotics for a minimum of five days. Colonic injuries were managed primarily by exteriorization or colostomy. Patients were routinely explored via midline xiphipubic celiotomy. Their wounds were closed primarily in the absence of colonic injury. In the presence of colonic injury, delayed primary closure was used.

Initial laboratory studies in all patients included complete blood count with differentials, serum electrolytes, and enzymes

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Table 1
Study Population Demographics

	Group 1 Gentamicin/Clindamycin	Group 2 Moxalactam
Age (years)		
Mean	27	27.1
Range	17-57	18-66
Gender		
Male	23	23
Female	2	2
Hospitalization (days)		
Mean	10.4	9.5
Range	3-28	3-21
Total	261	238

Table 2
Patterns of Injury

	Group 1 Gentamicin/Clindamycin	Group 2 Moxalactam
Number of patients	25	25
Hollow viscus injury	12	11
Colon injury	4	2
Gunshot wound	20	15
Stab wound	5	10
Solid organ injury (liver, spleen, pancreas, kidney, ovary)	7	15
"Negative" laparotomies	5	7

consisting of calcium, phosphorus, magnesium, SGOT, SGPT, lactic dehydrogenase alkaline phosphatase, creatinine phosphokinase, creatinine, total bilirubin, total protein, cholesterol, triglyceride, BUN, uric acid, and glucose. Urinalysis was obtained. Coagulation parameters, prothrombin time, and partial thromboplastin time with platelet count were obtained. Cultures of intraperitoneal fluid, blood, and wound surface were obtained aerobically and anaerobically within four hours of antibiotic administration. Organisms isolated in such cultures were tested for sensitivity to the antibiotics. In vitro susceptibility to moxalactam was evaluated by determination of minimum inhibitory concentration. The Kirby-Bauer disk diffusion method was used to test sensitivity of isolated organisms to gentamicin and clindamycin.

Inpatient follow-up included daily physical examinations, vital sign determinations every eight hours, and selected laboratory studies during the study period and three times weekly after the study period until discharge. Postdischarge follow-up was continued for at least two weeks. Failure of antibiotic therapy was defined as an oral temperature greater than 38°C on two occasions more than six hours apart, a WBC count greater than 20,000/ μ L, wound infection requiring drainage, intra-abdominal abscess formation, or positive blood cultures.

Results

Population demographics are summarized in Table 1. The 25 patients who received gentamicin and clindamycin (group 1) ranged in age from 17 to 57 years (mean 27 years). The 25 patients who received moxalactam (group 2) ranged in age from 18 to 62 years (mean 27.1 years). Both groups contained 23 men and two women. Patterns of injury are summarized in Table 2. Twelve of the patients randomized to the gentamicin/clindamycin group had hollow viscus injury at celiotomy, with four of the patients sustaining injuries to the colon. Eleven of the patients receiving moxalactam had hollow viscus injury, with two of the patients sustaining injuries to the colon. Of the patients randomized to the gentamicin/clindamycin group, 20 sustained gunshot wounds and five had stab wounds. Of the patients in the moxalactam group, 15 sustained gunshot wounds and ten had stab wounds. No stab wounds resulted in colonic injury in either group.

No patients in this study developed an infection requiring surgical intervention. Several patients had positive peritoneal or

wound cultures. Four patients receiving moxalactam had positive peritoneal cultures as opposed to three patients in the gentamicin/clindamycin group. One patient receiving moxalactam after multiple gunshot wounds to the chest, abdomen, and extremities had a positive wound culture for an enterococcus and developed a postoperative fever. The fever, however, resolved with intensive pulmonary toilet, and no obvious focus of enterococcal infection was identified.

After study antibiotics were discontinued, two patients receiving moxalactam had positive wound cultures for an enterococcus and *Staphylococcus epidermidis* but wound infection requiring drainage did not develop. Another patient receiving gentamicin and clindamycin had a positive wound culture for *Pseudomonas aeruginosa* and *Staphylococcus epidermidis* but wound infection requiring intervention did not develop.

No overt symptoms of toxicity developed in any patient. One patient receiving moxalactam had a transient elevation of serum creatinine (> 2.0 mg/dL), which resolved within 48 hours without specific change in therapy. Abnormal coagulation parameters, which also resolved without specific intervention, were observed in two patients receiving gentamicin and clindamycin and one patient receiving moxalactam. No clinical episodes of bleeding or ototoxicity were noted.

