Object: The objective of the investigation was to determine the comparative efficacy of cefoperazone/sulbactam versus cefazoline in the prophylaxis of patients undergoing neurosurgical procedures and to evaluate the choice of appropriate antibiotics for surgical prophylaxis.

Methods: Consecutive patients undergoing neurosurgery in 2003 were recruited for the study. Patients undergoing neurosurgical procedures were assigned randomly to groups, one receiving cefoperazone/sulbactam, and the other receiving cefazoline for antimicrobial prophylaxis. All patients were followed for a minimum of 2 weeks postoperatively and all surgical site infections (SSIs) were recorded.

Results: A total of 28 postoperative SSIs were identified from 483 cases, with 13 (5.3%) in the cefoperazone/sulbactam group and 15 (6.4%) in the cefazoline group, with a resulting overall infection rate of 5.8%. The difference between the 2 groups was not statistically significant ($P > 0.05$). The predominantly isolated microorganisms in patients with SSIs were *Staphylococcus aureus* [21 (75.0%)], *Acinetobacter baumanii* [4 (14.3%)], and *Staphylococcus epidermidis* [3 (10.7%)].

Conclusions: As no single regimen of prophylactic antibiotic agent is appropriate for all neurosurgical procedures at all hospitals, the expected organisms cultured from prior wound infections should determine the appropriate antimicrobial therapy for each institution.

Key Words: antibiotics, infection, neurosurgery, prophylaxis, wound infection

(Neurosurg Q 2007;17:166–169)

Surgeonal site infections (SSIs) are the most common complication for surgically treated patients, resulting in increased rates of morbidity and mortality, length of hospital stay, and cost.$^1$ The average SSI rate without antibiotics ranges between 5% and 11% in cerebrospinal fluid (CSF) shunts, between 1% and 5% in craniotomies or spinal surgeries in clean or clean-contaminated patients, and between 11% and 38% in CSF fistulas.$^2$$^5$

The use of antibiotic prophylaxis in neurosurgery is still controversial; although many centers, including ours, prefer to administer antibiotics to all patients. In randomized, controlled trials,$^3$$^4$$^6$$^6$$^16$ antibiotic prophylaxis has been shown to decrease the rate of SSIs in clean neurosurgical operations. In the United States antibiotic guidelines have been adopted widely.

Previous clinical trials have provided no evidence of superiority of one antibiotic to another for prevention of SSIs after clean neurosurgical operations.$^4$$^7$$^16$

Cefoperazone/sulbactam and cefazoline are among the antibiotics that have been effective for prophylaxis in neurosurgical operations.$^4$$^17$ At the outset of the prophylaxis in our clinic, most of the organisms isolated in our hospital were sensitive to the cephalosporins. Therefore, we have been using cefazoline since 1995 for surgical prophylaxis in our clinic. But the increase in infection rate in the clinic after the end of 2002, led us to the introduction of a more potent cephalosporin, which was cefoperazone/sulbactam. Although cefoperazone/sulbactam was superior to cefazoline because of its resistance to $\beta$-lactamase, the cost it had loaded to the health system had to be considered. Therefore, we planned this study to compare the efficacy of the 2 antibiotics used in the clinic with a final decision of selection of the most efficient antibiotic.

MATERIALS AND METHODS

The study was carried out between January 1, 2003 and December 31, 2003 at the Neurosurgery Department of Çukurova University Hospital, Adana, Turkey. All patients undergoing elective neurosurgical operations during the study period were eligible for inclusion, with the exception of the following: those who did not give their consent for inclusion in the study, those who were allergic to cephalosporins, those who had received antibiotic treatment within 48 hours before the operation, those with an infectious disease such as brain abscess, subdural or epidural empyema, osteitis, or scalp infection requiring antibiotic treatment, and those having an indwelling intraventricular catheter, either for...
the monitoring of intracranial pressure or for external ventricular drainage (as these patients regularly receive antibiotics until the catheter is removed).

This study was approved by the Ethics Committee of the Faculty of Medicine in Çukurova University.

