Intensive Care Med (2008) 34:1743–1745
DOI 10.1007/s00134-008-1194-5

EDITORIAL

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Tracheostomy timing, enrollment and power in ICU clinical trials

Received: 6 May 2008
Accepted: 7 May 2008
Published online: 1 July 2008

This editorial refers to the article available at doi:10.1007/s00134-008-1195-4.

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Tracheostomy is provided to between 5 and 11% of patients requiring mechanical ventilation, accounting for 26% of all ventilator days and 14% of all hospital days [1, 2]. The procedure has several theoretical advantages over continued endotracheal intubation, including the potential to improve patient comfort and communication, decrease sedation requirements, and facilitate liberation from mechanical ventilation [3]. However, tracheostomy is not without risk. A strategy of prolonged intubation may allow for many patients to be successfully liberated from mechanical ventilation without the potential for adverse events that are associated with the procedure [4]. These concerns result in an ongoing debate about the optimal timing of tracheostomy in the intensive care unit (ICU). Indeed, randomized trials in this area show mixed results [5], and wide variations in practice patterns persist [6].

In this issue of *Intensive Care Medicine*, Blot et al. [7] published the results of a randomized clinical trial designed to answer some of these questions. The trial enrolled patients from 25 ICUs in France expected to require at least 7 days of mechanical ventilation. Eligible patients were randomized to either early tracheostomy, in which the procedure was performed within 4 days following onset of mechanical ventilation, or prolonged laryngeal intubation, in which no tracheostomy was performed for at least 14 days. The study incorporated several important features to reduce bias, including recommendations for standard approaches to weaning and sedation, and systematic surveillance for infectious and procedural complications. However, no differences between groups were observed for the primary endpoint of 28-day mortality (hazard ratio 1.17, 95% confidence interval 0.63–2.17) or for the secondary endpoints of duration of mechanical ventilation, duration of ICU stay, and major infectious complications.

The study's inability to detect a statistically significant mortality difference is not surprising. The trial was originally designed to detect a 13% absolute mortality risk reduction in 470 patients, equivalent to a number needed to treat of about 8 patients to prevent one death. Although one small trial hinted at such an optimistic effect size [8], a mortality reduction of this magnitude would imply that this procedure is more effective than nearly every other established ICU treatment, including lung-protective ventilation for acute lung injury (number needed to treat ≈ 11) [9] or activated protein C for severe sepsis (number needed to treat ≈ 16) [10]. It seems unlikely that tracheostomy would result in a benefit of this magnitude. Additionally, slow recruitment necessitated that the trial be stopped early after enrolling only 123 patients, and baseline mortality was much lower than expected. As a

result the trial was vastly underpowered to detect anything but huge mortality differences. For example, to detect a similar relative risk reduction with the same power and alpha error would have required about 1,230 patients, or ten times the actual enrollment.

Research into optimal tracheostomy timing is undoubtedly a difficult undertaking [11]. Observational studies can be used to compare earlier to later tracheostomy (or to no tracheostomy) in large groups of patients with relatively little costs. Yet these studies must employ sophisticated analytical techniques to control for confounding, indication bias, and potential survivor treatment biases [12, 13]. Alternatively, a randomized clinical trial can prospectively allocate patients to different tracheostomy strategies, ensuring that differences between patient groups are due to chance rather than systematic bias. As evidenced in the study by Blot and colleagues, however, this approach also has inherent problems. Despite the investigator's best and honest efforts, enrollment was extremely slow, with less than 20% of screened patients ultimately enrolled. Predicting the need for prolonged ventilation proved to be a difficult task, and the authors cite this obstacle as the main reason for low enrollment. Additionally, many physicians may have been unwilling to subject the tracheostomy decision to random chance, akin to enrollment problems encountered in other trials of invasive ICU procedures [14].

Even if the study had reached its target enrolment, it seems improbable to us that early tracheostomy would substantially alter mortality rates. Any mortality benefit would likely occur though reductions in ICU complications stemming from decreased exposure to mechanical ventilation and sedating medications. Differences in these endpoints would not be expected to impact overall mortality when other proven routine care practices are in place [9, 15, 16]. More plausible primary endpoints for future study include duration of mechanical ventilation, ventilator associated pneumonia, and patient comfort. The study by Blot and colleagues did show slightly improved comfort ratings in the tracheostomy group, but these measurements were limited to slightly more than half of the total sample size. Future trials should include more rigorous evaluation of comfort-related endpoints such as mobility, sedation and analgesia requirements, patients' ability to communicate, emotional and neuro-cognitive sequelae, and family satisfaction.

Routine tracheostomy in mechanical ventilation is likely to become more common in future years as more physicians choose a percutaneous approach over an open surgical procedure [17]. Questions concerning the optimal timing of tracheostomy remain, and additional trials are ongoing [18]. Although this study does not settle the debate, it does offer an important lesson about conducting clinical trials of invasive procedures in the ICU. Patient enrollment will be challenging if physicians lack equipoise, if the indications for the procedure are controversial, or if determining eligibility involves making predictions about a patient's future clinical status. In the case of tracheostomy, patient enrollment was difficult for all these reasons. Ultimately, slow enrollment and lower than expected baseline mortality produced a trial that was underpowered to detect meaningful differences in any clinically relevant endpoint.

Clinical trials in the ICU represent an enormous investment of time and resources, and indeterminate results have implications that transcend the disappointment of the well-intentioned investigators. Patients and families who enroll in clinical trials assume potential risks with the understanding the knowledge generated in the trial will help future patients [19]. It is essential that any future clinical trials of tracheostomy be adequately powered to detect clinically important differences in patient-centered outcomes, and not just contribute indirectly to future health care benefits [20]. Perhaps the greatest lesson of this study is not what it tells us about the optimal timing of tracheostomy, but what it tells us about how we should conduct future trials in this important and vulnerable patient group.

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