Original Research

The effect of cephalothin prophylaxis on postoperative ventriculoperitoneal shunt infections

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Postoperative infection is an important complication after insertion of a ventriculoperitoneal (VP) shunt in children with hydrocephalus. A randomized double-blind placebo-controlled study was performed to determine the efficacy of cephalothin in preventing postoperative shunt infection. Sixty-three children who presented for elective VP shunt insertion between January 1982 and December 1985 and who did not have a history of shunt infections were randomly assigned to receive four doses of prophylactic cephalothin, 25 mg/kg (32 patients), or of a multivitamin placebo (31 patients). Postoperative infection developed in 6% of the treatment group, compared with 10% of the placebo group, a difference that was not statistically significant, although a clinical significance may have been masked by the small sample size. A large multicentre trial is needed to determine the efficacy of antibiotic prophylaxis in reducing the incidence of postoperative VP shunt infections.

L'infection postopératoire est une complication importante de la dérivation ventriculo-péritonéale (DVP) chez l'enfant hydrocéphale. La possibilité de la prévenir par la céphalothine fait l'objet du présent essai comparatif à double insu sur des sujets choisis au hasard. Il s'agit de 63 enfants s'étant présentés pour la pose non-urgente d'une DVP depuis janvier 1982 jusqu'en décembre 1985 et dépourvus d'antécédents d'infection de ce genre. Le sort a désigné 32 enfants pour la prophylaxie par la céphalothine à la dose de 25 mg/kg quatre fois; les 31 autres enfants prenaient un placébo polyvitaminé. Les taux d'infection postopératoire sont 6% dans le groupe expérimental et 10% chez les témoins. Vu le petit nombre de sujets, cette différence n'atteint pas le seuil de la signification statistique. Aussi faudra-t-il un essai multicentrique sur une grande échelle afin de savoir si une telle antibioprophylaxie abaisse la fréquence de ce genre d'infection.

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Infection is one of the most important complications of ventriculoperitoneal (VP) shunt insertion for the treatment of hydrocephalus.[1-7] The preventive efficacy of preoperative antibiotics has been evaluated,[2,8] but the studies have mostly been retrospective and have often lacked controls or used noncontemporary cohorts, factors that cast doubt on the conclusions drawn.[2] We designed a randomized double-blind placebo-controlled trial to evaluate the efficacy of cephalothin in preventing postoperative VP shunt infections.

Methods

All children who presented for elective (i.e.,

nonemergency) VP shunt insertion between January 1982 and December 1985 and who did not have evidence of active infection or a history of shunt infections were evaluated for participation in the study. Children who were immunosuppressed or receiving corticosteroid therapy or who had allergies to penicillin or cephalothin were excluded. No patients had received antibiotic therapy in the 4 weeks before VP shunt insertion.

After written consent was obtained from the parents or guardians, in accordance with the protocol of the Human Subjects Research Committee, University of Western Ontario, the patients were randomly assigned to one of two groups, by a pharmacist not otherwise involved in the patients' care, with the use of an envelope draw system. The first group, designated the treatment group, received 25 mg/kg of cephalothin intravenously in the operating room before incision and three times postoperatively, once every 6 hours. The maximum amount per dose was 1 g. The second group, designated the placebo group, received 0.2 ml of M.V.I.-1000 (USV Canada Inc., Mississauga, Ont.), an intravenously given multivitamin preparation the same colour as the intravenous formulation of cephalothin, by the same schedule as the treatment group. The cephalothin and the placebo were prepared in the hospital pharmacy and were supplied to the operating room and the wards in identical syringes (for infants) or intravenous bags (for older children), the only identification being a coding number. The clinical and nursing staff caring for the patients were unaware of which group the patients were assigned to. The initial infusions were completed before the surgical procedures were begun.

Shunt surgery was performed by one of two staff neurosurgeons, who obtained preoperative and postoperative leukocyte counts as well as skin swabs of the scalp and abdomen for bacterial culture both before and after incision.

The patients were followed up after the operation until discharge. At 6 weeks and at 3 months postoperatively they were evaluated for any evidence of shunt malfunction or infection. Infection was deemed to be present if culture of cerebrospinal fluid obtained immediately after surgery or subsequently yielded bacterial growth and there were symptoms suggestive of shunt infection, including irritability, reddening of the skin overlying the shunt tubing or unexplained fever. The 3-month period was selected because previous series have shown that 70% to 80% of postoperative infections occur within this period, the infection rate subsequently declining rapidly.[6-8]

Results

Sixty-three patients were studied. There were 31 patients (12 boys and 19 girls with a mean age of 29 months [extremes 1 week and 9 years]) in the treatment group and 32 patients (17 boys and 15 girls with a mean age of 23 months [extremes 2 weeks and 12 years]) in the placebo group. Chi-square testing showed no significant difference in age or sex between the two groups. The diagnoses were isolated hydrocephalus in 39, myelodysplasia in 15, posthemorrhagic hydrocephalus in 5 and a malignant disorder in 4. All the operations resulted in successful VP shunt insertion.

The rate of postoperative shunt infection was 8% overall — 6% in the treatment group and 10% in the placebo group (Table I), a difference that was not significant, according to Fisher's exact test (one-tailed). The patients of each of the two neurosurgeons had similar infection rates. There was no difference in the leukocyte count after surgery between the patients in whom a shunt infection developed and those who remained free of infection.

