Results of trimethoprim-sulfamethoxazole prophylaxis in ventriculostomy and shunting procedures

A double-blind randomized trial

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The author reports the results of a study to assess the effectiveness of a trimethoprim-sulfamethoxazole combination as prophylaxis in ventriculostomy or shunting operations. Between 1980 and 1983, 122 patients undergoing shunting procedures were randomly assigned to receive trimethoprim-sulfamethoxazole (Group 1, 62 cases) or a placebo (Group 2, 60 cases). The same regimen was followed at each operation, and the patients were followed for a minimum of 6 months. There was a higher infection rate in the placebo group (14 of 60 patients compared with 4 of 62 patients in the antibiotic group, p < 0.01). The antibiotic protected against early infections (nine of the 60 patients in Group 2 against none of the patients in Group 1), but not against late infections (four of the 62 in Group 1 compared with five of the 60 in Group 2). During the same period, 52 patients undergoing ventriculostomy only were also randomly assigned to receive trimethoprim-sulfamethoxazole (Group 3) or placebo (Group 4). There were no differences in the infection rates between these groups (one of 25 in Group 3 as against one of 27 in Group 4).

KEY WORDS: antibiotic therapy □ ventriculostomy □ shunt □ trimethoprim □ sulfamethoxazole □ infection

The prophylactic benefits of perioperative antibiotics are frequently a matter of dispute. High infection rates have been reported after shunt surgery; consequently, antibiotic prophylaxis is more commonly used in association with such procedures. Retrospective studies have been reported that argue for and against the use of prophylactic antibiotics in shunting procedures. Until now, no randomized trial of perioperative antibiotics has produced definite answers as to the efficacy of this regimen. This paper reports the outcome in patients undergoing shunt placement or ventriculostomy who were randomly assigned to receive perioperative antibiotics or placebo.

Clinical Material and Methods

This was a double-blind randomized trial on the prophylactic use of trimethoprim-sulfamethoxazole in shunt surgery, starting on April 1, 1980, and ending on June 14, 1983. The series included 174 patients. Of these, 122 patients underwent a total of 197 shunting procedures; 62 patients were randomly assigned to receive trimethoprim-sulfamethoxazole (Group 1) and 60 to receive the placebo (Group 2) (Table 1). The remaining 52 patients underwent an external ventriculostomy procedure only: 25 were randomly assigned to the antibiotic group (Group 3) and 27 to the placebo group (Group 4). The average duration of the external ventriculostomy was 1 day and 1 night, the longest duration being 1 week. With few exceptions, the ventriculostomy was performed for suspected low-pressure hydrocephalus.

Two hundred numbered sets of injectate, each containing eight ampoules, were supplied by Hoffmann-La Roche, Ltd. Each ampoule contained either trimethoprim (80 mg) and sulfamethoxazole (400 mg), or plain vehicle (sodium hydroxide 63.5 mg, diethanolamine 15 mg, sodium pyrosulfite 5 mg, ethanol 500 mg, phenylcarbinol 50 mg, and propylene glycol 2 gm, mixed with sterile water to a quantity of 5 ml). In the event of an emergency, the hospital pharmacist could have broken the code to discover what a particular set contained, but this was not necessary.

An extra set of ampoules with the same contents was
Antibiotic prophylaxis in ventriculostomy and shunts

PERCENTAGE OF ALL (18 PATIENTS)

<table>
<thead>
<tr>
<th>100%</th>
<th>I X</th>
<th>I X</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>XI</td>
<td>I X</td>
</tr>
<tr>
<td>0%</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

TIME BETWEEN LAST OPERATION AND INFECTION

Fig. 1. Time between last operation and infection in 18 of the 122 shunted patients. Each cross represents an infected patient in the placebo group and each asterisk an infected patient in the prophylaxis group. There were no early infections in the trimethoprim-sulfamethoxazole group. Half of all infections were early (up to 1 month after shunt placement).

Table 1: Etiology of hydrocephalus in 122 patients requiring shunt placement

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Antibiotic Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>trauma</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>vascular disease</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>infection</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>neoplasm</td>
<td>32</td>
<td>21</td>
</tr>
<tr>
<td>congenital disorder</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>aqueductal stenosis</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>low-pressure hydrocephalus</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>total cases</td>
<td>62</td>
<td>60</td>
</tr>
</tbody>
</table>

provided in the event that any patient might need extra doses for a shunt revision or an external ventriculostomy. Should the patient need even more infusions there was an extra store of sets, divided into six groups: A, B, C, D, E, and F. The hospital pharmacist had a key showing to which of the six groups a particular number belonged, and she was thus able to provide further sets of ampoules when required. The clinicians did not know to which group a particular number belonged, nor did the pharmacist know the contents of the ampoules in the six groups without breaking the code.

All patients undergoing a ventriculoatriostomy or an external ventriculostomy were included in the trial. Exceptions were patients under 12 years of age, patients allergic to either sulfa or trimethoprim, patients who had received antibiotics during the preceding week, and patients who already had a shunt in place when the trial started.

When the patient was brought to the operating theater, an intravenous cannula was inserted, and two ampoules in 250 ml of a 5% glucose solution were infused over 30 minutes. The operation was started regardless of whether the infusion was complete, although preparations before the initial incision often lasted longer than 30 minutes. After the operation the dose was repeated three times at intervals of 12 hours. Patients who had undergone an external ventriculostomy received one dose every 12 hours until the drainage tube was removed, and three more doses after that.

The same course was repeated at shunt revisions, and also if the patient underwent any other neurosurgical operation while a shunt was in place. The reason for repeating the course for any neurosurgical procedure was that a surgical wound often causes bacteremia that might contaminate the shunt.

