Dealing With Deaths in Clinical Trials and Meta-Analyses

Gutiérrez-Arias et al[1] undertook an interesting and highly relevant review into the potential efficacy of neuromuscular electrical stimulation to reduce mechanical ventilation duration for patients who are critically ill. The authors should be commended for the amount of work that obviously went in to this review. However, research in the ICU is fraught with difficulty, with high death rates and study participants not reaching primary end points, which typically results in missing data. In taking a study that looks at the use of neuromuscular electrical stimulation to reduce mechanical ventilation duration as an example, in which the intervention period has a fixed duration, the participants who do not reach an end point (in this case, liberation from mechanical ventilation) by the end of the study would normally be treated as censored, that is, they did not wean from mechanical ventilation within the intervention period. Dealing with deaths in a study is more difficult. One option is to also censor these participants when estimating the risk of being liberated from ventilation (and, conversely, to estimate the risk of death). This would result in a cause-specific hazard analysis. Although this approach can be suitable, it is important to note that it assumes that the risks are independent. The fact that a participant has reached one end point is treated as uninformative for the risk of an alternative end point.

Alternatively, the approach of subdistribution hazards by Fine and Gray[2] can be used to handle competing risks. Compared with the censoring approach, this method does not treat the competing events as censoring but instead includes these observations in the "at-risk" group. This can be understood as considering the (hypothetical) risk of a person being liberated from mechanical ventilation if the first event (death) had not occurred. The approach by Fine and Gray[2] is problematic in the context of a causal analysis but tends to give better predictions than censoring.[3] Which type of analysis is more appropriate depends on the context and aims. Both methods can produce misleading results if the model is misspecified, that is, if not all relevant risk factors are included in the model, especially if they affect multiple outcomes.

The scale of the problem of death in ICU studies is highlighted in the recently published study by Gutiérrez-Arias et al.[1] In one of their included studies, that by Routsi et al,[4] 50 of the 142 participants (35.2%) randomized to the study died. Neither Gutiérrez-Arias et al[1] nor the authors of the studies reported in the meta-analysis adopted the approach of censoring or subdistribution hazards to account for the proportion of the participants who were either not liberated from mechanical ventilation or died during these studies. Instead, all of these participants were excluded from the analysis. As such, the reporting of the studies in the meta-analysis by Gutiérrez-Arias et al[1] is inherently biased, with results only reported for those who were liberated from mechanical ventilation. We suggest that the use of a shared parameter model for the meta-analysis would help to reduce the bias due to competing risks.[5]

It should also be noted that there are a number of reporting errors in the article of Gutiérrez-Arias et al.[1] When considering the mechanical ventilation duration in the intervention and control groups for the study conducted by Dall'Acqua et al,[6] the mean ventilation duration for the experimental group is incorrectly reported as 10 days, as opposed to the 7 days reported in the original article. By following the reporting method used by Gutiérrez-Arias et al,[1] this correction would further strengthen the significance of the effect of neuromuscular electrical stimulation to reduce mechanical ventilation duration, which the authors currently describe as very weak. It should also be noted that the *P* value for the study by McCaughey et al[7] is incorrectly reported at .40, rather than .04. We hope that this letter provides some insight into how to deal with competing risks in clinical trials, and thank Gutiérrez-Arias et al[1] for their interesting article.

Euan J McCaughey
Neuroscience Research Australia
Randwick, New South Wales, Australia

School of Medical Sciences
University of New South Wales
Kensington, New South Wales, Australia

Queen Elizabeth University Hospital
Glasgow, Scotland

Peter Humburg
Neuroscience Research Australia
Randwick, New South Wales, Australia

Mark Wainwright Analytical Centre
University of New South Wales
Kensington, New South Wales, Australia

Angus J McLachlan
Liberate Medical LLC
Crestwood, Kentucky

Correspondence: Euan J McCaughey MEng PhD CEng, Neuroscience Research Australia, 139 Barker St, Randwick, New South Wales 2031, Australia. E-mail: e.mccaughey@neura.edu.au

REFERENCES

1. Gutiérrez-Arias RE, Zapata-Quiroz CC, Prenafeta-Pedemonte BO, Nasar-Lillo NA, Gallardo-Zamorano DI. Effect of neuromuscular electrical stimulation on the duration of mechanical ventilation. Respir Care 2021;66 (4):679-685.
2. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94 (446):496-509.
3. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. Am J Epidemiol 2009;170(2):244-256.
4. Routsi C, Gerovasili V, Vasileiadis I, Karatzanos E, Pitsolis T, Tripodaki E, et al. Electrical muscle stimulation prevents critical illness polyneuromyopathy: a randomized parallel intervention trial. Crit Care 2010;14(2):R74.
5. Thom H, López-López JA, Welton NJ. Shared parameter model for competing risks and different data summaries in meta-analysis: implications for common and rare outcomes. Res Synth Methods 2020;11(1):91-104.
6. Dall' Acqua AM, Sachetti A, Santos LJ, Lemos FA, Bianchi T, Naue WS, et al. Use of neuromuscular electrical stimulation to preserve the thickness of the abdominal and chest muscles of critically ill patients: a randomized clinical trial. J Rehabil Med 2017;49(1):40-48.
7. McCaughey EJ, Jonkman AH, Boswell-Ruys CL, McBain RA, Bye EA, Hudson AL, et al. Abdominal functional electrical stimulation to assist ventilator weaning in critical illness: a double blinded, randomised, sham-controlled pilot study. Crit Care 2019;23(1):261.

