Results of a randomized trial of vancomycin prophylaxis in craniotomy

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A single prophylactic dose of vancomycin was given in 143 supratentorial craniotomies with a bone flap and 26 suboccipital craniotomies. No antimicrobial agents were given to two similar groups of patients: 172 with supratentorial craniotomy and 19 with suboccipital craniotomy. The infection rate in the vancomycin groups was significantly lower (p < 0.013), and bone-flap infections alone, the most common infection after supratentorial craniotomy, were significantly fewer (p < 0.042). Antimicrobial prophylaxis is recommended only for selected high-risk groups. Since a bone flap is devascularized, its resistance to infection is reduced and, once infected, it usually requires surgical removal. Patients undergoing craniotomy with a bone flap therefore form a high-risk group, and antimicrobial prophylaxis is justified.

KEY WORDS • craniotomy • bone-flap infection • prophylaxis • vancomycin

In craniotomies, the bone flap is cut off from its blood flow and is therefore comparable to a foreign body, such as a ventricular shunt. Its resistance to infection is reduced, and it may become infected, usually by opportunistic skin bacteria. Prophylactic antimicrobial agents have been found beneficial in shunt surgery, so the aim of this study was to test the usefulness of antimicrobial prophylaxis in patients undergoing craniotomy, with special reference to bone-flap infection.

Clinical Material and Methods

This trial started on September 1, 1984, and ended on November 8, 1985. Patients undergoing craniotomy were randomly assigned to two groups, one receiving vancomycin, the other not receiving any antimicrobial agent. Assignment to a group was made by a numbered sealed envelope being drawn from a box of 300 similar envelopes at 7 a.m. every working day. The envelope contained a card stating whether the patients undergoing craniotomy that day were to receive vancomycin or not. No new envelope was opened during weekends or on public holidays, and the card from the preceding work-day remained in effect. The antimicrobial group received 1 gm of vancomycin intravenously (for children 20 mg/kg) in 100 ml of a 5% glucose solution. The infusion was started after induction of anesthesia, when the hemodynamics were stable, and was administered over a minimum of 1 hour (in the beginning of the study over a minimum of 30 minutes). No further doses were given. Patients undergoing a second operation were allocated to the same group as in the first operation. Patients were excluded from this study if they had previously been operated on in the same region, had a ventricular shunt or drain, had a traumatic wound in the vicinity of the surgical wound, had a known or suspected allergy to vancomycin, or had been receiving antimicrobial agents within the previous week. A second craniotomy in a previously untouched region was considered as a new case, whereas a second craniotomy in the same region as the first was not considered separately. Adverse effects possibly caused by vancomycin were registered. Since curare, like vancomycin, is known to induce histamine release, the use of curare was abandoned during the study. The patients were followed for a minimum of 6 months and all infections were recorded. Bone-flap infection was defined as a suppurating infection extending to the bone flap as verified by surgical exploration of the wound, or as a stubborn fistula responding inadequately to antimicrobial drugs and local debridement. The results were analyzed by means of Pearson's chi-square test.

Results

Composition of Study Groups

The method of randomization applied in the present study yielded 360 primary craniotomies, 315 supratentor-
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Incidence of Infection

Bone-flap infection received special attention in this study, and a detailed comparison between Groups 1 and 2 is therefore justified. A second craniotomy on the same side as the first was performed on two patients in Group 1 and five patients in Group 2. A second craniotomy after the trial had terminated but within the follow-up period was performed on the opposite side in two versus three patients (four for aneurysm, one for tumor), and on the same side on a single Group 2 patient (for tumor). In Group 1, four patients died within 3 days and three died within 1 week after the operation. In Group 2, four patients died within 3 days and six within 1 week after the operation. During the follow-up period, death occurred in 12 Group 1 and 15 Group 2 patients. One patient died in Group 3 and one in Group 4.

The overall age distribution in Groups 1 and 2 was (mean ± standard deviation): 46 ± 14 and 44 ± 14 years, respectively; for patients with tumor: 48 ± 15 and 49 ± 15 years; for patients with aneurysms: 45 ± 13 and 43 ± 9 years; for patients with trauma: 42 ± 14 and 39 ± 17 years; for patients with miscellaneous diagnoses: 52 ± 11 and 34 ± 16 years. There were 77 males and 66 females undergoing Group 1 operations (quotient 1.2), and 99 males and 73 females undergoing Group 2 operations (quotient 1.4). The quotients for Groups 1 and 2 were, respectively: 0.8 and 0.9 for patients with a tumor; 1.2 and 1.2 for patients with an aneurysm; and 1.0 and 1.4 for patients with miscellaneous diagnoses. Men are usually more prone to trauma, which was evident also in this study, the quotients for Groups 1 and 2 being 3.3 and 8.3, respectively.

