Antibiotic Prophylaxis in Cerebrospinal Fluid Shunting: A Prospective Randomized Trial in 152 Hydrocephalic Patients

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The authors report a prospective, randomized 18-month study on the effect of prophylactic antibiotic treatment in 152 hydrocephalic patients in whom dean shunt operations or revisions were done. The treated group received methicillin (totally 200 mg/kg) divided into six i.v. doses during 24 hours starting at the induction of anesthesia. Patients allergic to penicillin received erythromycin instead. Seventy-nine patients received antibiotics, and 73 (the control group) received none. All patients were followed at least 6 months after operation or to their death. Eleven patients developed signs of infection, giving an overall infection rate of 7.2%; however, the infection occurred less than 1 month after the operation in only half of these. Six of the patients had septicemia, 4 had peritonitis, and I had meningitis. In the treated group, the infection rate was 8.9%; in the control group, the rate was 5.5%. There was no statistically significant difference. The prophylactic antibiotic regimen in this investigation did not reduce the infection rate connected with cerebrospinal fluid shunting procedures. (Neurosurgery 17:1-5, 1985)

Key words: Antibiotic prophylaxis - Hydrocephalus - Randomized trial - Shunt infection.

In all surgical procedures involving foreign body implantation, postoperative infection is a feared complication, exposing the patient to a considerable risk. Hydrocephalic patients, in whom drains are inserted, seem particularly prone to disseminated infections because they are often in poor clinical condition and because the shunt opens either to the blood stream or to peritoneum.

In the literature, the frequency of shunt infections varies from a few per cent up to more than 30% (1, 6, 12, 18). The average in most series is approximately 15%. Antibiotic therapy could, therefore, be of prophylactic value if it decreased the risk of postoperative shunt infection and thus reduced the well-known lethality after shunting procedures (2, 7, 10, 14). Nevertheless, antibiotic prophylaxis in surgery has always been a controversial subject (4, 8) partly because of many uncontrolled and inconclusive studies. There are very few correctly arranged, prospective studies dealing with this problem in shunt surgery.

The purpose of the present investigation was to perform a "carefully designed large scale, randomized clinical trial" (8) to evaluate whether 24 hours of prophylactic antibiotic treatment would influence the infection rate in hydrocephalic patients subjected to clean shunt operations.

MATERIAL AND METHODS

Patients and study procedure

For 18 months, all hydrocephalic patients referred to two neurosurgical clinics (University Clinic of Neurosurgery, Hvidovre Hospital, and University Clinic of Neurosurgery Rigshospitalet) were consecutively considered for the study. Criteria for inclusion were that a shunt or the revision of a preexisting shunt was necessary and that no antibiotic had been given and no sign of infection had been present during the preceding 4 weeks. After inclusion, the patients were divided into two groups by random allocation (random numbers (5)): One group received antibiotics as prophylaxis, and the other smed as the control group, receiving no antibiotics. Stratification for age, type of hydrocephalus, shunt type, or number or type of previous operations was not done. The study was not blinded; i.e., all of the 12 neurosurgeons who operated on the patients were aware of the treatment. All standard procedures used by the participating departments in relation to shunt operations were followed. This applies to the system by which the operations were distributed among the neurosurgeons, the disinfection procedures, the types of shunts, and the types of operations, i.e., whether the drain was inserted into the atrium or the peritoneum. As standard procedure, the skin was prepared twice with a 2.5% iodinealcohol solution and exposed skin was draped with selfadhesive film. Ventriculoperitoneal shunting was done in some cases with an intervening incision, but usually tunneling was possible. The position of the atrial catheter in ventriculoatrial procedures was confirmed fluorscopically. Local antibiotics were not used.

A shunt was considered infected if the patient showed clinical signs of wound infection, septicemia in patients with ventriculoatrial shunts, peritonitis in patients with ventriculoperitoneal shunts, or meningitis and if bacteria could be cultivated from blood, peritoneum, cerebrospinal fluid, or the shunt system. Shunt malfunction was not regarded as representing a shunt infection. All patients were followed for at least 6 months after the operation or until their death and were seen in the outpatient ward every 3rd month.

All infections of the mentioned types recognized during this period were regarded as being caused by the shunting procedure. The study was terminated when the last patient had been followed for 6 months.

