COMPARISON OF AMPICILLIN/SULBACTAM VERSUS CLINDAMYCIN IN THE PREVENTION OF INFECTION IN PATIENTS UNDERGOING HEAD AND NECK SURGERY

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Abstract: *Background.* Patients requiring major oncologic head and neck surgery are at high risk for postoperative wound infection when the surgical site is contaminated by secretions from the upper aerodigestive tract. Studies to identify agents active in the prevention of postoperative wound infection may serve to reduce patient morbidity.

Methods. Patients scheduled for a major contaminated head and neck surgical procedure were randomly assigned to receive either ampicillin/sulbactam or clindamycin. Medication was administered 1 to 2 hours prior to surgery and every 6 hours, for a total of five doses. Postoperatively, patients were followed daily for the development of wound infection or other septic complication.

Results. A total of 242 patients were enrolled in the study; 119 received ampicillin/sulbactam, and 123 received clindamycin. A total of 169 patients were considered evaluable. Of the evaluable patients, 14% in each group developed a postoperative wound infection. There were no statistically significant differences between the number of days to onset of wound infection, nor was there a statistically significant difference in the rate of non-wound infections in the two groups. There were no statistically significant differences between the intent to treat group and the evaluable group of patients.

Conclusion. It is concluded that ampicillin/sulbactam is as safe and effective as clindamycin in preventing postoperative wound infection following major head and neck surgery. © 1997 John Wiley & Sons, Inc. *Head Neck* **19:** 367–371, 1997.

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Patients requiring major head and neck surgery during which time the upper aerodigestive tract is opened into the surgical field are at risk for major postoperative infectious complications. Postoperative infection rates in patients range as high as 87%.[1] Comparative studies of perioperative antimicrobial prophylaxis in head and neck cancer surgery have clearly documented the efficacy of antimicrobial prophylaxis and reducing postoperative infections and patient morbidity following head and neck surgery.[2–14]

The issue of duration of antibiotic administration which provides adequate suppression of pathologic flora has been summarized by Johnson and Vu.[10] The general consensus is that perioperative antibiotic administration should be initiated prior to surgery and that a 24-hour treatment regimen is effective. This relatively short

treatment minimizes the risk of drug side effects and reduces the risk of colonization/superinfection due to resistant organisms. This was confirmed by Weber,[15] where he demonstrated that maximum efficacy is achieved with immediate preoperative and short-term (less than 48 hours) postoperative antimicrobial administration.

In a recently performed meta analysis,[16] it was demonstrated that there was a 43.7% reduction in infection rates with the use of antibiotics in comparison with placebo, 8.3% advantage of multiple antibiotics versus a single antibiotic, 13.7% advantage of multiple antibiotics when cefazolin is compared, and 4.1% in favor of multiple-day prophylaxis versus single-day prophylaxis. The analysis also suggested that a 1-day course of clindamycin may be the most effective prophylactic antibiotic regimen for head and neck surgery.

Unasyn (ampicillin sodium/sulbactam sodium) has documented activity against anaerobic pathogens, especially bacteroides, with comprehensive gram-positive in vitro activity. Activity had also been demonstrated against gram-negative aerobic organisms such as *Bacillus catarrhalis, Escherichia coli, Klebsiella* species, *Proteus mirabilis,* and *Haemophilus influenzae.* Clindamycin phosphate is a semisynthetic derivative of linocymin effective against most gram-positive cocci and anaerobic bacteria. Both antibiotics had been previously demonstrated to be effective in the prevention of postoperative wound infection in patients undergoing major contaminated head and neck surgery.[1,4,5,9,16]

The objective of the present study was to compare the safety and efficacy of perioperative ampicillin/sulbactam vs clindamycin for the prevention of infection in patients undergoing head and neck surgery.