Senior surgeons performed most operations in both groups, the quotient between senior surgeons and residents being 4.7 for Group 1 and 3.5 for Group 2. When excluding cases of trauma, the quotients were 5.0 and 3.9, respectively. For the individual surgeon with three or more operations, obvious bias can be demonstrated by dividing the number of operations in Group 1 by the number in Group 2 (correction coefficient [172:143] = 1.2 due to the difference in the total number of operations in the groups). With the total number of supratentorial craniotomies performed by the surgeon shown in parentheses, the results for each surgeon were: 1.0 (56), 1.2 (54), 0.8 (39), 0.6 (36), 1.1 (29), 1.3 (29), 1.0 (27), 1.6 (21), 1.0 (9), and 1.2 (6). An underlying disease of such magnitude that it was mentioned in the file was found in only five patients in Group 1 (arterial hypertension, myocardial insufficiency, nephrotic syndrome, and pulmonary emphysema with chronic bronchitis), and in five patients in Group 2 (arterial hypertension, diabetes, psoriasis, and Down's syndrome). There were more cases of trauma in Group 2, but this difference was not significant (p < 0.27). In conclusion, Groups 1 and 2 were similar for all practical purposes.

The infections related to surgery and the results of this trial are summarized in Table 2. Since there was a

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slight preponderance of trauma cases in Group 2, a fact that may have had an effect on the rate of infection. Table 3 shows the results when the trauma cases are omitted.

In Group 1, infection occurred after two operations for benign tumor and one for aneurysm; in Group 2, infection developed after five operations for aneurysm, four for benign tumor, two for malignant tumor, and one for trauma. The mean age of those with infections in Groups 1 and 2 was 37 ± 5 and 45 ± 10 years, respectively. Senior surgeons had performed the craniotomy in two of three subsequently infected patients in Group 1 and in nine of 12 in Group 2. One Group 2 patient, who had a bone-flap infection after ligation of an aneurysm, had a second aneurysm ligated on the other side 3 months later, and this operation was also complicated by a bone-flap infection. After surgery for an acute subdural hematoma, one patient in Group 2 had a bone-flap infection extending to a subdural empyema. The patient died 2 weeks after the trauma and was found at autopsy to have a bacterial meningitis. This was the only patient who died while the infection was still active. Two other Group 2 patients who had had postoperative infection died from unrelated causes. The bacteria isolated in the 17 postcraniotomy infections are given in Table 4.

Bone-flap infection was found in 12 of 15 infected patients in Groups 1 and 2. In all 12 the bone flap was removed. The interval between the operation and removal of the bone flap varied between 8 and 126 days (mean 32 ± 31 days). *Staphylococcus aureus* was found in three bone-flap infections, two of which led to removal of the bone flap within 2 weeks, the third within 3 weeks. In Group 1, one bone-flap infection was caused by *S. aureus* and was removed after 9 days; the other was removed after 126 days, and no bacteria were found on culture.

Pneumonia occurred in four Group 1 patients, in six Group 2 patients, in one Group 3 patient, and in one Group 4 patient; urinary tract infection was diagnosed in nine, six, one, and one patient, respectively; and aseptic meningitis was found in five, six, one, and one patient, respectively.

### Adverse Effects of Vancomycin

Adverse reactions apparently caused by vancomycin were observed in 10 patients. Noteworthy skin reactions were found in six patients, mostly at the beginning of the study when the infusion was given over 30 minutes. An extension of the infusion time reduced this problem. Arterial hypotension was observed in five patients, and increased airway resistance occurred in one patient. The hypotension was reversed by slowing the infusion rate, although one patient did not tolerate any further vancomycin. The arterial oxygen tension decreased rapidly to critical levels after initiation of the vancomycin infusion in one 38-year-old man who was operated on in the sitting position for an acoustic neurinoma. After the infusion was discontinued the oxygen levels increased, but were so low after the operation that respirator treatment with up to 100% oxygen and a 10-cm H₂O positive end-expiratory pressure was necessary for 2 days. A chest x-ray film showed butterfly-form consolidations. The patient recovered completely in 3 days.

### Discussion

Malisε reported a strikingly low zero rate of infection after adopting a new routine of antimicrobial prophylaxis: a single perioperative dose of gentamicin (or tobramycin) and vancomycin combined with topical streptomycin irrigation. This report encouraged others to try the same regimen. In a randomized trial, Geraghty and Feelyδ found a significantly smaller infection rate in their treated group (p < 0.05), but were reluctant to recommend the regimen for fear that widespread and long-term use might have negative consequences. In a double-blind trial, Shapiro, *et al.*, achieved similar results (p = 0.046), and they recommended routine prophylaxis.