One hundred fifty-two patients entered the study - 43 from Hvidovre Hospital and 109 from Rigshospitalet; none of these 152 patients was excluded (Table 1).

During the same period, a total of 178 patients were shunted. Twenty-six of these patients did not enter the study for various reasons. By error, 3 were not randomized at the beginning of the study; 13 were either infected or already receiving antibiotics; 4 had shunt revision because of a clinical suspicion of infection; and, finally, 7 patients did not enter the study because they refused to participate.

The higher number of children from Rigshospitalet can be explained by differences in the underlying patient population and hospital structure. The cause of hydrocephalus was known in about 75% of the cases. There was no significant difference in the distribution of type of hydrocephalus and cause of the hydrocephalic state between the two departments. For patients with preexisting shunts who entered the study because they needed revisions, their cerebrospinal fluid and the removed part of the shunts were cultured. No infections were discovered in this way. Twelve patients had histories of infection more than 4 weeks before the operation, but had no sips of infection and had not been treated with antibiotics during the preceding 4 weeks.

Patients who became infected did not reenter the study when the reshunting procedure was performed after appropriate antibiotic treatment.

The Hakim shunt was used in 75% of the cases; the remaining shunts were distributed equally among four other types. Eleven operations lastod less than 30 minutes, 74 lasted between 30 and 60 minutes, and 67 lasted more than 60 minutes. The distribution between the two surgical departments was identical. In 77 patients, ventriculoatrial (VA) shunting was done, and 75 patients had ventriculoperitoneal (VP) shunts. The ratio of VA to VP shunt was not identical in the two departments involved (Table 1), but this is considered unimportant because the VA infection rate and the VP infection rate are approximately the same.

One patient showod signs of shunt malfunction, but no signs of infection. This VP shunt represented the only malfunctioning shunt in the study within the observation time. The malfunction was suspected after 5 months and was confirmed 2 months later. The shunt was then replaced and the patient did not reenter the study.

Of the total case material, 79 patients belonged to the antibiotic group, whereas 73 served as the control group (see Table 2). This table shows no clinically significant differences between the two groups in respect to sex, age, observation time, etiology, method of shunting, and duration of operation. The observation time is shown in Table 1. One hundred thirty-six patients were followed for 6 to 24 months, 8 were followed for 1 to 6 months, and 8 were followed for less than 1 month. The observation time of less than 6 months in 16 patients was in all cases due to death caused by the primary disease. None died because of infection or other shunt complications, and none of these 16 patients showed signs of infection during the observation period.

Table 1. *Differences between the Two Departments in Respect to Sex, Age, Observation Time, Method of Shunting and Infection, and Distribution between Antibiotic and Control Groups.*

	Rigshospitalet (n = 109)		Hvidovre Hospital (n = 43)		Total (n = 152)	
	No.	%	No.	%	No.	%
Sex						
Female	40	37	19	44	59	39
Male	69	63	24	56	93	61
Age						
<1 yr	11	10	0	0	11	7
1–14 yr	47	43	11	26	58	38
>14 yr	51	47	32	74	83	55
Observation time						
<1 mo	2	2	6	14	8	5
1–6 mo	6	6	2	6	8	5
>6 mo	101	92	35	80	136	90
Method of shunting						
VA	41 (3)[a]	38	36 (3)	84	77 (6)	51
VP	68 (4)	62	7 (1)	16	75 (5)	49
Treatment						
Antibiotic group	54	50	25	58	79	52
Control group	55	50	18	42	73	48

[a] Numbers in parentheses, number of infections.

Table 2. *Differences between Anitbiotic Group and Control Group in Respect to Sex, Age, Observation Time, Etiology, Method of Shunting, and Duration of Oberationa.*