STUDY DESIGN AND METHODOLOGY

Subjects. Patients 18 years of age or older—regardless of sex, race, and socioeconomic status—who were to undergo head and neck surgery for an upper aerodigestive tract neoplasm were eligible to be enrolled. Patients who were pregnant or likely to become pregnant; had known hypersensitivity to penicillins, cephalosporins, or clindamycin; had received a systemic antibiotic within 72 hours of planned procedure; had clinical or laboratory evidence of preexisting infection; had serious systemic disease, had severe renal disease or impaired immunologic function; or had received any investigational compound within 30 days prior to entering the study were excluded.

Past medical history including history of allergy and history of previous medications were taken, and a medical examination was performed within 4 weeks prior to receiving the study medication. After the examination, patients were stratified into the following groups: prior radiation vs no prior radiation, stage IV disease vs stage III or less disease, and laryngectomy vs other head and neck procedures.

Based on a computer-generated randomization code, patients were assigned in a 1:1 ratio to receive either 1.5 g ampicillin/sulbactam or 600 mg clindamycin within 1–2 hours prior to surgery. The hospital pharmacist maintained the randomization code and dispensed all study drug supplies. The clinical investigators and coordinators were blinded to drug assignment. All wounds were prepared with povidine-iodine and irrigated with normal saline before closure. After surgery, the patients continued receiving their assigned study drug at 6-hour intervals for a total of four doses. The allowable dosing window between the first and second postoperative dose was 12 hours; between the second and third and third and fourth doses, the allowable window was 9 hours. Patients were followed for the possible development of late infectious complications for the course of their hospital stay.

An attempt was made to document all postoperative wound infections by appropriate culture. Specimens for aerobic and anaerobic culture were obtained from any open wound drainage, aspirated seromas, and turbid suction drainage.

Until hospital discharge, patients were examined daily for signs and symptoms of infection. Any wound graded 4+ or above (4+ = purulent drainage, and 5+ = wound breakdown with mucocutaneous fistula) were considered infected. The infection rates, defined as the proportion of patients with wounds graded as 4+ or 5+ at any time during the healing process, were compared between patients randomized to ampicillin/sulbactam or clindamycin.

Evidence of the development of postoperative fever, presence of non-wound–related complications, including distant site infections (eg, urinary tract infection [UTI], pneumonia) and the length of hospitalization, were also recorded. Clinical laboratory studies consisting of complete blood count (CBC) with differential, serum chemistries, and urinalysis were performed. All adverse experiences were recorded.

The outcome at the operative site was the primary measure of prophylactic efficacy. The out-

come with respect to postoperative infectious complications at distant sites was identified as a secondary efficacy variable. Efficacy of prophylaxis was determined by the investigator for each patient using the following criteria: success, defined as an uneventful postoperative course without clinical evidence of operative or distant site infectious morbidity; or failure, defined as a postoperative course with documented clinical and/or microbiologic evidence of operative or distant site infectious morbidity.

Before study initiation, the study protocol and statement of informed consent were reviewed and approved by the institutional review committee. All patients signed informed consent prior to participation in the study.

Statistical Methodology. The following statistical analyses were determined for all evaluable patients.

Analyses were performed on all patients who completed the study per protocol. A patient who was a protocol violator (ie, who had taken incorrect study drug dosage or violated dosing schedules, taken concomitant antibiotics, or had a concurrent illness at baseline) was excluded from the efficacy analysis.

The comparability of ampicillin/sulbactam and clindamycin groups with respect to the demographic characteristics of age, weight, height, and systolic and diastolic blood pressures were assessed by Wilcoxon Rank Sum Test. Comparability of the demographic characteristics of sex and race, and baseline data of stratification code, primary site of neoplasm, and prior radiotherapy were assessed by Fisher's Exact Test (two-tail).

The proportions of patients with the presence or absence of wound and non-wound infection were compared between the two treatment groups using the Fisher's Exact Test. The mean duration of hospitalization (in days) between the two treatment groups were compared using the Wilcoxon Rank Sum Test.

