A randomized trial of ceftriaxone versus trimethoprim-sulfamethoxazole to prevent ventriculoperitoneal shunt infection

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Background and Purpose: Shunt infection represents a particularly morbid condition, which can also result in mortality. In order to decrease the high morbidity and mortality rates, prevention is an essential step. The purpose of this study was to compare the prophylactic use of ceftriaxone and trimethoprim-sulfamethoxazole (SXT) for the prevention of ventriculoperitoneal (VP) shunt infection.

Methods: In this prospective, single-institution, randomized clinical trial, 107 children with hydrocephalus and an indication for shunting were randomly assigned to prophylaxis with ceftriaxone (n = 50) or SXT (55), each administered as a single dose during anesthesia and two divided doses postoperatively. Patients were followed up for at least one year.

Results: The mean age of patients was 15 months, and 85% were aged 6 months or younger. During the first postoperative year, meningitis occurred in 13.5% of patients receiving ceftriaxone and 14.5% of the SXT group, with no statistically significant difference between the groups. Younger age, presence of cerebrospinal fluid leakage and aqueductal stenosis as a cause of hydrocephalus showed significant correlation with meningitis occurrence on univariate analysis. However, only the latter 2 factors were associated with meningitis on multivariate analysis. The risk of shunt infection did not correlate with the gender of the patient, time of VP shunt surgery, or duration of hospitalization for shunting.

Conclusion: Ceftriaxone and SXT showed similar efficacy in preventing shunt infection. Cerebrospinal fluid leakage before or after VP shunt placement and aqueductal stenosis were independent risk factors for meningitis after VP shunt.

Key words: Antibiotic prophylaxis; Ceftriaxone; Meningitis; Trimethoprim-sulfamethoxazole combination; Ventriculoperitoneal shunt

Introduction

Ventriculoperitoneal (VP) shunt placement is a frequent neurosurgical procedure, with high morbidity. Infection is one of the most devastating complications in this setting, which occurs with a variable rate of 0.3-39.0% [1-3]. However, this trend has changed somewhat, and reductions of up to 5-10% have been observed in recent series [4,5]. The development of shunt infections is higher in pediatric populations (mostly neonates and younger children) than in adults [2,6]. Shunt infection represents a particularly morbid condition, which can also result in mortality, with reported rates of up to 20% [6]. In order to decrease such high morbidity and mortality rates, prevention is an essential step.

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Historically, short-term antibiotic prophylaxis at the time of surgery was an accepted practice in only a few situations, such as craniotomy involving implantation of foreign material, re-operation, cerebrospinal fluid (CSF) leak following trauma, and operative procedures lasting more than 4 h [7]. The efficacy of prophylactic antibiotic agents in the setting of VP shunting is still controversial. There is disagreement about the type, dose and duration in the use of antibiotic agents.

We conducted a prospective randomized trial to compare the efficacy of ceftriaxone and trimethoprim-sulfamethoxazole (SXT) in the prevention of VP shunt infection in the pediatric age group.

Methods

This study, conducted at Children's Hospital Medical Centre in Tehran between May 2002 and April 2004, included 107 children with hydrocephalus aged from 1 month to 12 years, who were admitted for VP shunt surgery. From our previous work, we estimated that 15% of VP-shunted patients might be expected to experience meningitis over a one-year period. We aimed to recruit 50 patients per group, to give the trial 80% power at a significance level of 5% to detect a clinically relevant difference in exacerbation rate of 15% between the two groups.

Patients less than 1 month of age were excluded from the study, due to the contraindication of SXT in this age group. Written informed consent was obtained from patients' parents. The protocol was approved by the Ethics Committee of Tehran University of Medical Sciences.

Patients were assigned by a random number-producing system to receive either ceftriaxone or SXT, which resulted in 52 patients receiving ceftriaxone and 55 receiving SXT.

Those randomized to ceftriaxone received a 20 mg/kg intravenous infusion during anesthesia induction and two additional doses of 20 mg/kg, 6 and 12 h later. Patients randomized to SXT received 5 mg/kg intravenous infusion during anesthesia induction and two similar doses 6 and 12 h later. All VP shunt procedures were done by one neurosurgeon; all procedures had similar operating set-up and almost equal duration of operation. Prospectively, time of surgery during the day, history of CSF leakage from shunt-related incisions or other associated wounds, shunt revision and occurrence of infection were recorded.