Discussion

Antimicrobials have four clinical applications: 1) primary therapy, as in the treatment of pneumonia; 2) prophylaxis, as in coverage for an elective operation (where antibiotics are given prior to contamination); 3) preventive, as when contamination has already occurred; and 4) adjunctive, as in the management of an abscess where drainage is the primary therapy. Antibiotic treatment of the traumatized patient begins after injury (and therefore after contamination) and must be considered preventive. The therapy should be directed against pathogens most likely to cause infection, such as the microflora residing in the gut of the acutely traumatized patient. While the normal stomach and proximal small bowel contain relatively few bacteria in most patients, the distal small bowel and colon contain a high concentration (up to 10^{11} organisms per gram) (21,22) of aerobic and anaerobic species including *Bacillus fragilis*, aerobic enterococci, *Pseudomonas* species, and anaerobic *Streptococcus* and *Fusobacterium*. In patients with postsurgical intra-abdominal abscesses, mixed flora of anaerobes and aerobes are

recovered five times more frequently than either aerobes or anaerobes alone (21). Theories of microbial synergism abound (2). When risk factors of penetrating abdominal trauma were examined in 338 patients, colon injury and wounding by gunshot emerged as significant risk factors for trauma-related infections (5). In an experimental model of colonic perforation, 29 different regimens were compared for incidence of fatal peritonitis and abscess formation (11). The most effective regimens were those which combined agents effective against coliforms (aerobes) and *Bacillus fragilis* (11,13).

In a study of 295 patients sustaining penetrating abdominal trauma, those who received antibiotics preoperatively had a significantly lower incidence of wound infection, abscess, and sepsis (23). The question of how long to continue therapy postoperatively has not been resolved. In a prospective randomized study of 82 patients requiring celiotomy for penetrating abdominal trauma, a 12-hour postoperative course of antibiotics was comparable to a five-day course in the prevention of postoperative infection (4). Statistically significant differences of infection rate were not found between preoperative only and preoperative plus 24-hour antibiotic regimens in a series of 360 patients sustaining abdominal trauma (14).

Although antibiotics reduce the risk of infection in abdominal trauma, the choice of antibiotics remains controversial. Combination therapy with an aminoglycoside has been popular, even though aminoglycoside antibiotics tend to produce nephrotoxicity and ototoxicity. Of particular significance is that the ototoxic damage is often permanent due to destruction of cochlear hair cells. The new cephalosporins have antimicrobial spectra which compare favorably to that of combination therapy and may be less toxic (16,17,24).

Moxalactam has been noted to cause blood clotting derangements. The mechanisms are: 1) an acute interference with vitamin K metabolism superimposed on a chronic vitamin K deficiency, and 2) platelet dysfunction. Supplemental vitamin K reverses humoral clotting derangements (25). The frequency of moxalactam-induced bleeding events, most of which are serious, has been reported to be 2.5% for those receiving moxalactam for four or more days (24). Because of this incidence, use of moxalactam as a primary preventive antibiotic has been abandoned.

In our series, wound infection requiring surgical intervention did not develop even though positive cultures of the wounds were obtained. Culture of an organism from a wound does not represent infection but does indicate the presence of that organism in sufficient numbers to produce colony-forming units (26). The probability of infection in a wound is directly proportional to inoculum size and pathogen virulence and inversely proportional to local and systemic defenses (27). The results of this study provide support for previous reports indicating that broad spectrum cephalosporin therapy is clinically equivalent to combination therapy in abdominal trauma (9,11,13,14).

The populations included herein are insufficient to eliminate the possible existence of a type 2 error. Populations sizable enough to determine the exact difference in rates of post-penetrating abdominal trauma infections between the two regimens would be difficult to achieve given the overall low rate of infection with adequate surgical therapy. One obstacle to routine

use of the newer cephalosporins has been the perceived high cost of these antibiotics. In a previous study, the total cost of antibiotic therapy for patients with penetrating abdominal trauma was approximately \$125 higher per patient for the combination of gentamicin and clindamycin versus single agent therapy of moxalactam. This study considered cost per dose, personnel time, supply cost, and the cost of laboratory monitoring (28).

In our study, 2 g of moxalactam given intravenously every 12 hours was found to be of comparable efficacy to a gentamicin/clindamycin combination. Unfortunately, coagulopathy associated with use of moxalactam is serious enough to preclude its use in a preventive setting. Nevertheless, single antibiotic regimens with less toxic third generation cephalosporins appear to be a fruitful area for future research.

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