RESULTS

A total of 242 patients who enrolled into the study received drug therapy: 119 received ampicillin/sulbactam, and 123 received clindamycin. Of these 242 patients, 38 of 119 in the ampicillin/sulbactam group and 35 of 123 in the clindamycin group were considered nonevaluable. The main reasons for nonevaluability were protocol violations of the antibiotic dosing schedule and concomitant antibiotics. Therefore, the efficacy population totaled 169: 81 in the ampicillin/sulbactam group and 88 in the clindamycin group. One ampicillin/sulbactam-treated patient had a non-wound infection at postoperative day 3 and was treated with antibiotics. This patient was not included in the evaluation of wound infection.

There were no statistically significant differences between the two treatment groups for the demographic variables of sex, age, race, weight, height, and systolic and diastolic blood pressures. In addition, the baseline variables of stratification code, primary tumor site, and prior radiotherapy were also not statistically significant between the two treatment groups.

In the intent-to-treat analysis, 15 of 119 (13%) of ampicillin/sulbactam-treated patients had a wound infection, compared with 15 of 123 (12%) of clindamycin-treated patients. There were no statistically significant differences between the two treatment groups in the rate of wound infection ($p = 1.00$, Fisher's Exact Test).

Of the evaluable patients, 11 of 81 (14%) of ampicillin/sulbactam-treated patients had a wound infection, compared with 12 of 88 (14%) of clindamycin-treated patients. Of the evaluable patients, 12 of 82 (15%) of ampicillin/sulbactam-treated patients had a non-wound infection, compared with 15 of 88 (17%) of clindamycin-treated patients. There were no statistically significant differences between the two treatment groups in the rate of wound and non-wound infections.

In the intent-to-treat analysis, the mean number of days to onset of wound infection for the ampicillin/sulbactam and the clindamycin groups was 7.2 ± 2.05 days and 7.6 ± 2.98 days, respectively. There were no statistically significant differences between treatment groups ($p = .91$, Wilcoxon Rank Sum Test).

In the standard efficacy analysis, the mean number of days to onset of non-wound infection for the ampicillin/sulbactam and the clindamycin groups was 6.5 ± 2.61 days and 7.0 ± 3.16 days, respectively. There were no statistically significant differences between treatment groups ($p = .74$, Wilcoxon Rank Sum Test).

The overall mean duration of hospitalization in the ampicillin/sulbactam group was 15.3 ± 7.1 days, compared with 17.6 ± 14.0 days for the clindamycin group. The difference was not statistically significant ($p = .89$, Wilcoxon Rank Sum Test). In patients who developed wound infection, the mean duration of hospitalization was 23.7 and 25.3 days, respectively.

All patients who received at least one dose of

study drug were evaluated for safety. Respiratory and gastrointestinal adverse experiences were the most commonly reported, being reported by 35% of ampicillin/sulbactam-treated patients and 32% of clindamycin-treated patients. Most of these events were judged by the investigator to be unrelated to the antibiotic administered. One patient receiving ampicillin/sulbactam and seven patients receiving clindamycin were positive for *Clostridium difficile* or *C. difficile* toxin.

BACTERIOLOGIC FINDINGS

Overall, 23 wound infections occurred in the evaluable patient. Cultures were unavailable for one ampicillin/sulbactam patient and five clindamycin patients. Therefore, 10 ampicillin/sulbactam and seven clindamycin patients had cultures taken. Of these 17 cultures, 13 were polymicrobial. A summary of the cultured organisms is found in Table. 1.

Table 1. Bacteria isolated from infected patients (evaluable).

Organism	Ampicillin/ sulbactam	Clindamycin
Gram-negative aerobes		
Haemophilus (unspecified)		1
Serratia marcescens	1	
Pseudomonas aeruginosa	2	
Enterobacter cloacae	1	1
Klebsiella	3	3
Eikenella corrodens		1
Escherichia coli	1	1
Xanthomonas maltophilia		1
Citrobacter diversus		1
Proteus mirabilis	2	
Neisseria (unspecified)	2	1
Rods	1	2
Total	13	12
Gram-positive aerobes		
Coagulase-positive *Staphylococcus*	1	1
Coagulase-negative *Staphylococcus*	3	4
Streptococcus viridans	7	2
Diphtheroids	1	2
Enterococcus faecalis		2
Microaerophilic β-hemolytic strep	2	1
β-Hemolytic *Streptococci* (group C)	2	
β-Hemolytic *Streptococci* (group F)	1	
Nonhemolytic *Streptococci*		1
Micrococcus (unspecified)	1	
Rods		1
Total	18	14
Anaerobes		
Bacteroides melaninogenicus	3	1
Capnocytophaga (unspecified)		1
Lactobacillus (unspecified)		2
Peptostreptococcus asaccharolyticus	1	
Propionibacterium acnes		1
Peptostreptococcus (unspecified)	3	
Clostridium difficile		1
Clostridium subterminale		1
Clostridium (unspecified)	1	
Total	8	7