**Study Procedures**

Patients were selected randomly among patients applying to the neurosurgery unit using random numbers list by including the patients with odds numbers into the cefazoline group and those with even numbers to the cefoperazone/sulbactam groups. Emergency cases were not included because of uncertainties in randomization and the difficulty of administering the antibiotics when time was at a premium and the usual anesthetic and nursing staff, familiar with the regime of administration, were not present.

The anesthesiologist administered the study antibiotics according to the prescribing information. Cefoperazone/sulbactam or cefazoline, 1 g (50 mg/kg for children), was given intravenously. The infusion was started after the induction of anesthesia, so that peak blood levels of antibiotics were reached during the operation. Further doses were given for every 3 hours of the operation. If patients had been operated previously in the same anatomic localization, every one received 2 g of antimicrobial agent with the same protocol. In case of a second surgery in a previously untouched localization or a subsequent neurosurgical operation 6 weeks later, it was considered a new case. All patients underwent the same protocol in preparation for surgery. The hair in the operative field was shaved. The skin was prepared with povidone-iodine, followed by alcoholic chlorhexidine. The surgical field was draped with a sterile towel and sealed off with adhesive transparent plastic. For wound closure, the subcutaneous tissue was approximated with polyglandin and the skin with polyethylene.

If any infection occurred or was suspected, the causative pathogen was identified (except in cases with nonpurulent superficial infections) and appropriate antibiotics given as indicated clinically. Two physicians assessed patients for the occurrence of infectious complications. All patients were followed for minimum of 2 weeks postoperatively and SSI was recorded. SSIs were classified as superficial incisional, deep incisional (soft tissue), or organ/space infections (intracranial, osteomyelitis, disc space, spinal abscess, meningitis, or ventriculitis). Adverse effects possibly caused by cefoperazone/sulbactam and cefazoline were also registered.

During the study period in 2003, a total of 557 neurosurgical operations were performed in the Department of Neurosurgery, Çukurova University Hospital. Of these, 54 (9.7%) did not fulfill criteria for an inclusion in the study: among them 7 (1.3%) had received antibiotic treatment within 48 hours before the operation, 16 (2.9%) had an infectious disease requiring antibiotic treatment, and 31 (5.6%) were emergency cases, and a further 20 (3.6%) were excluded because of the following reasons: the addition of external ventricular drainage to the operation (8 cases), death shortly after the operation (7 cases), and absence of informed consent for participation in the study (5 cases) obtained from the patient or his/her companion in case of unconsciousness. Thirty patients (5.4%) underwent a second operation within 6 weeks of randomization and the same prophylactic antibiotics were used in these operations as in the original operation as specified by the study protocol, and the data from the second operations were not repeated in the study analyses.

The complete medical records of each of the remaining 483 (86.7%) cases were recorded.

The main outcome of the study was whether a patient developed a SSI. The $\chi^2$ was used. A result of at least $P < 0.05$ was accepted as “significant.”

**RESULTS**

The study included a total of 483 patients undergoing neurosurgical operations, grouped as 183 (37.9%) craniotomy, 151 (31.3%) spinal, 77 (15.9%) burrhole, and 72 (14.9%) shunt operations.

A total of 28 postoperative SSIs were identified among 483 cases included in the study, with a resulting overall infection rate of 5.8%. There were 13 (5.3%) cases of SSI in the cefoperazone/sulbactam group and 15 (6.4%) in the cefazoline group. The difference in infection rate between the 2 antibiotic groups was not statistically significant (Table 1).

Infections were classified as superficial incisional, deep incisional (soft tissue), or organ/space infections (intracranial, osteomyelitis, disc space, spinal abscess, meningitis, or ventriculitis) and presented according the antibiotic groups in Table 2. Our results showed that organ/space infections were the most common type of SSI after neurosurgical operations with 15 (53.6%) cases, but there was no statistical difference between antibiotic groups ($P = 0.752$) (Table 2).