In-vitro testing showed that the organisms causing infection in the placebo group were all sensitive to cephalothin, as was the *Escherichia coli* strain that caused one of the two infections in the treatment group. The responsible organism was not recovered from culture of the skin swabs obtained before and after incision in any case.

All the children recovered with appropriate antibiotic therapy and shunt removal. Two of the patients subsequently died from their underlying disease; there was no autopsy evidence of shunt infection.

Discussion

We chose cephalothin as the prophylactic antibiotic in our study because a retrospective analysis of shunt infections at our institution had shown that *Staphylococcus epidermidis* sensitive to cephalothin was the causative organism in 90% of cases. To avoid the biases in previous studies,[2,8] we conducted a randomized double-blind placebo-controlled trial.

The postoperative infection rate in the treatment group was not significantly lower than that in the placebo group. Infection most frequently

Table I — Postoperative ventriculoperitoneal shunt infections among patients who received prophylactic cephalothin or placebo

Sex/age	Diagnosis	Infecting organism
Treatment group (n = 32)		
F/2 wk	Myelodysplasia	*Escherichia coli*
M/1 wk	Myelodysplasia	*Pseudomonas aeruginosa*
Placebo group (n = 31)		
F/1 wk	Myelodysplasia	*Staphylococcus aureus*
F/4 yr	Malignant disorder	*S. epidermidis*
F/5 yr	Posthemorrhagic hydrocephalus	*S. aureus*

occurred during the first 2 months after surgery, a finding reported by other investigators.[2,8]

Retrospective analyses have revealed startling differences in VP shunt infection rates, from 3% to 29%.[2,4-7,9,10] However, the rates have been substantially lower since 1970; this has been attributed to such factors as improved technical expertise, better operating rooms and the introduction of prepackaged sterile shunt tubing.[2] Currently the expected rate of infection after insertion of a VP shunt is 5% to 7%.[2,5]

While the incidence of shunt infection is not high, the rates of illness and death among children with shunts, who are already neurologically at risk, are high. A retrospective but complete analysis by Schoenbaum and colleagues[10] of 10 years' experience with shunt infection at Boston Children's Hospital showed that when correction was made for severity of disease the death rate among patients with postoperative shunt infections was twice that among comparable peers. These investigators also noted that shunt malfunction was more common in infected than in uninfected patients. Although a higher death rate was not found by Odio and associates,[7] infection exposes the patient to the toxic effects of antibiotics used intravenously to treat the infection. Since the shunt usually has to be removed, the risks of further surgery and anesthesia are also introduced.[2,7,8]

Shunt infections have been implicated as possibly contributing to the lower mean intelligence quotients and psychologic testing scores among children who have meningomyelocele compared with children who have equally severe disease but have been spared postoperative infection.[11,12]

A variety of antibiotic regimens intended to prevent postoperative infections have been evaluated.[13-17] However, since most of the studies were retrospective, using historical controls[7,10,18-20] or comparing the results of antibiotic prophylaxis with those of other published series, the results are difficult to interpret.[21,22] The use of contemporary controls has not demonstrated significant reductions in infection rates with antibiotic prophylaxis, although reductions have occurred with time.[5,6] This poses a considerable problem for prospective studies using historical controls.[9,23] Increased infection rates with antibiotic prophylaxis have also been demonstrated.[24]

Like Yogev,[2] Haines and Taylor,[25] and Wang and coworkers,[26] we found that the rate of postoperative infection was not significantly lower in subjects who received prophylactic cephalothin before VP shunt insertion than in those who received placebo. Infection due to an organism sensitive to the prophylactic agent in a patient in our treatment group raises concern about the role of antibiotic prophylaxis or the suitability of the regimen used. However, the trend in all four studies was toward lower infection rates in the treatment groups.

The statistical power of a study is a function of the number of patients in the group of interest. There were 579 patients in the five randomized trials done to date. However, the number of patients with a VP shunt infection (the group of interest) was much smaller: there were 23 in the control groups and 10 in the treatment groups. This raises the possibility that a clinically significant difference might have been missed because of the small sample sizes.[27] As an example, a consistent reduction of 15% in the infection rate would probably be judged sufficiently significant to warrant routine antibiotic prophylaxis before VP shunt insertion, but no study has enrolled enough patients to detect a difference of that size. If there is truly no difference in outcome, routine antibiotic prophylaxis would expose patients to the risk of toxic effects and adverse drug reactions when no benefit could be expected.

The problem of small samples and how best to deal with supporting evidence from independent studies is not new to the medical literature. The traditional approaches to this problem have recently been supplemented by a process developed by Glass[28,29] and referred to as meta-analysis. This process can be used to combine the results of similar, independently done trials and yield a statistic that applies to the overall treatment effect.[30]

We applied meta-analysis to the five randomized trials done to date. It yielded a one-tailed Mantel-Haenszel chi-square value of 2.91; a value of 3.84 is required to fulfil the standard definition of statistical significance for a meta-analysis of this size. Again, the problem of small samples remains; the number of patients with infection, 33, is too small to enable detection of clinically significant differences that might influence practice patterns. Accordingly, a multicentre prospective randomized placebo-controlled study seems mandatory to generate sufficient numbers of patients to determine whether antibiotic prophylaxis afford some degree of protection from postoperative VP shunt infection.

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Meetings

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July 13–15, 1987

International Symposium on Occupational Asthma
Hyatt Regency Hotel, Vancouver
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August

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The Uremic Diabetic: a Status Report. Satellite Symposium to the 10th International Congress of Nephrology
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Aug. 26, 1987

Annual Meeting of the Canadian Medical Protective Association
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