DISCUSSION

Previous publications have demonstrated similar efficacy for a variety of antibiotics when used to prevent postoperative wound infection following major contaminated head and neck surgical procedures.[16] All of the antibiotic regimens have in common activity against flora normally found on the mucosal surfaces of the upper aerodigestive tract. This includes anaerobic bacteria and gram-positive cocci. Direct comparison between the various antibiotics tested is not currently possible, because the power of the studies reported is inadequate to distinguish between drugs of similar of efficacy. A study which included in excess of 1,000 patients would be necessary, for instance, to demonstrate a difference of incidence of infection between 7% and 10%.

These differences may not be clinically relevant, and the surgeon must consider other issues—such as ease of administration, toxicity, and cost—when choosing an antibiotic for prophylaxis following major head and neck surgery. An enduring single recommendation is not possible, because some health-care organizations may have contractual arrangements which influence the cost comparisons.

The clinician must remain aware of the continuing change in the spectrum of bacteria resistance to antibiotics. Fifteen years ago, most oral flora were sensitive to penicillin. This is no longer true inasmuch as both the gram-positive aerobic cocci as well as anaerobic bacteria currently have a high incidence of β-lactomase production. The head and neck surgeon is cautioned to remain tuned to the spectrum of bacteriologic resistance in his operating environment.

In spite of antibiotic prophylaxis and advances in surgical technology, anesthesia, and reconstructive capabilities, the incidence of wound infection following head and neck surgery remains 5% to 15%. The explanation for this is somewhat

elusive. Some physicians attribute postoperative complications to patient factors. Immunosuppression, malnutrition, and other comorbidities are common in patients undergoing major head and neck surgical procedures.

In a retrospective report, we have indentified a variety of factors which may contribute to the development of postoperative wound infection.[17] For instance, intraoperative decision making may retrospectively be questioned: Perhaps the wound was closed too tightly. In retrospect, the decision to use a flap would perhaps be more appropriate. Paradoxically, the highest infection rates are experienced in patients having pedicle flap reconstruction: Perhaps we should use free flaps, which tend to have very low postoperative wound separation rate. Free flaps require, however, special expertise, prolonged operating time, and donor site morbidity. These represent value judgments that cannot be made in a vacuum. Medicine is practiced at the bedside, and decisions must be made.

It is appropriate to retrospectively evaluate all complications and adverse events. Some of these problems can be readily attributed to avoidable errors and become part of our continuing education and learning curve.

When antibiotic prophylaxis is undertaken with an effective drug at adequate dose and is appropriately administered (perioperatively), it is rare that postoperative infection can be attributed to antibiotic prophylaxis. The surgeon must look at preoperative preparation, intraoperative technique and decision making, and postoperative care. Only in this way can a surgeon can hope to improve overall patient outcome.

CONCLUSION

Patients undergoing head and neck cancer therapy are at great risk for developing postoperative wound infection. In a previous study comparing ampicillin/sulbactam versus clindamycin, Weber[15] reported wound infections occurring in 13.3% of patients receiving ampicillin/sulbactam and 27.1% of patients receiving clindamycin. This difference was statistically significant.

Results from this study indicate similar efficacy when ampicillin/sulbactam is compared with clindamycin. It is concluded that ampicillin/sulbactam is as safe and effective as clindamycin in preventing infection in patients undergoing head and neck surgery.

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