Randomized Controlled Trial of Negative Pressure Ventilation

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Randomized Controlled Trial of Negative Pressure Ventilation: We First Need Characterized Physiology

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Respiratory support for children with (impending) acute respiratory failure (ARF) is intimately linked with our daily practice in PICUs across the globe. Implicit with this practice is the impression that practitioners are trusted experts or even geniuses when it comes to mechanical ventilation (MV). Rather disappointingly, however, much of what we do is based on personal preferences, education, institutional beliefs, or heavily borrowed from MV in adults, signifying the lack of personal equipoise. It appears that the interpretation of equipoise has shifted from traditionally being defined as a state of genuine uncertainty on the relative benefit of either of two approaches being compared in a trial to a representation of uncertainty within the medical community (1). In the absence of randomized controlled trials (RCTs), researchers often resort to existing PICU registries in an attempt to identify a relationship between a specific intervention and outcomes (2).

In this issue of *Pediatric Critical Care Medicine* (PCCM), Moffit et al (3) see to address the use of negative pressure ventilation (NPV) in modifying outcome of impending ARF. The authors studied a cohort in the Virtual Pediatric Systems, LLC database and in light of their observations, they now call for the creation of a national registry of NPV to help better understand safety and efficacy of NPV. In the accompanying PCCM viewpoint, Rotta (4) argues in support for such a registry as a vehicle to better design future RCTs of NPV. From one point of view, this call makes sense because retrospective database studies—irrespective of whether the data are collected "prospectively"—often lack a priori hypotheses, and hence the more granular physiologic data underpinning physician choices as well as clinical reasoning why NPV was used are absent (5). When such important information is missing, secondary analyses are at-risk of confounding by indication (6). Of note, confounding by indication can only really be overcome by randomization. Alternatively, propensity score matching can be used to account for covariates that predict receiving the intervention.

Therefore, perhaps a registry with specific data collection is a good idea. But, surely, better still is the idea of a RCT. However, when thinking about designing RCTs, it is important to identify if there really is an important clinical problem that needs to be addressed. It is fair to say that NPV is not a commonly accepted intervention in pediatric ARF (3, 4). Moffit et al (3) report that NPV appeared to be used rarely except for one site contributing most patients to the database. Thus, the question of whether NPV modifies patient outcomes does not appear to be an issue that most PICU practitioners struggle with.

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Perhaps, more importantly, we need to decide if the goal of any future study is to show efficacy or efficiency (7). If the primary goal is to understand the mechanism of action underlying a particular intervention, a RCT should be designed as an explanatory study completed under ideal study conditions. In contrast, if the desired outcome is, for example, a reduction in PICU length of stay, then the RCT needs to be designed as a pragmatic study completed under real-world conditions. It is not possible to design a trial that can detect both efficacy and effectiveness, simultaneously. Last, we should be also aware that an inadequately carried out trial in something as complicated as use of NPV may actually be a test of the operator rather than of the intervention if underpinning physiology is not taken into consideration (8, 9). For example, consider one of the studies of tidal volume in MV of adults with acute respiratory distress syndrome: higher mortality was observed in patients assigned to receiving a tidal volume that would not have been selected by the bedside treating team based on their understanding of the patient's known pulmonary compliance (10).

Taking all of the above together, three statements or questions arise when we consider future investigation of NPV in the PICU. How will another database or registry study help? We should not abandon RCTs, but do we know enough about NPV to plan one? Given the paucity of data, should we first identify biological/physiologic mechanisms before testing this potential therapy?

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