The primary endpoint of this study was defined as occurrence of shunt infection during the first year following surgery. The criteria for diagnosis of shunt infection were established according to either the presence of positive CSF culture or clinical evidence of infection with a negative culture but positive CSF parameters, including: positive smear, low level of serum glucose (<40 mg/dL), and high white blood cell count (>10/mm^3) with polymorphonucleosis [8]. CSF was obtained through needle aspiration of the shunt reservoir.

Univariate analysis for the primary endpoint and other variables (demographic data and shunt infection risk factors) was assessed using the chi-squared test (with Yates correction as needed) and Student's t test.

Variables that were significantly related to shunt infection ($p<0.05$) or with a p value of <0.3 in univariate analysis plus age (used as a continuous variable with a constant odds ratio for each score) were subjected to multivariate analysis with a logistical regression procedure and forward stepwise selection. Dependent variables were coded as zero for those who did not develop shunt infection and 1 for those who did. The significance level was determined to be 0.15 with the tolerance level at 0.0001. The maximum likelihood approach was used to estimate weights of the logistical parameters. Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows (Version 11.5; SPSS, Chicago, IL, USA) software package.

Results

107 patients were evaluated and randomized. Eighty five percent of patients were 6 months old or younger. The mean age of patients (± standard deviation) was 14.8 ± 26.2 months. Sixty six patients (61.7%) were male. The most common causes of hydrocephalus were myelomeningocele (31.8%) and aqueductal stenosis (28.0%). Operations were done as the first surgery of the day in 64.5% of cases. CSF leakage was evident in 16 patients (15%). The median hospital stay was 4 days, ranging from 1 to 120 days. The baseline and VP shunting-related characteristics of patients assigned to study groups are summarized in Table 1. There was no statistically significant difference between the two groups according to age, gender, cause of hydrocephalus, time of surgery during the day, and duration of stay in hospital for shunt operation.

Table 1. Baseline characteristics of study participants (intention to treat)

Characteristic	Ceftriaxone group (n = 52) No. (%)	SXT group (n = 55) No. (%)
Age (months; mean ± SD)	17.4 ± 29.6	12.3 ± 22.5
Male gender	33 (63.5)	33 (60)
Accompanying disease		
Myelomeningocele	17 (32.7)	17 (30.9)
Aqueductal stenosis	16 (30.8)	14 (25.5)
Hemorrhage	5 (9.6)	9 (16.4)
Other	14 (26.9)	40 (72.7)
Time of surgery		
First operation of the day	40 (76.9)	29 (52.7)
Cerebrospinal fluid leakage	5 (9.6)	11 (20.0)
Shunt revision	7 (13.5)	16 (29.1)
Hospitalization days (mean ± SD)	7.1 (10.2)	7.2 (15.9)

Abbreviations: SXT = trimethoprim-sulfamethoxazole; SD = standard deviation

All cases attended the scheduled follow-up visits during the first postoperative year, during which 15 patients (14.0%) acquired shunt infection, 7 (13.5%) in the ceftriaxone group and 8 (14.5%) in the SXT group. Chi-squared test showed no statistically significant difference in infection rate between the two antibiotics used for prophylaxes (p=1.00). All cases of meningitis occurred within 9 months of the procedure, ranging from 15 days to 9 months postoperatively, with 66.7% occurring during the first 2 months.

Meningitis was diagnosed by positive CSF culture in only 5 cases. In the remaining cases, CSF analysis parameters, including leukocyte count, polymorphonuclear percentage and glucose level, were helpful in the diagnosis. CSF leucocytes were more than 10/mm^3 in 93% of shunt infections, and polymorphonuclear cells >50% in 73%. Serum glucose was less than 40 mg/dL in 73% of infected shunts (Table 2). No adverse clinical event occurred related to the study medications (except for skin rash in two patients receiving SXT).