	Antibiotic Group (n = 79) (7)		Control group (n = 73) (4)		Total (n = 152) (11)	
	No.	%	No.	%	No.	%
Sex						
Female	30 (2)	38	29 (1)	40	59 (3)	39
Male	49 (5)	62	44 (3)	60	93 (8)	61
Age						
<1 yr	3 (0)	4	8 (2)	11	11 (2)	7
1–14 yr	31 (4)	39	27 (0)	37	58 (4)	38
>14 yr	45 (3)	57	38 (2)	52	83 (5)	55
Observation time						
<1 mo	4 (0)	5	4 (0)	5	8 (0)	5
1–6 mo	4 (0)	5	4 (0)	5	8 (0)	5
>6 mo	71 (7)	90	65 (4)	90	136 (11)	90
Etiology						
Known						
HPH[b]	58 (6)	73	53 (3)	73	111 (9)	73
NPH	6 (0)	6	3 (0)	4	9 (0)	6
Unknown						
HPH	0 (0)	0	3 (0)	4	3 (0)	2
NPH	15 (1)	21	14 (1)	19	29 (2)	19
Method of shunting						
VA	42 (4)	53	35 (2)	48	77 (6)	51
VP	37 (3)	47	38 (2)	52	75 (5)	49
Duration of operation						
<60 min	8 (0)	10	3 (0)	4	11 (0)	7
30–60 min	38 (3)	48	36 (3)	49	74 (6)	49
>60 min	33 (4)	42	34 (1)	47	67 (5)	44

[a] Numbers in parentheses, number of infections.
[b] HPH, high pressure hydrocephalus; NPH, normal pressure hydrocephalus.

Choice of antibiotics and treatment schedule

Methicillin was selected as the most expedient antibiotic for prophylaxis in this situation as *Staphylococcus albus* and *Staphylococcus aureus* are the bacteria most frequently found to complicate shunt operations. Thus, not being a broad spectrum antibiotic, methicillin is directed more toward the microbiological problems to be expected. Furthermore, methicillin is bactericidal and virtually nontoxic. The duration of the treatment was limited to 24 hours to reduce the risk of developing resistant bacteria. The time to start the prophylactic treatment was chosen to achieve a high blood concentration of methicillin before possible bacterial contamination and during the insertion of the shunt, which is considered essential (19). Fifteen minutes after the used dose of methicillin, the serum concentration is approximately 70 μg/ml, a concentration about 20 times the minimal inhibitory concen¬tration of sensitive strains (13).

The standard treatment was 33.3 mg of methicillin per kg of body weight given in six i.v, doses (total, 200 mg/kg). The first dose was administered immediately after the induction of anesthesia, and the last dose was given 20 hours later. In patients with known hypersensitivity to penicillin, erythromycin was used instead (20 mg/kg body weight i.v. divided into three doses, the first dose given when anesthesia was introduced and the last given 16 hours later).

Methicillin was given to 75 patients, and 4 patients received erythromycin (Table 3).

Ethics

Informed consent was obtained in all cses, either from the patient or from the relatives. Except for the treatment/nontreatment with antibiotics, all procedures were routine for shunt operations. Special care was taken to initiate immediate antibiotic treatment in øses of postoperative infection.

RESULTS

The overall infection rate was 11 among 152 patients or 7.2% (95% confidence limits: 3.7 to 12.7). Of these, 7 patients belonged to the group treated with antibiotics (8.9%; 95% confidence limits: 3.6 to 17.7) and 4 belonged to the control group (5.5%: 95% confidence limits: 1.5 to 13.4) (Tables 2 and 3). The distribution between the two surgical departments was almost the same (Table 1). There was no difference between the infected and the noninfected group regarding sex, age, cause of hydrocephalus, shunt type, or duration of the operation. Likewise, there was no difference in the distribution of infections or in sex, age, or other characteristics of the infected patients between the two surgical departments. Six patients with VA shunts and 5 patients with VP shunts became infected. The distribution between the two departments was identical (Table 1). No patient with shunt infection demonstrated clinical signs of shunt malfunction. No patient with a length of operation of less than 30 minutes became infected.

Two patients developed signs of infection during the 1st week after operation, 4 showed signs between the 1st and the 4th weeks, 2 became infected between 1 and 6 months after operation, and 3 developed infection from 6 to 7 months after the operation (Table 4). Six of the patients had septicemia; among these, 1 also showed signs of wound infection. Four patients had peritonitis: among these, two also showed signs of meningitis. 1patient had meningitis only. In 8 of the 11patients, *S. albus* was found. 1 patient was infected with *S. aureus*, and 1 was infected with both. In 1 patient who showed severe clinical signs of septicemia, it was not possible to identify the bacteria.

