Analgesics in the Pre-hospital Setting: Implications on Hemorrhage Tolerance - Ketamine

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Statistical Analysis Plan

Statistical analysis

The primary outcome variables are tolerance to the LBNP challenge with and without analgesic administration, as well as the hemodynamic and autonomic responses to the simulated hemorrhage insult. The effects of any specific drug on LBNP tolerance will be evaluated via a paired T-test (i.e., placebo versus drug). The enrolled subject will not be required to participate in the trials for all three drugs, but they will be required to complete both the placebo and drug trial for each specific drug. To determine which study drug is the least detrimental on tolerance to the simulated hemorrhagic insult, and thus would be recommended to be employed for a soldier experiencing a hemorrhagic injury, we will use one way ANOVA to compare the magnitude of reduction in LBNP tolerance between each drug and the respective placebo condition.

The effects of the administered drugs on hemodynamic and autonomic responses to each LBNP stage will be compared via two way mixed model ANOVA design, with main factors of drug and LBNP level (analyzed both by stage and by % completion of the entire LBNP protocol to pre-syncope). A significant interaction from those ANOVAs will be further explored via pairwise multiple comparison analyses.

Analysis assumptions will be carefully evaluated, data transformations considered, and Bonferroni-Hochberg will be used to adjust for multiple testing as appropriate.

Justification of sample size

No study has evaluated the effects of analgesics on LBNP tolerance in humans. The power and sample size estimates are based on findings from Dr. Crandall's laboratory showing reduced LBNP tolerance in the heat-stressed individuals. In that study heat stressed reduced LBNP tolerance by ~70% (997 cumulative stress index units to 303 cumulative stress index units; $P<0.001$). Though we expect the analgesics to likewise reduce LBNP tolerance, we do not anticipate as large of a reduction as that observed with heat stress. Thus, the sample size calculation was based upon an anticipated reduction in LBNP tolerance of half that seen with heat stress, i.e., ~35% reduction in the cumulative stress index. Given this anticipate outcome, coupled with the associated variances observed in that study (101), we anticipate 15 subjects per drug trial will be sufficient to address the primary hypothesis that the administered analgesic reduces tolerance to a simulated hemorrhagic insult, with a study power=0.80 at an adjusted alpha=0.015 to account for comparisons between drugs. That value was inflated to 30 subjects in total (15 male and 15 female) to permit a comparison in the primary responses between sexes for each of the administered drugs. That said, interim power analyses will be performed, with the number of required subjects adjusted based upon the variance of the obtained data.