The authors respond

I sincerely thank Dr McCaughey and his collaborators for their interest in our work.[1] With respect to your comments, I agree that it is problematic to adequately estimate the risks of favorable or unfavorable events when the different outcomes are related and, rather, when the probabilities of their occurrence compete with each other, as you have well exemplified with respect to mortality and liberation from mechanical ventilation. Furthermore, I agree that our results are applicable only to the population that finally achieved liberation from invasive mechanical ventilation, which does not mean that such estimations of the difference in mechanical ventilation duration between the group of subjects who were critically ill and who received neuromuscular electrical stimulation and the control or sham neuromuscular electrical stimulation group is biased but rather responds to a different and more specific research question.

It would be interesting to consider using a shared parameter model[2] to estimate the risk of "suffering" of a specific event through a meta-analysis, as you suggest, as opposed to an intervention research question, which involves a "risk competition." For this, randomized clinical trials included in a meta-analysis should consider among their outcomes the evaluation of the incidence of these events at a fixed follow-up time, such as mortality versus liberation from invasive ventilation at day 28 from the start of ventilatory support. In this way, the relative risks of dying and achieving liberation from invasive ventilation could be estimated for a given follow-up. Therefore, future systematic reviews that seek and can conduct meta-analyses according to the data available in the included randomized clinical trials could adequately estimate the risk of different outcomes at a given time[2] (categorical variables, such as death, liberation of mechanical ventilation, discharge from the ICU at a given time),

and also establish the effect of an intervention on quantitative outcomes, such as the ICU length of stay or the duration of invasive ventilation, thus providing a more complete picture of the landscape studied.[2]

However, it should be noted that the determination of a single quantitative estimator, such as "time on mechanical ventilation," is not free of problems that can introduce biases in this estimation, as was detected in our work.[1] This is the case of the study by Routsi et al[3] due to the large loss of participants, as you rightly point out, and which we did consider because we rated the risk of bias arising from attrition as high.[4] In any case, it should be considered that, although the losses were high in the study by Routsi et al,[3] they were balanced between the groups (66% in the intervention group and 61% in the control group), which could have an impact on the estimation of the risk of discontinuation of mechanical ventilation within the groups rather than on the difference in risk between the groups, thanks to the random assignment of the participants to the different groups.

Finally, and regretting the inaccuracy in the data extracted from the study by Dall'Acqua et al[5] and in the reporting of the statistical significance value of the study by McCaughey et al[6] (not included in our meta-analysis), I reaffirm our conclusion of the effect of neuromuscular electrical stimulation on the duration of mechanical ventilation,[1] because, although the mean difference changes slightly when all studies are considered (mean difference −2.83 [95% CI −3.88 to −1.78] d), the "low certainty of evidence" rating for the totality of studies was not determined by such mean difference, together with its 95% CI (input to assess imprecision and inconsistency within the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach,[7] but, due to the very serious risk of bias of the included studies, mainly derived from problems in the generation and concealment of the random sequence.

Ruvistay E Gutiérrez-Arias
Critical Care Unit
Instituto Nacional del Tórax
Santiago, Chile
Escuela de Kinesiología
Facultad de Ciencias de la Rehabilitación
Universidad Andres Bello
Santiago, Chile

Correspondence: Ruvistay E Gutierrez-Arias PT MSc, Critical Care Unit, Instituto Nacional del Tórax, José Manuel Infante 717, Providencia, Santiago 750000, Chile. E-mail: rgutierrez@torax.cl

REFERENCES

1. Gutiérrez-Arias RE, Zapata-Quiroz CC, Prenafeta-Pedemonte BO, Nasar-Lillo NA, Gallardo-Zamorano DI. Effect of neuromuscular electrical stimulation on the duration of mechanical ventilation. Respir Care 2021;66(4):679-685.

2. Thom H, López-López JA, Welton NJ. Shared parameter model for competing risks and different data summaries in meta-analysis: implications for common and rare outcomes. Res Synth Methods 2020;11(1):91-104.

3. Routsi C, Gerovasili V, Vasileiadis I, Karatzanos E, Pitsolis T, Tripodaki E, et al. Electrical muscle stimulation prevents critical illness polyneuromyopathy: a randomized parallel intervention trial. Crit Care 2010;14(2):R74.

4. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

5. Dall' Acqua AM, Sachetti A, Santos LJ, Lemos FA, Bianchi T, Naue WS, et al. Use of neuromuscular electrical stimulation to preserve the thickness of abdominal and chest muscles of critically ill patients: a randomized clinical trial. J Rehabil Med 2017;49(1):40-48.

6. McCaughey EJ, Jonkman AH, Boswell-Ruys CL, McBain RA, Bye EA, Hudson AL, et al. Abdominal functional electrical stimulation to assist ventilator weaning in critical illness: a double-blinded, randomised, sham-controlled pilot study. Crit Care 2019;23(1):261.

7. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336(7650):924-926.