Steroid Therapy Attenuates Acute Phase Reactant Response Among Children on Ventricular Assist Device Support

Jonathan W. Byrnes, MD, Adnan T. Bhutta, MD, Mallikarjuna Rao Rettiganti, PhD, Alberto Gomez, BA, Xiomara Garcia, MD, Umesh Dyamenahalli, MD, MRCP(UK), Charles Johnson, CPP, Robert D. B. Jaquiss, MD, Michiaki Imamura, MD, PhD, and Parthak Prodhan, MD

Department of Pediatrics, Department of Biostatistics, College of Medicine, and Department of Surgery, University of Arkansas Medical Sciences, Arkansas Children's Hospital, Little Rock, Arkansas; Department of Surgery, Duke University, Durham, North Carolina; Department of Pediatrics, Cincinnati Children's Hospital, Cincinnati, Ohio; Department of Pediatrics, University of Maryland, Baltimore, Maryland; and Department of Pediatrics, Comer Children's Hospital, Chicago, Illinois

Background. **Hyperfibrinogenemia, which can create a procoagulant milieu, is frequently observed in patients supported with the Berlin EXCOR (Berlin Heart GmbH, Berlin, Germany) ventricular assist device (VAD). We began initiating corticosteroids in patients with systemic inflammatory response syndrome (SIRS) episodes to mitigate hyperfibrinogenemia. We set forth to describe the impact of corticosteroids on the hyperfibrinogenemic state in our institutional experience.**

Methods. **Retrospective data was collected on 44 consecutive patients implanted with the Berlin EXCOR VAD from April 15, 2005 through May 6, 2013. Pertinent information was abstracted from the electronic medical record. The reduction of C-reactive protein (CRP) and fibrinogen levels among days from corticosteroid treatment were described. Infections and insulin use were reported based on whether patients received steroids and if steroids were given for SIRS.**

Results. **Over the initial 44 Berlin EXCOR VAD implantations, 14 patients were treated with 21 courses of corticosteroids for SIRS episodes as identified by clinical features and rise in CRP. Treatment with corticosteroids reduced fibrinogen levels by day 2 to a statistically significant degree ($p = 0.008$). No difference in hyperglycemia or infections occurred among patients receiving corticosteroids for SIRS.**

Conclusions. **Treatment with corticosteroids can potentially mitigate the SIRS response among children supported on the Berlin EXCOR VAD. In patients who received corticosteroids to mitigate inflammation, there was no increase in infections or hyperglycemia requiring insulin administration compared with patients who did not receive steroids.**

(Ann Thorac Surg 2015;99:1392–8)

Ventricular assist devices (VAD) are increasingly being deployed for end-stage heart failure in children as a bridge to heart transplantation [1–3]. Recent evidence suggests that systemic inflammatory response syndrome (SIRS) is a common occurrence among children supported on VADs [4]. This response is similar to that seen among patients supported on cardiopulmonary bypass and extracorporeal membrane oxygenators (ECMO) [4–6]. Host blood-biomaterial interaction in these support modalities are among the mechanisms shared for this SIRS response [4–6].

The C-reactive protein (CRP), an acute phase reactant protein, has been extensively used as a marker of SIRS due to both noninfectious and infectious causes. Shortly after VAD implantation in children, CRP levels are known to increase to a magnitude similar to those reported in patients supported on ECMO or cardiopulmonary bypass [4, 7–10].

High preoperative CRP level, a marker of the degree of SIRS response, is clearly associated with increased hospital mortality among children on VAD support [2]. Furthermore, the extensive crosstalk between immune, inflammatory and hemostatic systems, wherein each drive the other in a positive feedback loop [11], has the potential to create a potent prothrombotic milieu in patients on VAD support. This may explain the heightened risk of thromboembolic phenomenon seen among adult patients with infections on VAD support [12–15].

Accepted for publication Nov 18, 2014.

Address correspondence to Dr Prodhan, Division of Pediatric Cardiology and Critical Care Medicine, College of Medicine, University of Arkansas Medical Sciences, Arkansas Children's Hospital, 1 Children's Way, Slot 512-3, Little Rock, AR 72205; e-mail: prodhanparthak@uams.edu.

The Appendix can be viewed in the online version of this article [http://dx.doi.org/101016/j.athoracsur.2014.11.046] on http://www.annalsthoracicsurgery.org.

