



Antithrombotic Therapy for Secondary Stroke Prevention in Bacterial Meningitis in Children

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Objective To assess the safety and efficacy of antithrombotic therapy (ATT) for secondary stroke prevention of childhood bacterial meningitis.

Study design A retrospective study of cases of stroke associated with bacterial meningitis in 2 pediatric hospitals during a period of 15 years. Patients were included in the study if they were between 28 days and 18 years of age and had at least 2 serial neuroimaging studies during the acute phase of their illness. The safety of ATT was assessed by the presence or absence of intracranial hemorrhage. Efficacy was assessed by the failure in preventing stroke recurrence. Neurologic outcome was determined by the last documented Pediatric Stroke Outcome Measure score.

Results Twenty-two cases of childhood bacterial meningitis complicated by stroke were identified. Six cases were treated with heparin after either initial or recurrent infarction. None of the cases receiving heparin had further recurrence. Aspirin (acetylsalicylic acid [ASA]) was started after the initial or after recurrent infarction in 10 cases. Four (40%) had infarctions on ASA; 3 of these patients subsequently received heparin. In the 14 cases in which no ATT was begun, 8 (57%) had further recurrence of infarction. None of the patients, whether receiving heparin or ASA, had intracranial hemorrhage.

Conclusion In this small sample, heparin and ASA appeared to be safe in childhood bacterial meningitis complicated by stroke and may be effective in improving outcome. Heparin may be more effective than aspirin in preventing recurrent infarction. (*J Pediatr* 2014;165:799-806).

Bacterial meningitis continues to take a toll on society despite population-wide immunization. Mortality has remained at approximately 15%.¹ In childhood bacterial meningitis, morbidity is significant and includes long-term neurologic abnormalities in up to 40% of patients who have acute neurologic complications.² Ischemic stroke is a major cause of morbidity and mortality in meningitis, occurring in 10%-25% of cases.^{3,4}

Advances in supportive care and the early administration of antibiotics have improved outcomes. Dexamethasone has been well studied as an adjuvant therapy to decrease morbidity, such as hearing loss.⁵ The management of stroke in children with the use of antithrombotic therapy (ATT) has been established in international protocols for many systemic and neurologic disorders.⁶ However, no clear role has been established for ATT in prophylaxis against stroke in bacterial meningitis. The objectives of the current study were to retrospectively evaluate the safety and efficacy of acute ATTs (acetylsalicylic acid [ASA] and/or heparin) for secondary stroke prevention in children with acute bacterial meningitis.

Methods

Children between 28 days and 18 years of age who had ischemic strokes between 1992 and 2010 in the context of acute bacterial meningitis were identified retrospectively from 2 sites of the Canadian Pediatric Ischemic Stroke Registry (The Hospital for Sick Children [HSC], Toronto, and B.C. Children's Hospital [BCCH], Vancouver, Canada). In HSC, stroke case ascertainment was performed during the study period (1992-2010) by querying Canadian Pediatric Ischemic Stroke Registry via the use of *International Classification of Diseases, 9th and 10th Revision* search codes and trained chart reviewers validated the diagnosis of stroke. In BCCH, stroke cases were identified through weekly neuroradiology rounds. In both centers, meningitis case

ASA	Acetylsalicylic acid
ATT	Antithrombotic therapy
BCCH	B.C. Children's Hospital
CSF	Cerebrospinal fluid
EVD	External ventricular drain
HSC	The Hospital for Sick Children
ICH	Intracranial hemorrhage
LMWH	Low-molecular-weight heparin
PSOM	Pediatric Stroke Outcome Measure
TB	Tuberculosis

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ascertainment was validated through chart reviews. Therefore, the series in this study attempts to be a true fully ascertained consecutive cohort of stroke and meningitis. Exclusion criteria included: (1) having fewer than 2 serial neuroimaging studies during the hospital admission of the acute presentation; and (2) the presence of cerebral sinus venous thrombosis before the detection of ischemic arterial stroke. The study was approved by the Research Ethics Board of HSC, Toronto.

