Perioperative Antimicrobial Prophylaxis in Neurosurgery: Clinical Trial of Systemic Flomoxef Administration and Saline Containing Gentamicin for Irrigation

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Abstract

The efficacy of a new protocol consisting of a prophylactic antibiotic regimen of peri- and postoperative intravenous administration of flomoxef and irrigation of the operative field with saline containing gentamicin was assessed by comparing infection rates in two consecutive series of patients who underwent neurosurgical procedures. Group A received postoperative flomoxef administration, with saline containing no antibiotics for irrigation, from July 1988 to December 1989. Group B received the new protocol from January 1990 to December 1991. For further evaluation, this protocol was continued in most patients who underwent surgery from January 1992 through December 1993 (Group C). Only adult or adolescent patients who underwent clean neurosurgical procedures were included. The number of patients and procedures in each group were: 76 patients (97 procedures) in Group A, 103 (133) in Group B, and 107 (137) in Group C. There were no significant differences between Groups A and B in age, sex, clinical category, coexistent disease, clinical outcome, surgical procedures, general anesthesia, emergency operation, steroid administration, and the timing (season), duration, and frequency of surgery. Meningitis developed in three patients and subcutaneous infection in one in Group A. None of the patients in Group B experienced postoperative infection. This difference in infection rates (4.1% vs. 0%) was statistically significant (p = 0.0305). Furthermore, no postoperative infections developed in the Group C patients. The most appropriate interval for multiple dose administration was determined by analyzing intraoperative time-related changes in the serum flomoxef concentration during surgery in 21 recent patients. Serum flomoxef concentrations fell below therapeutic levels (3.0 μg/ml) by the 6th post-administration hour in 70% of patients. We conclude that this antibiotic regimen significantly reduces the postoperative infection rate following neurosurgical procedures. Multiple dose administration of flomoxef is recommended when the duration of surgery is 6 hours or more.

Key words: antibiotic prophylaxis, flomoxef, gentamicin, meningitis, neurosurgery, postoperative infection

Introduction

The incidence of postoperative wound infection, deep or superficial, in clean neurosurgical procedures is low. However, this complication carries the risk of particularly devastating clinical results. Therefore, it is essential to keep postoperative infection to an absolute minimum. The majority of studies have focused on the prophylactic use of antibiotics as well as the meticulous care, including operative techniques, which must be exercised by all personnel, during and after operative procedures.

Perioperative antibiotic administration intended to prevent postoperative neurosurgical infection is
not yet widely applied in Japan. In many patients systemic antibiotic administration is started just after surgery and is continued for a week. This emphasis on postoperative treatment stems from the National Health Insurance system not covering prophylactic treatments. Overall postoperative infection rates of 3.1–5.8% in the patients who underwent clean neurosurgical procedures have been reported in Japan. In contrast, zero, or nearly zero, postoperative infection rates for the patients who underwent clean neurosurgical procedures have been achieved by utilizing pre- and/or intraoperative administration of antimicrobial agents in the U.S.A. and European countries.

Our previous analyses of postoperative infection rates in our facility revealed that the incidence was significantly lower in patients who had received a second generation cephem (all cephamycins and cephalosporins are categorized as cephems) than in those who had been given penicillin, a first or third generation cephem, or other types of antimicrobial agents. Although flomoxef is categorized as a third generation cephem from the historical viewpoint, its activity against Staphylococcus aureus, both methicillin-resistant and susceptible, and epidermides, streptococci, and propionibacteria, which are the major microorganisms causing postoperative infection following neurosurgical procedures. Therefore, flomoxef is considered to be suitable for empiric or prophylactic use in neurosurgery. However, an 18 month retrospective study conducted in our facility revealed that postoperative infection occurred in 4 of 97 operations (4.1%) in which flomoxef had been administered postoperatively only. This infection rate was slightly higher than that experienced during the previous decade in our facility (3.3%), although the difference was not statistically significant.

The present prospective study was initiated in January 1990, to assess the regimen of intravenous flomoxef given before and after the operation, combined with irrigation using saline containing gentamicin for the duration of the operative procedure, because gentamicin-susceptible Pseudomonas aeruginosa was isolated in two of the four cases of postoperative infection. The results of the prospective study using the new regimen were compared to those of the retrospective study. The most appropriate interval for multiple dose administration was determined by analysis of the changes in the serum flomoxef concentration during surgery in patients who underwent surgery in the first 8 months of 1994.

