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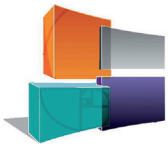

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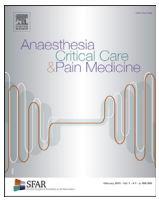

Editorial

How to improve research on management of critically ill patients: Lessons learned from negative randomised clinical trials in the intensive care unit

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Currently, the standard of care in intensive care medicine should be based in well-designed, larger scale, multinational randomised trials focused on improving clinically relevant outcomes. Unfortunately, fewer than 20% of recommendations in clinical practice guidelines are supported by randomised controlled trials [1]. Moreover, observational cohort studies, which are used to develop recommendations, often overestimate potential benefits, particularly when end-points are physiological variables or biomarkers, rather than pre-defined meaningful clinical outcomes [2].

During the 1990s, potential life-saving therapeutic strategies, such as early goal-directed therapy or lung recruitment manoeuvres, were introduced in intensive care medicine because they were thought to benefit patients, despite the weak evidence to support many of these interventions. The example of the Rivers et al. [3] trial, in which the survival benefit of early goal-directed therapy in the treatment of severe sepsis and septic shock could not be confirmed by subsequent trials, illustrates the difficulty to produce recommendations in critical care guidelines. Moreover, observational cohort studies usually ignore adverse events [4], as was demonstrated in studies of nebulisation of antimicrobials in mechanically ventilated subjects. Similarly, recent well-designed trials have discouraged the use of recruitment manoeuvres as a general measure of rescue therapy in patients with acute lung injury or acute respiratory distress syndrome (ARDS), as one strategy does not fit all patients [5]. Interestingly, Constantin et al. [6] tested whether a mechanical ventilation strategy that was personalised to individual patients' lung morphology would improve the survival of patients with ARDS when compared with standard of care and found that personalisation of mechanical ventilation did not decrease mortality in patients with ARDS, possibly because of the misclassification of 21% of patients among other potential explanations. This finding highlights that all patients with ARDS are not the same and that different phenotypes for lung morphology of lung inflammation need to be considered when setting the mechanical ventilator [7].

Observational studies have demonstrated an association between vitamin D deficiency and increased risk of mortality and morbidity in mechanically ventilated patients. Cohort studies and pilot trials have suggested potential benefit effects of vitamin D supplementation in critically ill patients with severe vitamin D deficiency. Recently, the 2019 ESPEN guidelines [8] recommended vitamin D3 supplementation in critically ill patients with low plasma levels, with an agreement of 86% of experts. The proof of efficacy of this approach is still awaited, but it is clearly not supported by the findings from the VIOLET trial [9]. This recent randomised, double-blind, placebo-controlled trial which enrolled 1360 patients, found that early vitamin D3 supplementation in critically ill patients with low plasma levels, in the form of single high-dose vitamin D3, did not provide an advantage over placebo (and that it can even be deleterious in the subgroups with sepsis or ARDS) with respect to 90-day mortality or other non-fatal outcomes, among critically ill vitamin D-depleted subjects. However, we argue that this well-executed study did not focus on the appropriate population of severely vitamin D-deficient patients. The study population was not very ill as evidenced by a SOFA score ≤ 5 in half of the patients. Only 8% of the cohort at high risk for ARDS, effectively had ARDS, and only 4% developed new ARDS within 7 days. Furthermore, the intervention (one bolus of 540.000 IU of vitamin D3) could have been insufficient, as 25% of subjects who received high-dose vitamin D did not respond with a plasma 25 (OH)D $\geq$ 30 ng/ml at day 3. Hence, the clinically relevant closely related research questions "Does a severe vitamin D deficiency represent a potentially modifiable risk factor" and "Is supplementation with sufficient doses of vitamin D in severely deficient patients an efficient secondary prevention?" are left unanswered. Hopefully, the ongoing multicentre European VitDalize trial [10] will reliably answer these important issues.

The first implication of these observations is the need to use innovative research strategies, such as network meta-analyses and adaptive platform trials (APTs), which are potential tools to overcome methodological flaws of randomised clinical trials. In APTs, researchers should be able to allocate a patient to different

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treatment options and analyse the difference between two different interventions, provided that severity of illness, comorbidities and other therapeutic interventions are equally distributed between different study arms [11].

The second implication is that therapeutic interventions may have a different impact on outcomes depending on severity of illness. This helps in the interpretation of contradictory findings of studies on adjunctive therapy with corticosteroids in community-acquired pneumonia [12]. Thus, it is important in the design of RCT in critical care to guarantee that patients enrolled are adequately selected, for instance, based on severity of illness or multi-organ dysfunction when necessary. The need is to focus on patients who are proper candidates, e.g. severely ill, and not on those who can only get small benefit.

The third implication is the need to develop personalised medicine. Due to the heterogeneity of phenotypes, the same intervention may be of benefit for some phenotypes, indifferent for others and even harmful for a different subgroup. Artificial intelligence and machine learning have been of help to identify different phenotypes in ARDS or sepsis, which would explain contradictory trials regarding administration of activated protein C or PEEP setting depending on the degree of inflammatory response manifested by different individuals in ARDS or sepsis [5]. Similarly, data sciences applied to large observational databases could help understanding and improving the management of ventilated patients. Mechanically ventilated critically ill patients continuously generate huge volumes of complex data. Medical monitors and devices connected to a patient generate millions of data points per day and represent real ICU-world data. These are potentially very interesting and useful, but still underexploited nowadays, which precludes the discovery of new physiologic patterns to support complex diagnosis or predict potentially dangerous events or outcome [14,15]. The ultimate step should be the implementation of personalised medicine to critical care management, based on theragnostic methodology [4,13].

In summary, the current, often limited understanding of pathophysiology is often associated with a lack of progress in clinical trials, such as the VIOLET trial reporting the effects of early, high-dose vitamin D3 supplementation for critically ill vitamin D-deficient patients [9]. These findings partially reflect the complexity of the ICU patient, the impact of the underlying disease (and severity of illness) on outcomes and the insufficient appreciation of the heterogeneity of the cohorts. Consequently, more patient-specific approaches need to be developed with subsequent implementation of individualised interventions in clinical management, based on measurable biomarkers or specific phenotypes.

Disclosure of interest

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