Indiscriminate use of antimicrobial agents has caused much damage, and a cautious attitude toward antimicrobial prophylaxis is understandably widespread. The more antimicrobial drugs used, the greater the risk, but rejecting antimicrobial prophylaxis altogether deprives surgeons of one means of reducing the rate of infection. Prophylactic routines should be designed to minimize...
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the antimicrobial load but to maximize the benefits. 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 (while interfering as little as possible with the general bacterial flora in the hospital) should be established. Patients undergoing implantation of foreign bodies such as heart valves, hip endoprostheses, and (in neurosurgery) ventricular shunts form a well-defined group. Bacteria harbored in a foreign body are not easily eradicated by the defense system of the body or by antimicrobial drugs. Surgical removal of the foreign body is therefore usually required. Prophylaxis in shunt infections seems reasonable and, although still debated, has been found beneficial.

Patients undergoing craniotomy with reimplantation of the bone flap may also form a special group for which prophylaxis is justified. A devitalized bone flap, like a shunt, presumably has no resistance to infection, although neither precipitates a reaction per se. As seen in Table 4, the skin bacteria causing most shunt infections (Staphylococcus epidermidis, S. aureus, and Propionibacterium acnes) cause most bone-flap infections as well. In both instances, infection can be mild but persistent and resistant to antimicrobial drugs; the best results are usually achieved by surgical removal. Unlike foreign bodies, the bone flap may eventually become revascularized. This may explain why patience in some cases is rewarded.

Bone-flap infections are the most common types of infection after craniotomy and are therefore of great concern in neurosurgery, although rarely life-threatening as is the case with bacterial meningitis.

In the present study, vancomycin was chosen because its spectrum is narrow but it still covers the most common agents causing infections. Bacteria do not readily develop resistance to vancomycin. No doubt, an increased use may lead to resistance, as has been reported recently; however, a single-dose regimen should be fairly safe in this respect. Combining antimicrobial drugs probably adds little to the reduction of infection, but increases the risk of developing resistant strains of bacteria and of causing intestinal upset or toxic effects. Bone-flap infection probably arises from contamination during the operation. The patient's system should therefore be loaded with antimicrobial drugs before the skin incision is made, and the infusion be continued until the wound is closed. This should be possible to achieve with a single dose, and there is no evidence indicating that further doses offer any advantage.

Skin flushing and hypotension are the most common adverse effects caused by vancomycin. Flushing is usually not an allergic reaction, since patients with severe flushing may well tolerate vancomycin on a second occasion. This type of flushing has been termed "red man's syndrome" or "red neck syndrome." Vancomycin may cause hypotension secondary to histamine release, direct myocardial depression, and peripheral vasodilatation. Cardiac arrest has been reported in a 2-year-old girl who had undergone bilateral nephrectomy for polycystic kidney disease. Malis reported no adverse effects in his series of 1732 cases of major clean surgery. In a randomized trial reported by Geragthy and Feely, four of 203 patients developed a generalized rash, which disappeared shortly after drug administration was stopped. Vancomycin caused no adverse effects in over 200 consecutive patients in a double-blind trial by Shapiro, et al. In our study, "red man's syndrome" occurred in six patients. With prolongation of the infusion from 30 minutes to a minimum of 1 hour, this complication was noted less frequently. One serious reaction requiring respirator treatment for 2 days was observed in our study, and a similar case has been reported previously. We believe that a slow vancomycin infusion under close surveillance is safe.

This trial, although randomized, was not blinded, which undoubtedly is a shortcoming, because of the difficulties in some cases of deciding what is an infection and what is not. Bone-flap infections, which were of special interest in this study, may initially be hard to separate from superficial wound infections and suture fistulas but the diagnosis usually becomes clear with time. In this trial all bone-flap infections led to removal of the flap. When the results of this trial became available, the policy of the department was changed to include routine single-dose vancomycin prophylaxis for all patients undergoing craniotomy.

Conclusions

The conclusions of this study are that antimicrobial prophylaxis should be reserved for groups of patients with an exceptionally high risk of infection, and for infections that are unusually dangerous or difficult to treat. Craniotomy leaves a bone flap that is totally or almost totally devascularized. Bone-flap infection is the most common infection after craniotomy and is usually treated by surgical removal. Craniotomy patients thus form a group at risk for infection. To reduce the hazards of antimicrobial prophylaxis, there should be a narrow spectrum of agents aimed at common bacteria causing bone-flap infection, and the regimen should be short. A single dose of perioperative vancomycin reduces the risk of bone-flap infections, and is as effective as previously reported antimicrobial combinations.

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References


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