Patients who developed meningitis ranged in age from 1 month to 3 years; 11 were male and 4 female. Eighty percent of the observed shunt infections occurred during the first 6 months, and 93% in the first year of life. Only younger age, presence of CSF leakage and aqueductal stenosis as a cause of hydrocephalus showed significant correlation with meningitis occurrence (Table 3). Comparisons according to gender, shunt revision, time of surgery (i.e., first operation of the day or not), and length of hospitalization for shunting revealed none of these parameters to be associated with increased risk of meningitis.

Multivariate analysis showed that the presence of CSF leakage and aqueduct stenosis were independent prognostic factors associated with shunt infection (Table 4). No death occurred among the 107 cases studied.

Discussion

Different factors have been proposed as predisposing to infection after VP shunt, including age, cause of

Table 2. Organisms isolated from cerebrospinal fluid culture in patients suspected to have meningitis

Organism	Ceftriaxone group (n = 7) No. (%)	SXT group (n = 8) No. (%)
Positive culture	2 (28.5)	3 (37.5)
Group D streptococci	1 (14.3)	1 (12.5)
Coagulase-negative *Staphylococcus*	1 (14.3)	1 (12.5)
Candida albicans	0 (0.0)	1 (12.5)
Positive smear	0 (0.0)	1 (12.5)
Glucose <40 mg/dL	5 (62.0)	6 (85.7)
WBC >10/mm^3	7 (100.0)	7 (87.5)
PMN >50%	6 (85.7)	5 (62.5)

Abbreviations: SXT = trimethoprim-sulfamethoxazole; WBC = white blood cells; PMN = polymorphonuclear leukocytes

Table 3. Comparison of demographic characteristics and shunt-related variables according to the development of shunt infection

Characteristic	With meningitis (n = 15) No. (%)	Without meningitis (n = 92) No. (%)	p
Age (months; mean ± SD)	5.7 ± 9.0	16 ± 27.6	0.007
Male gender	11 (73.3)	55 (59.8)	NS
Accompanying disease			
Myelomeningocele	4 (26.7)	30 (32.6)	NS
Aqueductal stenosis	6 (40.0)	24 (26.1)	0.025
Hemorrhage	2 (13.3)	12 (13.0)	NS
Time of surgery			
First operation of the day	9 (60.0)	60 (65.2)	NS
Cerebrospinal fluid leakage	5 (33.3)	11 (11.9)	0.010
Shunt revision	5 (33.3)	18 (19.6)	NS
Hospitalization days (mean ± SD)	4.7 ± 1.3	7.5 ± 14.4	NS

Abbreviations: SD = standard deviation; NS = not significant (p>0.05)

hydrocephalus, prolonged operating time, experience of the operating surgeon, shunt revision (versus initial shunting), shunting done late in a day, operative room traffic and perioperative antibiotics. However, the role of each of these factors in shunt infection is controversial [1,2,6,9]. Our randomized, double-blind study showed that there was no statistically significant difference between two antibiotics (ceftriaxone versus SXT) in the prevention of shunt infection.

Antibiotics appropriate for prophylaxis must cover a broad range of organisms likely to be seen in neurosurgical infections, with special emphasis on Gram-positive bacteria. Ceftriaxone is a broad-spectrum antibiotic with good activity against Gram-negative bacteria, and mild activity against Gram-positive organisms [10]. SXT is effective against both Gram-positive and Gram-negative organisms. It penetrates the central nervous system even in the presence of non-inflamed meninges [11,12]. No previous study has compared the efficacy of these two antibiotics in the prevention of shunt infection.

Although many studies evaluated the efficacy of prophylactic antibiotic administration, their statistical power was generally too low to detect any meaningful significant difference [13-19]. These studies' designs and results are summarized in Table 5. Among the seven previously published clinical trials, just two

(oxacillin) could document superiority of antibiotic over placebo [18].

In a meta-analysis of data published before 1994, a 50% infection risk reduction was found with antibiotic prophylaxis. The effect was strongly related to the baseline infection rate of more than 5% [20]. Due to small sample sizes of prospective controlled clinical trials and their low statistical power, it is not possible to make a recommendation for or against the use of prophylaxis or regarding the type of antibiotics in shunt surgery.

