Double-Blind Placebo-Controlled Trial of Corticosteroids in Children with Postpericardiotomy Syndrome

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SUMMARY. The objective of this study was to assess the efficacy of corticosteroids in hastening the recovery of children with postpericardiotomy syndrome, using a randomized double-blind placebo-controlled trial in a tertiary care referral center for pediatric cardiology and cardiac surgery. Twenty-one children, 6 months of age or older (mean age 3.9 years) with postpericardiotomy syndrome following open or closed heart surgery were administered either prednisone 2 mg/kg/day reducing to zero over 14 days (n = 12) or placebo (n = 9). Progress was monitored by daily clinical assessment and alternate day cross-sectional echocardiograms. The primary measures of efficacy were the number of patients in remission at 72 h and at 1 week. No difference in remission rates were found at 72 h, but at 1 week significantly more children treated with prednisone were in remission (placebo 3/9; prednisone 10/12, p = 0.03). A trend to faster resolution of all symptoms and signs was seen in the prednisone-treated group but this was not associated with earlier hospital discharge. Enlargement of pericardial effusion was seen in two children treated with steroids. No complications of treatment were encountered. Prednisone hastens the recovery of children with postpericardiotomy syndrome. Pericardial effusions may increase in size despite the use of corticosteroids.

KEY WORDS: Postpericardiotomy syndrome — Pericardial effusion — Corticosteroids

Postpericardiotomy syndrome is the most common complication of open heart surgery in childhood, occurring after 25–30% of intrapericardial procedures [5, 9]. It may also occasionally occur after closed surgical procedures if the pericardium has been opened [5]. It is associated with significant morbidity due to distressing symptoms, delayed hospital discharge, and—on occasion—cardiac tamponade, which has been responsible for rare fatalities [1, 13].

Despite the frequent occurrence and significant morbidity associated with this condition, its treatment has been poorly studied. Anecdotal reports and uncontrolled studies have described the use of enforced bed rest [15], salicylates [4, 6, 8, 11, 16, 19], and corticosteroids [4, 8, 17, 18]. The response to aspirin has been variable but reports of corticosteroid usage have all been favorable. Thirty years ago, Engle drew attention to the difficulty of assessing therapy in this self-limiting illness of variable severity and duration [7]. Despite the clear need, therefore, for controlled clinical trials, no randomized placebo-controlled studies of the treatment of postpericardiotomy syndrome in children have been reported. The current study reports the first randomized double-blind placebo-controlled trial of corticosteroids in either adults or children.

Patients and Methods

Patients

Between May 1988 and January 1990, all children greater than 6 months of age undergoing open or closed heart surgery at our institution were prospectively studied to identify those developing postpericardiotomy syndrome. Children were examined daily...
following surgery and postpericardiotomy syndrome was diagnosed when two or more of the following criteria were met: (1) fever > 37.8°C; (2) clinical evidence of pericarditis (i.e., characteristic chest pain or pericardial rub); and (3) echocardiographic evidence of pericardial effusion with or without radiological evidence of pleural effusion. In all cases, the diagnosis was confirmed independently by two physicians, including the patient's cardiologist. Of those children enrolled in the current study, all but one in fact fulfilled all three criteria. The remaining patient had very low grade fever (<37.8°C) with pericarditic chest pain and moderate pericardial effusion. In addition, all but three of the patients had an elevated erythrocyte sedimentation rate. Patients with pericardial friction rubs present in the immediate postoperative period were eligible for inclusion if the above diagnostic criteria were fulfilled after postoperative day 5. Elevation of white cell count was not included in the definition of postpericardiotomy syndrome, as we have found this to be insensitive and nonspecific in the diagnosis of this disorder.

**Study Protocol**

Prior to instituting treatment, complete blood count, blood culture, urinalysis and culture, and chest radiograph were performed. Patients with any clinical or laboratory evidence of infection were excluded from entry into the study, but blood culture results were not required prior to instituting treatment if sepsis was not suspected. Other exclusion criteria were: (1) diabetes mellitus; (2) hypertension; (3) immune deficiency states; (4) postoperative use of steroids or nonsteroidal antiinflammatory agents; (5) poor wound healing; (6) failure to obtain informed parental consent; and (7) postoperative Fontan patients. The latter group were excluded because of the frequent difficulty encountered in confidently defining the etiology of postoperative effusions in this group of patients. Concomitant use of antibiotics was not considered a contraindication to entry into the study, in the absence of evidence of active infection.