The microorganisms causing postoperative SSIs and the drug-sensitivity analyses were listed in Table 3. *Staphylococcus aureus* with 21 (75.0%) cases, *Acinetobacter baumanii* with 4 (14.3%) cases, *Staphylococcus epidermidis* with 3 (10.7%) cases were isolated frequently from patients with SSIs. The sensitivity of *S. aureus* to

**TABLE 1. The Distribution of Surgical Site Infections According 2 Antibiotic Groups**

<table>
<thead>
<tr>
<th>Antibiotic Groups</th>
<th>SSI (+)</th>
<th>SSI (-)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%*</td>
<td>n</td>
</tr>
<tr>
<td>Cefoperazone/sulbactam</td>
<td>13</td>
<td>5.3</td>
<td>234</td>
</tr>
<tr>
<td>Cefazoline</td>
<td>15</td>
<td>6.4</td>
<td>221</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>5.8</td>
<td>455</td>
</tr>
</tbody>
</table>

$P = 0.607$.  
$df = 1$.  
$\chi^2 = 0.26$.  
*Line percentages.  
*Column percentages.
Table 2. The Distribution of Surgical Site Infection Types According to 2 Antibiotic Groups

<table>
<thead>
<tr>
<th>Antibiotic Groups</th>
<th>Type of Infection</th>
<th>n</th>
<th>%*</th>
<th>n</th>
<th>%*</th>
<th>n</th>
<th>%*</th>
<th>Total</th>
<th>%†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Superficial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefoperazone/sulbactam</td>
<td>5</td>
<td>38.4</td>
<td>2</td>
<td>15.4</td>
<td>6</td>
<td>46.2</td>
<td>13</td>
<td>46.4</td>
<td></td>
</tr>
<tr>
<td>Cefazoline</td>
<td>47</td>
<td>26.7</td>
<td>2</td>
<td>13.3</td>
<td>9</td>
<td>60.0</td>
<td>15</td>
<td>53.6</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
<td>32.1</td>
<td>2</td>
<td>13.3</td>
<td>15</td>
<td>53.6</td>
<td>28</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

P = 0.752.  
df = 2.  
χ² = 0.57.  
*Line percentages.  
†Column percentages.

cefoperazone/sulbactam and to cefazoline was found to be 42.0% and 29.0%, respectively. The sensitivity of A. baumannii to cefoperazone/sulbactam was 47.0%, whereas it was completely resistant to cefazoline (Table 3). The frequency of methicillin-resistant S. aureus was 32.0% in our clinic.

Adverse effects possibly caused by cefoperazone/sulbactam and cefazoline were not seen in either group.

**DISCUSSION**

Neurosurgeons have traditionally reported postoperative infection rates substantially lower than their general surgeon colleagues. However, the introduction of longer microsurgical procedures and the increasing use of implanted foreign materials such as shunts, clips, implant material for spinal stabilization, and cranioplasty plates have increased the theoretical risk of perioperative infection. Although, in terms of importance, postoperative wound infection is well down the list of causes of mortality and morbidity in neurosurgical practice, the occurrence of this presumably preventable complication is a recurring frustration.

Since 1980, there have been several controlled trials that support the use, in clean neurosurgical cases, of prophylactic antibiotics, including vancomycin, cephalosporins, gentamicin, nafcillin, oxacillin, piperacillin, chloramphenicol, ampicillin/sulbactam, clindamycin, streptomycin, erythromycin, and trimethoprim-sulfamethoxazole. However, use of prophylactic antibiotics is widespread and often inappropriate, and there is less agreement concerning the timing and duration of treatment, and the choice of antibiotics.

The range of infection in clean neurosurgical operations in randomized, controlled trials is 4.0% to 12.0% without prophylactic antibiotics and 0.3% to 3.0% with prophylactic antibiotics. Currently, an incidence of infectious complications < 5% is considered acceptable. We have been using cephalosporin group antibiotics since 1995 for surgical prophylaxis in our clinic. Between 1995 and 2003, before the introduction of this trial, the prevailing SSI rate in our institution for clean neurosurgical cases ranged between 2% and 5%. In our comparison of cefoperazone/sulbactam and cefazoline for prophylaxis in neurosurgical operations, the infection rate was slightly higher in the cefazoline group (6.4%) than in the cefoperazone/sulbactam group (5.3%), although the difference was not statistically significant. Our results do not suggest that cefoperazone/sulbactam have produced better protection against infection than cefazoline. However, the total rate of our SSI was 5.8%, which was slightly higher than acceptable range and neither cefoperazone/sulbactam nor cefazoline was found to present any superiority to the other for the prophylaxis in our neurosurgical operations. Only the cost-effectiveness was a criterion for the selection of the prophylactic antibiotic in that case.