All cultured bacteria were sensitive to methicillin, cephalosporins, streptomycin, and gentamicin, but were resistant to penicillin.

All patients with signs of infection were subsequently treated with antibiotics after thorough microbiological diagnostic procedures. The shunt system was replaced in 10 of the infected patients, whereas the last patient recovered completely after antibiotic treatment alone. None of the 11 patients showed any signs of recurrent infection during the follow-up period.

DISCUSSION

In the present group of 152 hydrocephalic patients, there was no prophylactic effect (i.e., relative to a nontreated control group) of methicillin in adequate doses administered just before and 24 hours after a clean shunt operation. The risk of having overlooked a reduction of the infection rate of up to 50% is about 85%. However, the risk of having overlooked a reduction of more than 50%, a more clinically relevant consideration, is only about 15%. This impression is strengthened by the fact that relatively more infections were actually found in the tested group.

The value of prophylaxis has been heavily debated and investigated, although only a few studies will be mentioned here. Savitz et al. compared the effect of two different antibiotics used against wound infection (17) and claimed, in a subsequent series, no primary wound infection in more than 1000 different, consecutive neurosurgical operations (16). However, the latter investigation was uncontrolled, the observation period was not stated, and several changes in the surgical procedures took place. Similar criticisms can be made of many investigations of prophylactic antibiotic treatment in shunt operations (1, 10, 11, 15, 18, 23), and the results are therefore often difficult to interpret. A control group may be absent (11), and the number of patients may be limited (15). Some studies are retrospective (15, 18), lack a clear definition of the observed infection, or have no description of the applied treatment (23). Prophylactic intraventricular instillation (gentamicin) has also been used in addition to systemic treatment (21) with a significantly better result compared to controls, but the surgical procedure was also changed. It is therefore difficult to draw safe conclusions, although these results are supported by a similar consecutive series (22).

These studies were frequently not randomized or were poorly controlled, and they often concluded that antibiotic prophylaxis should be preferred in shunt operations. However, other series have not demonstrated an effect of

Table 3. *Distribution of Infections between the Antibiotic Group and the Control Group.*

	Total No.	Infections		95% Confidence Limits
		No.	%	
Antibiotic group	79 (4)[a]	7 (1)	8.9	3.6–17.7
Control group	73	4	5.5	1.5–13.4
Total	152	11	7.2	3.7–12.7

Table 4. *Debut of Shunt Infection.*

	No. Infections Debuting					
	<1 wk	1–4 wk	1–6 mo	6–7 mo	>7 mo	Total
Antibiotic group	1	3	0	3	0	7
Control group	1	1	2	0	0	4
Total	2	4	2	3	0	11

prophylactic treatment (7, 10, 18), which was also the øse in three randomized investigations (3, 9, 20). In one of these, however, the number of cases was small (20). In the other study, information about how and for how long the patients were followed was missing (3). In a recently published article on the effects of prophylactic methicillin on the incidence of shunt malfunction and infection, the authors described a wellplanned, randomized, and double-blind study that failed to demonstrate any statistically significant difference in infection rate and overall malfunction rate between the two groups (8). However, this study indicated a significantly greater tisk of shunt malfunction from the 2th to the 6th month after operation in the antibiotic group. These results do not seem to justify prophylactic antibiotics. The tisk of developing resistant bacteria should still not be underestimated.

Thus, from the literature it can be seen that the picture is far from clear. Inadequate trial methods may explain part of the often contradictory results, but other factors may well play a role. In the present randomized study, it was not possible to demonstrate any prophylactic effect of methicillin in hydrocephalic children and adults.

The present findings of methicillin-sensitive bacteria might lead to the conclusion that methicillin should have been given earlier and for a longer period, but the low infection rate in the nonantibiotic group makes such a conclusion difficult.

Furthermore, one can raise the question of whether infections recognized later than 1 month after the operation are caused by bacterial contamination during the operation (6). It is, however, our experience that these late infections show the same bacterial pattern as the early infections and very often can be traced back to the operation. Thus, we agree with Gardner and Gordon, who consider that a "careful surgical technique is the single most important factor in the preventing of shunt infections" (6).

On the other hand, the result of the present investigation does not exclude the possibility of further reducing the already low infection rate by applying a different prophylactic antibiotic program after thorough evaluation.