Materials and Methods

I. Study design

Infection rates were compared in two consecutive series of patients who underwent neurosurgical procedures prior to (Group A) and following (Group B) the introduction of the new protocol. The retrospective study revealed that postoperative infection occurred in four (4.1%) of 97 operations using the conventional regimen (postoperative administration, saline containing no antibiotics for irrigation). If infection rates of zero could be achieved with the new protocol, a fixed sample size design with a p value (exact test) below 0.05 would require more than 59 cases in the new group. If postoperative infection was to occur in one or two cases, a sample size of more than 162 or 244, respectively, would be necessary in the new group. If three patients or more were to experience this complication, the trial would have to be abandoned. Group A patients underwent surgery during the period from July 1988 to December 1989, and Group B patients during the following 2 year period from January 1990 to December 1991. For further evaluation, the new protocol was used in the majority of patients who underwent surgery from January 1992 through December 1993 (Group C), because the sample size in Group B would not have been sufficient for a p value below 0.05 if one additional patient had experienced postoperative infection.

II. Selection of participants

Only adult or adolescent patients who underwent clean neurosurgical procedures were included. Patients with an allergy to flomoxef, brain abscess or other central nervous system infections, intervention via the rhinoseptal route, or placement of a cerebrospinal fluid drainage device were excluded. Other reasons for exclusion were: clean-contaminated or contaminated neurosurgical procedure, concomitant preoperative infection or antibiotic therapy, renal or hepatic dysfunction, and early postoperative death (28 days or less after surgery). Patients operated on more than once in this study period were counted separately on each occasion, except for those undergoing immediate reoperation for postoperative complications. The final number of patients (procedures) in each group was: 76 patients (97 procedures) in Group A, 103 (133) in Group B, 371

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and 107 (137) in Group C.

III. Antibiotic protocols

Group A patients received 100 ml saline containing 1.0 g flomoxef by drip infusion over half an hour in the recovery room or the ward, starting immediately after return from the operating room, repeated at 8- or 12-hour intervals for 6 or 7 postoperative days. Group B patients received drip infusion of 1.0 g flomoxef in saline started just after induction of general anesthesia in the operating room, and continued for 6 or 7 postoperative days. If the operation was prolonged for 6 hours or more, flomoxef was re-administered intraoperatively. Saline containing gentamicin (20 mg/l) was used for irrigating the operative field only in the Group B and C patients.

IV. Antiseptic procedures and postoperative management

Our antiseptic procedures, which have been described in detail elsewhere, were unchanged during the study period. All surgical procedures were performed in one of the two operating rooms designated for neurosurgical procedures at our facility. Although two senior and four junior neurosurgeons participated in this series of operations, surgical techniques and general postoperative management are standardized in our clinic.

V. Infection criteria

The following criteria was used for diagnosis of a postoperative infection based on the criteria reported by Malis: 1) drainage and/or accumulation of pus at the operative site with signs of cutaneous inflammation, with or without positive culture; 2) bacterial meningitis; and 3) meningismus with a significant increase in cerebrospinal fluid leukocytes and signs of systemic infection, which eventually subsided with additional antibiotic treatment. All patients were followed up for a minimum of 6 months or until death.

VI. Analysis of data

The chi-square test, Wilcoxon’s rank sum test, and the exact test were used for statistical analysis. The p value is presented only when statistical significance (p < 0.05) was achieved.

VII. Serum flomoxef concentration during surgery

Intraoperative serum flomoxef concentrations were determined in 21 patients who underwent elective surgery, whether clean or clean-contaminated, for brain tumors, aneurysms, and other neurosurgical disorders, during the first 8 months of 1994. Serum samples were obtained at hourly intervals after completion of the drip infusion. All samples were placed in sealed polypropylene tubes for storage at -20°C until analysis. Antibiotic concentrations were determined by the agar well method, a biological assay using Escherichia coli 7437 as the standard strain. The “fitting of the two compartment model” method was used to obtain a curve estimating the serum flomoxef concentration level.

