

Repurposing of Fibrinogen Concentrate as a Cost-Effective and Safe
Hemostatic Agent in Infants Undergoing Cardiac Surgery on
Cardiopulmonary Bypass

Statistical Analysis Plan

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Intention-to-Treat (ITT) Analysis Set

The ITT Analysis Set consists of all enrolled subjects. Efficacy summarization and analysis will be conducted using the ITT analysis set.

Per Protocol Analysis Set (PPAS):

The subset of subjects in the full analysis (ITT) set who complied with the protocol sufficiently (see below) without any major protocol deviations. Confirmatory analysis was performed using the PPAS dataset. Final definition of PPAS were defined prior to data lock. Elements of PPAS may include exclusion criteria such as:

- Violation of inclusion or exclusion criteria
- Did not receive study medication
- Did not go on cardiac bypass during surgical intervention
- Patients unable to wean from bypass in operating room

Statistical Analysis for Primary outcome (using ITT):

The primary analysis followed the ITT principle and was performed using a linear regression adjusted for the randomization strata of institution and complexity of surgery. PP analysis was also performed for the primary outcome of total units of intraoperative allogenic blood transfusions.

Results for Primary outcome:

Patients in the FC group received significantly fewer total units of allogenic blood transfusions when compared to patients in the cryoprecipitate group (5 units [IQR 4.00,7.00] in the ITT analysis and 6 units [IQR 5.00,7.00] in the PP analysis in the control group, and 4 units [IQR 3.00,5.00] in the ITT analysis and 4 units [IQR 3.00,5.00] in the PP analysis in the study group). In the ITT analysis, the FC group received a mean of 1.61 [95% CI 0.3-2.91, p-value =0.02] less allogenic donor exposures than the cryoprecipitate group when adjusted for institution and complexity. In a PP analysis, the FC group received a mean of 2.67 [95% CI 1.75-3.59, p-value <0.001] less allogenic donor exposures than the cryoprecipitate group when adjusted for institution and complexity.

Statistical Analysis for Secondary Outcomes (using Per Protocol population)

In secondary analyses, we used a Mann-Whitney U test to test whether the secondary outcomes measured continuously differed by arm. For categorical secondary outcomes, we used a Chi-squared test when the expected count in each cell was > 5, otherwise we used a Fisher's exact test. All secondary analyses were conducted on the subset of PP patients. Sensitivity analyses were performed for the secondary outcomes adjusting for site, complexity, weight, and CPB time. For continuous outcomes, we log-transformed the secondary outcomes then fit a linear regression model and for the outcome of any AE, we fit a logistic regression model.

Sample Size Justification: We designed our study to have 90% power to detect a reduction of two allogenic blood product transfusions when assuming that the mean number of units in patients receiving cryoprecipitate was 7 with a standard deviation of 2.2 units in both arms. Using a two-sample t-test and performing a two-sided test with an alpha = 0.05 we found that 27 patients per arm were needed. We assumed approximately 10% of patients would be missing their primary outcome and enrolled 30 patients per arm.