A pilot trial to determine the effective dose of N-acetylcysteine for opioid reduction in patients undergoing spine surgery.

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Statistical Analysis Plan

An *a priori* sample size calculation was conducted to determine the precision of the estimated mean difference in opioid consumption at 12-hours between treatment groups in phase 2 for a fixed sample size. A sample size of 20 subjects per group was needed to estimate a 95% confidence interval for the mean difference in opioid consumption with a width of + 0.64 standard deviations from the mean.

The primary outcome of interest in phase 2 was opioid consumption at 12-hours postoperative. Additional opioid outcomes included opioid consumption over time (every 6 hours postoperatively up to 48 hours) and difference in opioid consumption between groups. Mean differences between treatment groups in opioid consumption at different postoperative times, including the primary outcome of 12 hours postoperative, were estimated from a linear mixed model including fixed effects for group, postoperative time, and their interaction and a random patient effect to account for correlation between measures collected on patients over time.

Descriptive statistics were calculated for patient and procedural characteristics across all treatment groups in phases 1 and 2. Additional phase 2 outcomes included time to first PACU opioid rescue dose, PACU VAS pain score, postoperative NRS pain scores, PACU duration, and time to hospital discharge. Descriptive statistics by treatment group were calculated to allow for comparisons between groups. Average NRS pain score over postoperative time within and between groups was estimated from a linear mixed model including fixed effects for treatment group, postoperative time at pain score measurement, and their interaction as well as a random subject effect to account for correlation between pain scores collected on the same patient over time. Confidence intervals for the median time to first opioid rescue dose was estimated using the Brookmeyer-Crowley approach using the log-log complement transformation.[23] Confidence intervals for the median PACU and hospital length of stay confidence limits are calculated using the distribution free approach described by Hahn and Meeker.[24] All analyses were conducted in SAS v. 9.4 (SAS Institute, Cary NC, USA).