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2014.11.046

Abbreviations and Acronyms

CI = confidence interval
CRP = C-reactive protein
CVE = cerebrovascular event
DDD = daily defined dose per 100 hospital bed days
ECMO = extracorporeal membrane oxygenator support
IQR = interquartile range
SD = standard deviation
SIRS = systemic inflammatory response syndrome
VAD = ventricular assist device

Based on this physiologic rationale and the growing evidence among adults, our institution chose to aggressively use corticosteroids to attenuate the SIRS response seen among children supported on VADs. Fibrinogen, which is an integral part of the coagulation cascade, is also an acute phase reactant, increases dramatically with a SIRS response, and can contribute to a procoagulant state. Both of these biomarkers are readily available in most clinical laboratories, including ours, and could be used to objectively demonstrate an increase in the inflammatory and procoagulant states.

In this study we examine our institutional experience in using corticosteroids to attenuate the SIRS response among children supported on VADs. We hypothesize that corticosteroid therapy would dramatically attenuate CRP response and the concurrent rise in fibrinogen levels among these patients.

Material and Methods

Study Population

This retrospective single institution study included 44 consecutive patients with advanced heart failure who were supported on pediatric mechanical cardiac support (VAD only or ECMO followed by VAD support) as a bridge to transplantation for children below 18 years of age from January 2005 to April 2013 at Arkansas Children's Hospital, a large tertiary care academic children's hospital. The study protocol was approved by the University of Arkansas Medical Sciences Institutional Review Board approval and they waived the need for consent for this study. Pertinent medical information was abstracted from the physical and electronic medical records.

Ventricular Assist Device Support

During the study period the Berlin Heart EXCOR pediatric ventricular assist device (EXCOR Pediatric; Berlin Heart GmbH, Berlin, Germany), a paracorporeal volume-displacement VAD specifically designed for placement in young patients (neonates to adolescents) with advanced heart failure, was utilized to bridge these patients to cardiac transplantation. All patients were anticoagulated in the postimplantation period using the Edmonton anticoagulation protocol as a basic template, with deviations tailored to individual patient requirement as monitored by routine coagulation parameters as well as the routine use of thromboelastography [1].

Variables and Definitions

Data on patient demographics, pre-support characteristics, VAD support characteristics, and clinical outcomes were collected. Variables specific to corticosteroid use, CRP levels, and fibrinogen levels were also collected. The primary study endpoints were the following: (1) decrease in CRP; and (2) decrease in fibrinogen levels with corticosteroid therapy among children undergoing VAD implantation. Study definitions [16, 17] are detailed in the Appendix.

Indication for Steroids

Steroids were utilized in our patient cohort under 3 scenarios; for extubation for upper airway edema, relative adrenal insufficiency, and to control the inflammatory state. Additional details of corticosteroid utilization are provided in the Appendix.

Corticosteroid Protocol for SIRS

Once the SIRS episode was identified, corticosteroid therapy (methylprednisolone 2 mg/kg initial dose followed by methylprednisolone 1 mg/kg/dose every 12 hours) was then started if the CRP was more than 30 mg/dL, fibrinogen was greater than 500 mg/dL, and the after the preliminary blood cultures (within 12 hours of culture) were negative. Dosage is increased to 4 mg/kg per day if CRP and fibrinogen elevation was persistent after starting therapy. Simultaneously, heightened anticoagulation monitoring (bi-daily CRP, fibrinogen levels, daily TEGs [Thrombelastograph hemostasis analyzer system; Haemonetics Corp, Niles, IL], and platelet mapping) occurs as well as optimization of VAD filling and emptying (titrate volume status; may need to increase VAD pressure to optimize emptying, monitor plasma free hemoglobin daily). Once CRP and fibrinogen were in an acceptable range and demonstrated a decreasing trend (CRP is below 30 mg/L and fibrinogen is below 300 mg/dL), steroids are weaned based on CRP and fibrinogen levels.

Statistical Analysis

All demographic variables and outcomes of interest were summarized as either mean and standard deviation or median and quartiles for continuous variables and frequency and percent for categoric variables. Dichotomous patient outcomes were compared between 2 independent groups using the Fisher exact test. All statistical analysis was generated using SAS/STAT software, Version 9.3 of the SAS System for Windows 7 (SAS Institute Inc, Cary, NC) All tests were 2-sided assuming a significance level of 5%. Additional details of biostatistical methodology are provided in the Appendix.