Results

There were no significant differences between Groups A and B with respect to sex, age, clinical category, coexistent disease, and clinical outcome (Table 1), or in surgical procedures, general anesthesia, emergency operation, steroid administration, and the timing (season), duration, or frequency of surgery (Table 2).

Postoperative infection developed in four patients (meningitis in 3 and subcutaneous infection in 1) among a total of 97 operations in Group A. Pseudomonas aeruginosa was isolated from the subcutaneous discharge in Case 2 and from cerebrospinal fluid in Case 3, but cultures were negative in the other two (Table 3). In contrast, there were no postoperative infections among 133 operations in Group B. This difference is statistically significant (p = 0.0305). Furthermore, no postoperative infections developed in the Group C patients. None of the Group A, B, or C

<table>
<thead>
<tr>
<th>Table 1 Clinical characteristics of patients in Groups A and B</th>
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<tr>
<td>Sex:</td>
</tr>
<tr>
<td>female</td>
</tr>
<tr>
<td>male</td>
</tr>
<tr>
<td>Age (yrs):</td>
</tr>
<tr>
<td>≤ 19</td>
</tr>
<tr>
<td>20–29</td>
</tr>
<tr>
<td>30–39</td>
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<tr>
<td>40–49</td>
</tr>
<tr>
<td>50–59</td>
</tr>
<tr>
<td>60–69</td>
</tr>
<tr>
<td>70+</td>
</tr>
<tr>
<td>Clinical category:</td>
</tr>
<tr>
<td>brain tumor</td>
</tr>
<tr>
<td>cerebrovascular diseases</td>
</tr>
<tr>
<td>cranial trauma</td>
</tr>
<tr>
<td>spinal disorder</td>
</tr>
<tr>
<td>other disorders</td>
</tr>
<tr>
<td>Coexistent disease:</td>
</tr>
<tr>
<td>diabetes melitus</td>
</tr>
<tr>
<td>hypertension</td>
</tr>
<tr>
<td>Clinical outcome:</td>
</tr>
<tr>
<td>good</td>
</tr>
<tr>
<td>moderately disabled</td>
</tr>
<tr>
<td>severely disabled</td>
</tr>
<tr>
<td>died</td>
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</tbody>
</table>

*aExact test, bWilcoxon’s rank sum test.*
patients experienced significant side effects or serious systemic infections caused by a flomoxef-resistant microorganism.

Intraoperative serum flomoxef concentrations were determined in 21 patients who underwent elective surgery (Table 4). Figure 1 shows the estimated curve of serum flomoxef concentrations and the 95% confidence intervals for each post-administration hour. The mean serum flomoxef concentration was lower than 3.0 μg/ml at the 5th post-administration hour. There were no patients with serum flomoxef concentrations lower than 3.0 μg/ml by the 3rd post-administration hour. However, concentrations were lower than 3.0 μg/ml in 13 of 20 or 11 of 14 patients at the 5 or 6 hour point, respectively, after administration. No postoperative infections have thus far developed in 20 of these 21 patients, but the other developed meningitis. In this patient, frontal craniotomy was carried out for a pituitary tumor and the frontal sinus was extensively opened. No microorganisms were isolated from the cerebrospinal fluid.

Cyst fluid was obtained 1.5 hours after administration from one patient with a cystic glioma. The flomoxef concentration was 5.06 μg/ml, and the serum-cyst penetration rate was 0.38. The flomoxef concentration within the cerebrospinal fluid was less than 0.3 μg/ml 2 hours after administration in one patient with a hemangioblastoma.

