Second-Line Uterotonics in Postpartum Hemorrhage: A Randomized Clinical Trial

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Biostatistical Analysis Plan

An a priori power analysis determined that enrollment of 37 patients per group would provide 80% power at a 2-sided alpha level of 0.05 to detect a 1-point difference, with estimated within-group standard deviation of 1.5, in mean uterine tone at 10 minutes after study drug administration using a two-sample t-test. Randomization of 100 patients was planned to account for protocol violations. Uterine tone at 10 minutes (primary outcome) and 5 minutes (secondary outcome) after study drug administration were compared between groups with adjustment for baseline tone and trial site using the generalized estimating equations (GEE) method with an identity link to account for the correlation between repeated measurements on the same patient. The primary analysis was a complete-case analysis, where 3 patients (3%) missing uterine tone at baseline and/or 10 minutes were excluded from the analysis. A multiple imputation sensitivity analysis was also performed which used the multivariate imputation by chained equations approach to impute missing uterine tone values using observed tone measurements (baseline, 5, and 10 minutes), parturient characteristics (age, race, BMI, parity), infant characteristics (number of fetuses, infant birth weight), trial site, interventions (randomized study drug, administration of second study drug, intraoperative transfusion), and outcomes (intraoperative blood loss, change in hematocrit from baseline to 24 hours post-delivery) to create 10 complete datasets. The primary outcome was compared in each of the 10 imputed datasets, and results combined using Rubin's rule.

All continuous secondary outcomes were initially assessed for the normality of residuals from a multivariable linear regression model with trial site and baseline uterine tone as covariates. Outcomes displaying normally distributed model residuals were analyzed using multivariable linear regression, with effect size presented as adjusted difference in means with 95% CI. Outcomes with all non-zero values that displayed skewed linear regression model residuals were natural log-transformed and analyzed using multivariable linear regression, with effect size presented as adjusted ratio of geometric means with 95% CI. Outcomes containing at least one zero value that presented skewed linear regression model residuals were compared between groups using multivariable quantile regression, with effect size presented as adjusted difference in medians with 95% CI.

All binary outcomes were initially considered for comparison using multivariable logistic regression (for single measurements) or generalized estimating equations with a logit link (for repeated measurements) with trial site and baseline uterine tone as covariates. If the multivariable regression converged, effect size was presented as adjusted odds ratios with 95% CI. If the model did not converge due to low incidence, groups were compared using a Fisher's exact test and effect size presented as risk difference with exact 95% CI.

Time to receive second study drug was compared between groups using a multivariable Cox proportional hazards model, with effect size presented as adjusted hazard ratio with exact 95% CI. Complete-case analysis was performed for all secondary outcomes. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).