After obtaining informed parental consent, patients were randomized to receive either prednisone suspension 2 mg/kg/day (maximum 40 mg/day) tailed to zero over 14 days or equivalent appearing placebo supplied by the hospital pharmacy. Simple analgesics (e.g., paracetamol or codeine phosphate) were prescribed as required during the study period, but nonsteroidal antiinflammatory agents, including aspirin, were not given.

The clinical progress of each child was assessed daily by one investigator (NJW or SAW), who recorded current symptoms, physical signs, and laboratory results on a daily record sheet. Cross-sectional echocardiograms were performed on alternate days to assess progress of pericardial effusions. In addition, one parent and the physician each recorded independently a daily score of the child's condition using a linear 1-5 scale (1, characteristic chest pain or pericardial rub; 5, normal). Remission rates between study and placebo groups are shown in Table 1. Twelve children were randomized to receive prednisone and nine to receive placebo. There were no significant differences in age, sex distribution, or time to onset of postpericardiotomy syndrome between the two groups. The clinical course of the two groups is shown in Table 2. No difference in remission rates was present at 72 h, but after 1 week the remission rate was greater in the prednisone-treated group \( (p = 0.03) \). Time to hospital discharge was not shortened by treatment with prednisone but there was a trend to faster resolution of symptoms, physical signs, and effusions in the steroid-treated group (Table 2). No patient developed cardiac tamponade, but in two children significant increase in the size of pericardial effusions occurred during treatment with prednisone. Two patients from each group relapsed during the course of treatment, and one from each group relapsed after the 14-day course of treatment was completed. No complications of treatment with steroids were encountered.

**Assessment of Efficacy**

The primary measure of efficacy was the proportion of patients in complete remission at 72 h and at 1 week after starting treatment. Remission was defined as the complete absence of all symptoms and signs of the syndrome, for at least 24 h with static or decreasing effusions. Remission rates between study and placebo groups were compared using Fisher's exact test. The following individual variables were assessed. Time to: (1) loss of fever; (2) loss of rub; (3) resolution of effusions; (4) physician clinical score 1 or 2; (5) parent clinical score 1 or 2; and (6) hospital discharge. Because of the small sample size, multiple hypothesis testing for all the individual variables was not performed, but descriptive statistics (median, means) are presented.

**Results**

Of the 290 patients studied, 34 developed postpericardiotomy syndrome, with all but two episodes occurring following open heart surgery. The incidence was 21% (32/149) following open procedures and 1.4% (2/141) following closed procedures (pulmonary artery banding and modified Blalock-Taussig shunt). Twenty-one children were enrolled in the study after informed consent was obtained. Reasons for nonenrollment were: bacterial sepsis (2), suspected bacterial sepsis (2), parental refusal (3), physician refusal (1), poor wound healing (2), diabetes mellitus (1), and late onset of postpericardiotomy syndrome after hospital discharge (2).

The characteristics of the prednisone and placebo groups are shown in Table 1. Twelve children were randomized to receive prednisone and nine to receive placebo. There were no significant differences in age, sex distribution, or time to onset of postpericardiotomy syndrome between the two groups. The clinical course of the two groups is shown in Table 2. No difference in remission rates was present at 72 h, but after 1 week the remission rate was greater in the prednisone-treated group \( (p = 0.03) \). Time to hospital discharge was not shortened by treatment with prednisone but there was a trend to faster resolution of symptoms, physical signs, and effusions in the steroid-treated group (Table 2). No patient developed cardiac tamponade, but in two children significant increase in the size of pericardial effusions occurred during treatment with prednisone. Two patients from each group relapsed during the course of treatment, and one from each group relapsed after the 14-day course of treatment was completed. No complications of treatment with steroids were encountered.

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When no clinical improvement was seen after 7 days of treatment, or if tamponade developed, the drug code was broken and further treatment was given at the discretion of the cardiologist. Suitability for discharge home was determined on usual clinical grounds by the child's cardiologist. When symptoms or signs were still present at discharge, children were followed at least twice weekly in the outpatient clinic until asymptomatic and until effusions had resolved. In addition, all children were reviewed at 2 weeks and at 3 months in the outpatient clinic when history of relapse was sought.

During treatment in hospital, blood pressure and urinalysis for glycosuria were performed at least once daily and clinical surveillance for infection was continued.