Prehospital Intubation: Further Confounders in Trial Results

Iqbal Sayeed, Fahim Atif, Claudia Espinosa-Garcia, Bushra Wali, Nefize Turan, Seema Yousuf & Donald G. Stein

To cite this article: Iqbal Sayeed, Fahim Atif, Claudia Espinosa-Garcia, Bushra Wali, Nefize Turan, Seema Yousuf & Donald G. Stein (2018): Prehospital Intubation: Further Confounders in Trial Results, Prehospital Emergency Care, DOI: 10.1080/10903127.2017.1402111

To link to this article: https://doi.org/10.1080/10903127.2017.1402111

Published online: 19 Jan 2018.
Dear Editor,

In “Prehospital Intubation is Associated with Favorable Outcomes and Lower Mortality in ProTECT III,” Denninghoff et al. (1) evaluated the relationship between prehospital intubation, functional outcomes, and mortality using data from the patients enrolled in the ProTECT III multicenter, randomized, double-blind, placebo-controlled trial of early administration of progesterone after traumatic brain injury (2). The authors report that prehospital intubation and air medical transport together were associated with much more favorable outcomes and lower mortality. This observation is interesting and potentially very important for improving emergency services in the field, but their findings also raise concerns regarding how the factors examined in this study may have modified the outcomes of the ProTECT III trial.

As far as we can discern, Denninghoff et al. retrospectively analyzed morbidity, mortality and functional outcomes from patients enrolled in ProTECT III regardless of whether they received progesterone treatment or placebo (1). The paper accounts for many of the characteristics of patients at baseline (age, sex, race, cause of injury, method of transport, Index GCS at randomization, injury severity, and Rotterdam CT classification), but fails to indicate which patients were in the treatment group and which got placebo. We think that the effect of progesterone treatment could be impacted by the salutary effects of prehospital intubation coupled with method of transport to the hospital or vice versa. In the original clinical trial report (2), the authors summarized factors that could have contributed to the negative results obtained with progesterone, but we could not find mention of the fact that 39.6% (349 out of 882) of patients were intubated prior to hospitalization and the other ∼60.4% were not. Furthermore, some of the intubated patients would have received progesterone or placebo while others did not.

As the trial authors themselves noted (2), the negative findings of the ProTECT III clinical trial were affected by several critical problems in how the study was done. The current results on the important and beneficial effects of pre-hospital intubation on patient mortality and functional outcome now add to the growing list of potential confounds that could have masked any effects of the progesterone treatments given post-injury. This may be especially important as “different EMS systems were allowed to intubate or not based on their standard treatment protocols” (1). Furthermore, Denninghoff and colleagues noted that a number of drugs can be given with intubation that could interact with progesterone treatment and affect progesterone’s agonist activity, receptor binding, genomic regulation, and clearance (1). These agents include lidocaine, fentanyl, etomidate, ketamine, propofol, succinylcholine, and rocuronium, among others that could have been used depending on the...
prehospital and in-hospital emergency services (3). Moreover, the paper states that “randomization was performed with the use of a combination of minimization and biased coin algorithms to avoid imbalances in initial injury severity, sex, age, and enrollment site” (1). However, it is not clear whether randomization was also performed according to pre-hospital intubation and method of transport. What we have learned from this paper is that, in designing and interpreting clinical trials (in addition to dose and duration of treatment) and outcome measures (4,5), greater scrutiny must also be given to other potentially critical prehospital factors (e.g., intubation and air vs. ground transport) that could affect patient enrollment criteria and patient response to postinjury treatments.

References