Bacterial meningitis was defined as having both clinical evidence of central nervous system infection on history and physical examination and laboratory evidence, including either pathogen isolation or cerebrospinal fluid (CSF) analysis consistent with probable bacterial meningitis (based on 2 of 3 measurements: protein level >0.40 g/L, low glucose <2.1 mmol/L, and/or leukocytosis). If CSF culture was negative but serum or other culture determined a pathogen, this pathogen was considered the causative pathogen. The incidences of causative bacteria (excluding tuberculosis [TB]) isolated from cultures of CSF collected as the result of meningitis in non-neonates were queried from the HSC laboratory database over the years these data were available (2000-2010).

Data extracted from chart reviews included initial symptoms of infection, presenting neurologic symptoms, subsequent clinical course, and management, including neuroimaging and timelines between all of these clinical events. Laboratory investigations were followed over time, in particular coagulation profiles and microbiology. Antithrombotic treatment (either standard unfractionated heparin or low-molecular-weight heparin [LMWH] and/or ASA) was documented in terms of the timing of its initiation, the ASA doses by weight, and when therapeutic heparin levels were achieved.

Neuroimaging studies were centrally reviewed by a pediatric neuroradiologist (M.S.) who was blinded to the ATT received. Infarcts were defined on magnetic resonance imaging as persistent diffusion-weighted and/or T2 signal hyperintensity on serial imaging with subsequent infarct evolution over time. On computed tomography, infarcts were seen as decreased signal and/or loss of gray-white differentiation with subsequent evolution. Vascular imaging (magnetic resonance angiography, computed tomography angiography), when available, also was reviewed.

Assessment of Safety and Efficacy of ATT

There are no institutional protocols or guidelines regarding the initiation of ATT for stroke prevention secondary to bacterial meningitis. The decision to initiate ATT for the patients included in this study was based on personal clinical judgment and experience.

Safety of ATT was determined by: (1) presence or absence of intracranial bleeding other than petechial hemorrhage expected at the sites of neurosurgical intervention (eg, external ventricular drain [EVD] or ventriculoperitoneal shunt tract); and (2) presence or absence of systemic bleeding.

Stroke recurrence was defined by the detection of new ischemic lesion on follow-up neuroimaging with or without

clinical neurologic deterioration. The presence of new radiologic findings consistent with an ischemic lesion was considered to be failure of ATT. ASA efficacy or failure was evaluated based on stroke recurrence after the initiation of ASA dose.

Evaluation of neurologic outcome used the most recent complete and documented neurologic physical examination. A blinded reviewer retrospectively calculated an outcome score by the validated Pediatric Stroke Outcome Measure (PSOM), which assesses 5 areas of neurologic function: right sensorimotor, left sensorimotor, language production, language comprehension, and cognitive/behavioral performance.⁷

Data Analyses

Although the study included the largest cohort of pediatric patients with ischemic stroke secondary to meningitis, the number of patients was too small to perform statistical analysis between groups. Therefore, the results were analyzed qualitatively.

Results

Incidence and Inclusion of Stroke and Meningitis Cases

Between 1992 and 2010, 515 children older than 1 month of age (98 HSC, 417 BCCH) were identified in the Canadian Pediatric Ischemic Stroke Registry to have suffered an ischemic stroke. Twenty-four (4.6%) of these children had stroke and bacterial meningitis (18 HSC, 6 BCCH), of which 2 were excluded from this study because of inadequate neuroimaging. Between 2000 and 2010, HSC documented 128 cases of positive CSF-culture bacterial meningitis in non-neonates (excluding TB), of which 8 (6.3% overall; 24.0% due to *Streptococcus pneumoniae* and 18.2% due to *Streptococcus agalactiae* group B) had strokes and were included in the remaining 22 cases. There were 256 cases of non-neonatal strokes at HSC between 2000 and 2010, and 17 (6.6%) of these were associated with meningitis and included as part of the 22 cases in this study.

Case Features

The demographics and clinical features of the 22 cases with meningitis complicated by stroke and met the inclusion criteria of the study are shown in the [Table](#). The median age was 13 months (range, 35 days to 17.5 years) with 14 males (64%). There were no cases with a family member with history of stroke younger than the age of 50 years or with a history of coagulopathy.

The median time between onset of symptoms and admission to hospital was 3 days (range, 0-32 days). Initial signs and symptoms of infection described in the history or noted on presentation to medical attention included fever (18; 82%), common upper respiratory tract infectious symptoms (10; 45%), vomiting (11; 50%), otitis media (4; 18%), headache (4; 18%), lethargy (3; 14%), and respiratory distress

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