Table 3 Clinical characteristics of patients with postoperative infection

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/ Sex</th>
<th>Clinical diagnosis</th>
<th>Procedure</th>
<th>Duration (hrs)</th>
<th>Type</th>
<th>Latency period (days)</th>
<th>Microorganism isolated</th>
<th>Clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61/F</td>
<td>ruptured BA aneurysm</td>
<td>VP shunt</td>
<td>1.25</td>
<td>meningitis</td>
<td>18</td>
<td>negative</td>
<td>died (re-resection)</td>
</tr>
<tr>
<td>2</td>
<td>50/M</td>
<td>petroclival meningioma</td>
<td>subtotal removal clipping</td>
<td>11</td>
<td>subcutaneous abscess</td>
<td>50</td>
<td>Pseudomonas aeruginosa</td>
<td>good</td>
</tr>
<tr>
<td>3</td>
<td>33/F</td>
<td>ruptured PICA aneurysm</td>
<td>totural removal*</td>
<td>4.5</td>
<td>meningitis</td>
<td>7</td>
<td>Pseudomonas aeruginosa</td>
<td>good</td>
</tr>
<tr>
<td>4</td>
<td>16/F</td>
<td>tentorial hemangioectactoma</td>
<td>total removal**</td>
<td>9.5</td>
<td>meningitis</td>
<td>6</td>
<td>negative</td>
<td>good</td>
</tr>
</tbody>
</table>

*Reoperation 5 years after inadequate clipping which had been performed at a local clinic. **Reoperation 2 months after partial removal which had been performed at our facility. BA: basilar artery, PICA: posterior inferior cerebellar artery, VP shunt: ventriculoperitoneal shunt procedure.
Fig. 1 Intraoperative decreases in serum flomoxef concentration with time following intravenous drip infusion. The estimated mean and 95% confidence intervals (dotted lines) were obtained by the "filling of the two compartment model" method. Each sample is indicated by a dot. Seven samples have been omitted at the 0 hour point because concentrations exceeded 125 μg/ml.

Discussion

Prophylactic use of antibiotics in clean neurosurgical operations remains controversial, but most related studies, which have been instructively reviewed by Brown, Dempsey et al., and Haines, indicate that it is effective in preventing postoperative infections. Recently, Barker and Haines and Walters concluded that meta-analysis of published randomized studies comparing prophylactic antibiotics to a placebo showed that antibiotics are advantageous in craniotomies and ventriculoperitoneal shunt operations. Many different antimicrobial agents, alone or in combination, have been used for this purpose. One of the most effective antibiotic combinations appears to be intravenous administration of vancomycin and gentamicin (or tobramycin), with an irrigation solution containing streptomycin, as proposed by Malis and subsequently others. Nevertheless, the Japanese Ministry of Public Welfare had not approved the use of vancomycin in any clinical setting at the time that this study was started. Therefore, we chose flomoxef for intravenous administration. Flomoxef has antimicrobial activities against Gram-positive as well as Gram-negative microorganisms, so we did not consider an additional antibiotic necessary for systemic administration. Thus, gentamicin was chosen for the intraoperative irrigation solution. The disadvantage of flomoxef is minimal penetration into the cerebrospinal fluid when the blood-brain barrier is intact, although flomoxef penetrates well into the cyst of a glioma, as seen in this study.

This clinical trial is a pilot study of a new combination of anti-microbial agents, aimed at preventing postoperative infection: systemic administration of flomoxef and topical use of gentamicin. No blind or randomized technique was undertaken. However, the postoperative infection rate of zero, which was significantly lower than that obtained using the conventional regimen, and the absence of significant side effects, encourages further investigation; a double-blind randomized study at the multi-center level.

Debate continues as to whether postoperative administration is necessary. Many previous studies have discontinued antibiotic administration postoperatively or after only 1 postoperative day. Cartmill et al. found no significant difference in postoperative infection rates between patients receiving prophylactic penicillin for 5 days (0%) versus 1 day (1.4%) in elective neurosurgical operations. However, postoperative infection was a problem for some patients in the 1-day group. Therefore, the next study should be designed to evaluate whether flomoxef should be continued for several days postoperatively.

Few studies have analyzed chronological changes in the serum concentration of a systematically administered antibiotic during surgery. Therefore, the interval for multiple dose administration in prolonged surgery has been determined empirically based on the results of post-administration time-related changes analyzed in non-surgical patients. We found that the serum flomoxef concentration drops below 3.0 μg/ml by 5–6 hours after administration. The 90% minimum inhibitory concentration of flomoxef against Staphylococcus aureus is 0.39 μg/ml. Serum to bone penetration rates are reported to be 0.11–0.21, and serum to soft tissue penetration rates 0.28–0.49. Based on these results, the therapeutic serum level of flomoxef is considered to be around 3.0 μg/ml. Therefore, a second administration of flomoxef is necessary if surgery is prolonged for 6 hours or more.

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