The sample size of this study is not large because many patients in this setting are aged less than 1 month or receiving other antibiotics for associated urinary or pulmonary infections. Another weakness of this study was the high rate of non-diagnostic culture results in our series, which could be attributed to inefficient microbiological techniques in our hospital. However, in these cases, changes in CSF parameters were reliable and helpful.

The present study could not show a significant relationship between type of prophylactic antibiotics (ceftriaxone versus SXT) and infection rate. Due to the utilization of similar shunt devices in all patients, and similar operating personnel and operating time, we were not able to explain the role of these variables in shunt infection. According to our univariate

Table 4. Independent predictors of shunt infection in 107 patients[a]

Variable	p	RR (95% CI)
Cerebrospinal fluid leakage	0.010	6.712 (1.588-28.366)
Aqueductal stenosis	0.056	3.702 (0.968-14.148)

Abbreviations: RR = relative risk; CI = confidence interval
[a]beta (β) = –2.785, standard error of the mean (β) = 0.527, goodness-of-fit chi-squared = 0.81, df = 1, p=0.775

Table 5. Published randomized controlled clinical trials on the efficacy of antibiotic prophylaxis in the prevention of ventriculo-peritoneal shunt infection

Trial (year)	Antibiotic	Intervention (n)	Placebo (n)	*p*
Haines and Taylor (1982) [16]	Methicillin	26	26	NS
Wang et al (1984) [17]	Trimethoprim-sulfamethoxazole	55	65	NS
Schmidt et al (1985) [13]	Methicillin	79	73	NS
Djindjian et al (1986) [18]	Oxacillin	30	30	<0.05
Rieder et al (1987) [14]	Cephalothin	32	31	NS
Bayston et al (1990) [19]	Intraventricular vancomycin	78	80	NS
Zentner et al (1995) [15]	Cefotiam	-	-	NS

Abbreviation: NS = not significant (*p* >0.05)

analyses, the risk factors associated with a higher rate of meningitis were younger age (less than 6 months), presence of aqueductal stenosis and CSF leakage. However, in multivariate analysis, just the presence of CSF leakage and aqueductal stenosis were proved to be independent risk factors of meningitis, and age showed no significant association with the risk of shunt infection.

Although Rotim et al [5], Piatt and Carlson [21], and Davis et al [22] have reported that patients aged less than 6 months had a higher risk of infection, in our series, the association between age and meningitis found in univariate analysis was potentially due to the higher incidence of CSF leakage in our younger patients. The mean age of patients who had CSF leakage was 6.37 ± 8.5 months, versus 16.3 ± 29.9 in those without CSF leak (*p*=0.018). In our study, the presence of CSF leakage was found to increase the odds of meningitis 7-fold. CSF leakage and poor skin condition have also been reported to be highly associated with shunt infection in most studies [4,23].

Enger et al found that the presence of myelomeningocele per se enhances the risk of shunt infection [23]. Several other studies did not find any significant differences between etiological subgroups with a higher infection rate [24,25]. In this study, aqueductal stenosis was accompanied by an increase of about four-fold in the odds of meningitis, a finding not reported previously.

Our study revealed that the probability of shunt infection was highest during the first two months after a shunt procedure and was less likely after six months. Thus, during the first 6 months after shunting, it is important to give special attention to even nonspecific symptoms, to rule out infection.

Infection is still a major complication in pediatric CSF shunt operations. We report an incidence of 13% in our hospital. Most infections occurred in patients aged less than 6 months at the time of shunt placement and within 8 weeks following the procedure. There was no significant difference between ceftriaxone and SXT in the prevention of shunt infection. However, a large multicenter trial is needed to determine the value of prophylactic antibiotic administration in shunting.

In conclusion, to prevent shunt infections, it is better not to shunt, but if the case needs shunt placement, the procedure should be deferred to a later age as much as possible (because of thin skin, poor wound repair and a high chance of CSF leakage) with careful surveillance of CSF leakage. Notwithstanding the benefits of addressing the significant risk factors, a dramatic reduction in the number of shunt infections will only be obtained by limiting shunt replacement whenever possible. This objective can be achieved by preventing hydrocephalus and by the increased use of alternative surgical procedures such as neuroendoscopic techniques.

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