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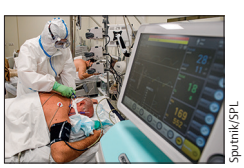
Awake prone positioning in COVID-19: is tummy time ready for prime time?

Prone positioning reduces mortality in moderate to severe acute respiratory distress syndrome requiring invasive mechanical ventilation.[1,2] Before COVID-19, evidence supporting prone positioning for awake non-intubated patients with hypoxaemic respiratory failure was limited to small case series.[3] Early in the COVID-19 pandemic, use of awake prone positioning (or so-called tummy time) to avoid intubation quickly gained traction in the media.[4] Several observational studies reported that prone positioning improved oxygenation in awake non-intubated patients with COVID-19.[5,6] Globally, many health-care jurisdictions adopted awake prone positioning for COVID-19, despite no high quality evidence from randomised controlled trials of improved clinically meaningful outcomes, including invasive mechanical ventilation or mortality. Of note, the Surviving Sepsis Campaign Guidelines highlighted this equipoise, stating that there was insufficient evidence to recommend awake prone positioning for COVID-19.[7]

In the *Lancet Respiratory Medicine*, Stephan Ehrmann and colleagues[8] report a meta-trial on awake prone positioning to reduce intubation or death in patients with COVID-19. The meta-trial pooled individual patient-level data from six independent randomised controlled trials with harmonised eligibility criteria, randomisation procedures, and outcomes. 1126 patients with COVID-19 and hypoxaemic respiratory failure from six countries were randomly assigned to either awake prone positioning or standard care. The composite primary outcome was treatment failure (either intubation or death within 28 days). Composite outcomes generally are controversial, with misplaced belief that combining events will increase power, and such outcomes ignore additional problems that treatment effects across components might be unequal in magnitude and importance. However, Ehrmann and colleagues' two outcomes are reasonable and clinically meaningful: awake prone positioning reduced treatment failure (relative risk 0·86, 95% CI 0·75–0·98), primarily driven by a reduction in intubation (Hazard ratio [HR] 0·75, 95% CI 0·62–0·91), compared with usual care, with strong overlap between the components (almost three quarters of deaths were preceded by intubation).

This novel meta-trial study design has several notable strengths. It is more efficient, cheaper, and quicker to initiate than a single multinational trial.[9] These advantages are particularly important during a pandemic, and the authors deserve praise for their innovation and organisation to rapidly answer this important clinical question. However, the study was necessarily open (unblinded). Therefore, to minimise potential bias in primary outcome assessment, they used a composite of all-cause mortality (which was completely objective) and need for intubation (by standardising the potentially subjective criteria for intubation). The study used a group sequential design, using a Kim-DeMets alpha spending function to reduce the chance of a false positive treatment effect with multiple interim analyses, scheduling four of them and permitting early stopping. The study did indeed terminate for benefit at the third scheduled interim analysis, planned for 600 participants with complete



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follow-up to 28 days for primary outcomes (which, with a 60–70% event rate, would be triggered at about 400 primary events observed). However, the actual third interim analysis used 928 patients, with an observed event rate of only 45% (about 400 events). Therefore, the analysis took place roughly on schedule by information and time (driven by events), which is what matters statistically. By study close, the final analysis included 1126 participants. This number illustrates the challenges of successfully implementing such adaptive designs, in which recruitment and event rates can well deviate from assumptions, necessitating corrective actions. In Ehrmann's study, there was additional heterogeneity of six simultaneously but independently conducted trials, proceeding at their own pace. It is very encouraging to see such a design successfully implemented.

There is natural curiosity regarding optimal duration and frequency of prone positioning. This meta-trial was not designed to assess dose-response effect (usually determined in earlier phase 2 efficacy studies, with different prone sessions randomised). The target duration varied between trials, but the overall protocol goal was to maintain prone positioning for as long as possible, ideally for 16 h or more daily. Here, the observed mean prone duration did vary considerably across trials, but any differences could be confounded by patient and site characteristics. Therefore, the authors refrained from presenting non-randomised analyses. Nonetheless, with those important caveats in mind, the raw data here suggest that longer duration of prone positioning might be more beneficial, supported by two observations. 25 (17%) of the 151 patients who proned for at least 8 h had treatment failure versus 198 (48%) of 413 patients who proned for less than 8 h. This is similar to the proportion (257 [46%] of 557 patients) who had overall treatment failure in the control group. Secondly, given no statistical heterogeneity in overall effect (six trials, I^2=0%, 95% CI 0–69), there is apparent effect size variation with prone duration within the three larger individual trials (Mexico [n=430], France [n=402], and USA [n=222]; 94% of all patients]. The largest effect (Mexico; RR 0·78, 95% CI 0·63–0·96) had the highest prone duration (mean 9·0 h [SD 3·2]), whereas lower effects in France (RR 0·97, 95% CI 0·77–1·23) and USA (0·92, 0·68–1·26) had lower durations (mean 2·9 h [SD 2·9] and 4·4 h [4·7], respectively).