The patients were followed for a minimum of 6 months. Only after all information had been collected and fed into a computer file was the key to the code given to us by Hoffmann-La Roche.

Results

Twenty-six patients had to be excluded from the trial for several reasons. The regimen was inadvertently not completed or was forgotten at a repeat operation in 19 patients. Six patients were inadvertently receiving another antibiotic during the study, and in one patient an allergic reaction was suspected. Thus, all but one of the exclusions were due to forgetfulness, an unavoidable factor in clinical trials where the investigator is dependent on many colleagues and nurses.

The age and sex distributions of the patients undergoing shunt placement were similar in the two treatment groups, as was the incidence of malignant tumors. There were more patients with communicating hydrocephalus in the placebo group (38 of 60 patients) than in the prophylaxis group (23 of 62 patients). The 122 patients undergoing shunting procedures had an average of 1.6 operations. Among those with infections, the average was 1.8 operations before the infection, 2.3 in the trimethoprim-sulfamethoxazole group, and 1.7 in the placebo group.

The incidence of infection in the two groups of patients undergoing shunt placement (Groups 1 and 2) is given in Table 2. The bacteria isolated in the 18 patients with infections in these two groups are listed in Table 3. This double-blind randomized trial showed a significant difference ($p < 0.01$, Fisher's exact test) in favor of prophylaxis for shunt procedures (Table 2). In the trimethoprim-sulfamethoxazole group there were no early infections and four late infections (Fig. 1). In
the placebo group, nine of the 14 infections occurred in the early postoperative period.

The incidence of infection was similar in both treatment groups (Groups 3 and 4) in patients undergoing an external ventriculostomy procedure only. In each group there was one case of infection.

**Discussion**

Bacteremia and direct contamination during surgery are likely causes of infection, but any sporadic bacteremia is also a source of shunt contamination. The infection rate in patients who had undergone a craniotomy before shunt implantation at this institution between 1975 and 1977 (20 patients) was compared with the rate for those who had had a craniotomy after shunt placement (21 patients). Infections were found in one (5%) of the former group, and six (29%) of the latter. This suggested that bacteremia during the craniotomy increases the infection rate. Consequently, the prophylactic regimen should be repeated before any operation in patients with a shunt.\textsuperscript{3,16,27} Traumatic wounds might also cause bacteremia, but in these the antibiotics would obviously be started too late.\textsuperscript{1,3,4}

The use of prophylactic antibiotics in surgery is controversial; fashions change.\textsuperscript{13,14,17,22} The increasing incidence of antibiotic-resistant bacterial strains in hospitals is causing grave concern, and favors this regimen.

Two principles have emerged over the years: the antibiotic should be present at the time of contamination (that is, at the time of the operation)\textsuperscript{1,3,4} and it should be administered over a short period of time.\textsuperscript{3,30} To these might be added a third principle, namely that prophylaxis should be used in procedures where foreign materials are implanted, such as ventriculoatrial shunting. Natural defenses are believed to be less efficient when bacteria adhere to such materials.\textsuperscript{8,31} Moreover, it is reported that *Staphylococcus epidermidis*, the bacteria that is found most commonly in shunt infections,\textsuperscript{3,5,9,16,20,23,25,26,32} (see Table 3) does not provoke a defense reaction because it is not recognized as foreign, as it occurs everywhere on the skin.\textsuperscript{16,31} The published randomized trials of prophylactic antibiotics in shunts have included either too few patients or too few infections to show the effect of prophylaxis.\textsuperscript{2,6,15,36,37}

Trimethoprim-sulfamethoxazole\textsuperscript{6} was chosen for this trial for two reasons: 1) both trimethoprim and sulfamethoxazole penetrate into the cerebrospinal fluid, even in the absence of infection;\textsuperscript{18,35,38} and 2) the spectrum of this drug combination covers the organisms commonly causing shunt infections.\textsuperscript{3,5,9,16,20,23,25,26,32}

When the results of this trial became available the policy of the Department was changed to include routine prophylactic use of trimethoprim-sulfamethoxazole in shunting procedures, and in other operations on patients with a shunt. Although the infection rate was reduced during the 38 months of this trial, the situation might change over the years if antibiotic-resistant bacterial strains are encountered. Using a short antibiotic regimen should reduce the risk of resistance developing. At the time that this trial was designed, long prophylactic regimens were common, but, after discussions with our consultant on infectious diseases, four doses of antibiotics were chosen for this trial. However, according to recent reports\textsuperscript{14,22} even a single dose may be adequate. Another way to reduce the risk of development of resistant bacterial strains might be to alternate with other antibiotics, such as vancomycin\textsuperscript{39} or rifampin.\textsuperscript{29}

**TABLE 3**

Bacterial findings in the 18 infected cases among 122 shunted patients\textsuperscript{*}

<table>
<thead>
<tr>
<th>Organisms Found</th>
<th>Source of Sample</th>
<th>Total Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ventricular CSF</td>
<td>Lumbar CSF</td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td>2 (2)</td>
<td>1</td>
</tr>
<tr>
<td><em>Microoccus</em></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>Streptococcus</em></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>Microaerophilic Streptococcus</em></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>Acinetobacter</em></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>Propionibacterium acnes</em></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>total samples</td>
<td>5</td>
<td>12</td>
</tr>
</tbody>
</table>

\textsuperscript{*} *Staphylococcus epidermidis* was the organism found most frequently in both groups. No development of resistant bacteria occurred despite the use of antibiotics. Cultures from blood and the shunt appear most likely to give a positive result, whereas lumbar punctures are of minor importance. Numbers in parentheses indicate samples from the four trimethoprim-sulfamethoxazole-treated patients with infections. CSF = cerebrospinal fluid.

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