In addition to having good penetration into the CSF, an adequate half-life and minimal adverse effect, an antibiotic for neurosurgical prophylaxis should be effective against the bacteria commonly associated with SSI, which are mainly gram-positive cocci, particularly S. aureus and S. epidermidis. Thus, when antibiotic prophylaxis is indicated, adequate gram-positive bacterial coverage, including protection against Staphylococcus infection, is required, and prophylactic routines should be designed to minimize the antimicrobial load, but to maximize the benefits. However, when prophylaxis is considered, choice of antimicrobial agents should take account of up-to-date local information in relation to the relevant microbial ecology in hospitals and in the community setting. Infections that are exceptionally dangerous or resistant to treatment should be defined; the bacteria most likely to cause the infection should be identified, and the antimicrobial regimen likely to cover these bacteria should be established while interfering as little as possible with the general bacterial flora in the hospital. Both sources of infection should be assessed periodically by performing appropriate diagnostic studies, including stains and cultures. With the widespread use of antibiotics, β-lactamase–producing S. aureus has become quite common in hospitals like in our hospital. As seen in Table 3, the skin bacteria cause most of SSIs and the organism most commonly identified as causative agent was S. aureus (75.0%) in these cases.

In hospitals with a proven incidence of methicillin-resistant S. aureus (> 10%), like our hospital with a rate of 32.0%, or where methicillin-resistant coagulase-negative

Table 3. The Sensitivity Distribution of S. aureus and A. baumannii to Different Antibiotics

<table>
<thead>
<tr>
<th>Sensitivity of S. aureus (%)</th>
<th>Sensitivity of A. baumannii (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teicoplanin</td>
<td>100</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>100</td>
</tr>
<tr>
<td>Trimethoprim + Sulbactam</td>
<td>97</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>85</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>82</td>
</tr>
<tr>
<td>Imipenem</td>
<td>46</td>
</tr>
<tr>
<td>Cefoperazone/sulbactam</td>
<td>42</td>
</tr>
<tr>
<td>Cefazoline</td>
<td>29</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>26</td>
</tr>
<tr>
<td>Meropenem</td>
<td>100</td>
</tr>
<tr>
<td>Netilmicin</td>
<td>100</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>100</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>92</td>
</tr>
<tr>
<td>Imipenem</td>
<td>86</td>
</tr>
<tr>
<td>Cefoperazone/sulbactam</td>
<td>47</td>
</tr>
<tr>
<td>Cefazoline</td>
<td>0</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>0</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>0</td>
</tr>
</tbody>
</table>
Staphylococci are associated with postoperative SSIs; the use of vancomycin is suggested. But the association of vancomycin is not recommended routinely because of the risk for resistance development. Djindjian suggests alternatively the use of second generation cephalosporins in cases with methicillin-resistant S. aureus.

We did not detect any substantial differences between the antibiotic regimens with respect to β-lactamase sensitivity. But as our total SSI rates are slightly over the acceptable range, the replacement of the used prophylactic antibiotics should be considered. The absence of a control group prevents us from judging the exact effectivity of these antibiotics in preventing SSIs.

After this preliminary study, we suggest complementary studies to detect other factors that would contribute to the development of SSI. At the same time, great emphasis should be placed on aseptic technique and wound care because prophylactic antibiotics can never compensate for inattention to detailed and inadequate surgical technique.

CONCLUSIONS

Excellent studies have been performed that support the notion that preoperative antibiotics do provide modest benefit regarding the incidence of postoperative SSIs, which virtually is a universally accepted standard. But, no single regimen of prophylactic antibiotic agent is appropriate for all neurosurgical procedures at all hospitals. The organisms cultured from the prior wound infections should determine the appropriate antimicrobial drug. However, dangerous multiresistant nosocomial organisms may develop and nosocomial flora may change in neurosurgical patients. In this condition, prophylactic antibiotics should be changed.

REFERENCES