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COMMENT

The authors have contributed useful information to our knowledge of the value of antibiotic prophylaxis in preventing shunt infection. They are to be commended for conducting a controlled trial of a method that many neurosurgeons have dogmatically adopted without a clear demonstration of its effectiveness.

The chosen antibiotic, dosage, and duration of administration are appropriate. The infection rate in the control group is in accord with that recently reported from other institutions, and the shunt technique seems to be reasonably standard. The concurrent control group was chosen by appropriate random allocation methods. The duration of follow-up is generally adequate as most shunt infections will appear within 6 months of operation and it is logical to expect that antibiotic prophylaxis will be most effective in preventing early post-operative shunt infections.

There are a few aspects of the study open to criticism. The authors chose not to use any masking (or blinding) procedure. Although blinding is sometimes impossible in surgical trials, when the intervention is drug administration it is almost always possible to administer an acceptable placebo. Although no surgeon would consciously allow his knowledge of the treatment given to affect his care of the patient, the unconscious influence of such information is too well known and documented to ignore. Masking procedures should be used whenever possible and should be considered a standard part of the conduct of such trials.

The problem of patient follow-up is complicated in two ways. It is not clear how many of the patients who were considered for entry actually were entered into the study. This information is important in assessing the actual patient population to which the results may be generalized. Complete information is given on the fate of the patients actually entered into the study. The variable length of follow-up also complicates the analysis. Patients followed the longest have the greatest chance of developing infection. If there is a major discrepancy in duration of follow-up between the treated and control patients, the results may be affected. In this study, almost half of the infections in the antibiotic-treated group occurred more than 6 months after operation, whereas no infections were encountered that long after operation in the control group. Fortunately, truncating the follow-up in both groups at 6 months results in equal numbers of infections in the treatment and control groups and does not alter the authors' conclusions. Another method for handling this problem would be to use life tables to analyze time to infection. There are not sufficient data presented to allow this analysis to be done.

The authors suggest that this study has less than a 15% chance of overlooking an important treatment effect, but they do not tell us how this figure was calculated. My calculations indicate that, for a two-tailed comparison of proportion of infections using an alpha significance level of 0.05 with an infection rate of 5.5% in the control group and the numbers of patients actually entered in the study, the probability of finding a 50% reduction in infection rate (to 2.75%) is approximately 0.21. This means that the results, although providing no support for the hypothesis for a prophylactic effect of antibiotics, cannot be considered as strong evidence against such an effect.

Despite these reservations, the use of a randomly allocated control group makes useful the information obtained in this study. The tesults provide no support for the concept that perioperative methicillin administration reduces the incidence of shunt infection. As the authors point out, this result is not in conflict with previously published literature. The three previous randomized studies cited by the authors are each flawed in important ways. Bayston had such a low infection rate that there was no real prospect of identifying an antibiotic effect (1), Weiss and Raskind had too few patients and infections to allow any conclusions to be drawn (7), and our own study, although showing fewer infections in the antibiotic group, also had insufficient statistical power to allow firm conclusions to be drawn (5). The recently published trial of prophylactic sulfamethoxazole and trimethoprim provided no support for the concept that this antibiotic combination was effective in preventing shunt infection, but was also of insufficient size to conclude that no protective effect exists (6). The only randomized trial of which I am aware that has demonstrated a benefit of prophylaxis was reported by Epstein at the AANS meeting in 1982 (3). The control group in that study had such a high infection rate (21 %) that it is not clear that the results can be meaningfully extrapolated to the usual population undergoing shunt procedures. Gardner and Gordon reported a series of 200 shunt operations done without antibiotic coverage with an infection rate of 1.5% (4). Taken together, these studies indicate a remarkably large interinstitutional variation in base line infection rate and a lack of consistent antibiotic effect.

There is a large number of variables that may affect antibiotic effectiveness. It may be that the studies done to date have used the wrong antibiotics, the wrong dose, or the wrong administration schedule. It may be that the shunt itself interferes with infection prevention (2). There is certainly enough suggestion that antibiotics may be effective to justify further efforts to establish an effective infection prevention protocol. Until such a protocol has been established, most neurosurgeons will probably continue to use prophylactic antibiotics, although many of us do it with a certain amount of intellectual indigestion.

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