Does wide variation in awake prone positioning duration reflect different patient populations, socio-cultural factors, or institutional factors that modify ability to prone, or the medical centre's ability to adhere to study protocols? Although longer prone duration might better avoid intubation, prone duration might simply be a confounder, whereby sicker patients maintain shorter prone durations due to their illness severity. Many factors influence ability to lie prone, including age; cognitive impairment; body size; comorbidities; comfort; illness trajectory; and caregiver's encouragement, prompting, and repositioning support. Most observational studies have also found that few patients could lie prone for more than 8 h.[3] A pilot feasibility trial reported intolerance by four of six patients of a standardised prone positioning intervention deemed the intervention, and most nursing staff deemed the intervention not feasible.[10] 96% in the meta-trial were in intensive or intermediate care units, and not on general medical wards with less favourable nursing-to-patient ratios. Future studies should identify effective strategies to optimise prone duration at the hospital, nursing unit, and patient level.

These findings could directly impact patient care during future COVID-19 waves. There are several other large trials of awake prone positioning, either ongoing (NCT04402879) or recently completed (NCT04383613, NCT04350723). Despite the meta-trial size, additional data are needed to confirm these findings and provide further insights into feasibility and effectiveness of awake prone positioning in different populations (eg, on general wards or those with do-not-intubate goals of care). In Ehrmann and colleagues' study,[8] the number needed to treat with awake prone positioning to prevent one intubation was 14, which is impressive for such a safe intervention in a population with acute disease. Caution is needed however: the fragility index[11] is 5, meaning that if only five fewer control patients had treatment failure, the results would have been no longer statistically significant. More trials, more data, and more patients could change the direction, magnitude, and precision of the estimated effect, especially since the meta-trial positive results appear driven by one large trial (Mexico) with the longest mean prone duration. Nevertheless, this important study reinforces the safety and probable utility of awake prone positioning for averting intubation, which will reassure those already

using it and might persuade critics that tummy time is probably worth a try.

JW is co-principal investigator of the CORONA trial (NCT04402879). KKSP is co-principal investigator of the CORONA trial (NCT04402879). JN declares no competing interests.

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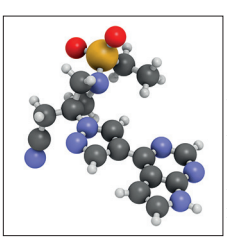
Baricitinib: the first immunomodulatory treatment to reduce COVID-19 mortality in a placebo-controlled trial

Antibacterial, antifungal, antiviral, and antiparasitic treatments developed in the past century have improved survival outcomes, even in high-mortality conditions such as sepsis, a condition that is mostly caused by bacteria but can also be due to other infections. In the 21st century, of all therapies that have improved the outcomes of patients with sepsis, the appropriate and early administration of antibiotics has been shown to be the most effective therapy to save lives.[1] However, despite highly effective antibiotics that can kill microorganisms causing sepsis, and cultures showing eradication of these organisms, overall mortality from the condition remains high. In part, this high mortality might be explained by dysregulated immune responses arising from redundant pathways in the human immune system, which have developed—along with the array of defensive mechanisms involving the innate and adaptive responses, inflammation, and coagulation—as a result of the selective pressure of thousands of years of exposure to infections, zoonoses, and resulting epidemics and pandemics. This dysregulated immune response can be as harmful as, or more harmful than, the pathogens themselves.[2] Accordingly, two original studies showed significant reduction in mortality due to sepsis among solid organ transplant recipients compared with patients without transplants.[3,4] This finding suggests that immunosuppressive drugs, required lifelong to avoid transplant graft rejection, might have been protective by decreasing dysfunctional responses to sepsis. These lessons learned from bacterial sepsis are highly relevant in the context of COVID-19.

Although one antiviral, remdesivir, has already shown significant clinical benefits in hospitalised patients with COVID-19,[5] death from COVID-19 can occur because of a dysregulated immune response (akin to sepsis despite the use of effective antibiotics). This fact poses the question of whether any host immune interventions could improve the survival of patients with COVID-19. Again, similar to bacterial sepsis, studies evaluating steroid use in COVID-19 have produced both positive and negative results. However, the only positive study was an open-label trial,[6] and no placebo-controlled double-blind studies have shown positive results to date.

Another immunomodulatory approach that has been evaluated is the use of Janus kinase (JAK) inhibitors. Baricitinib, an inhibitor of JAK1 and JAK2, has been appraised in artificial intelligence and mechanistic laboratory studies and human clinical trials, with multiple



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