# Awake prone positioning in COVID-19

# Awake prone positioning for hypoxemic respiratory failure in COVID-19: is “tummy time” ready for prime time?

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Prone positioning reduces mortality in moderate-severe Acute Respiratory Distress Syndrome requiring invasive mechanical ventilation.[1,2] Prior to COVID-19, evidence supporting prone positioning for awake non-intubated patients with hypoxemic respiratory failure was limited to small case series.[3] Early in the COVID-19 pandemic, using awake prone positioning, (or "tummy time"), to avoid intubation quickly gained traction in the media.[4] Several observational studies reported prone positioning improved oxygenation in awake non-intubated COVID-19 patients.[5,6] Globally, many health care jurisdictions adopted awake prone positioning for COVID-19, despite no high quality randomized control trial evidence demonstrating improved clinically meaningful outcomes, including invasive mechanical ventilation or mortality. Of note, recent Surviving Sepsis Campaign Guidelines highlighted this equipoise, stating there was insufficient evidence to recommend awake prone positioning for COVID-19 patients.[7]

In today's *Lancet Respiratory Medicine*, Ehrmann[8] reports a meta-trial on awake prone positioning in COVID-19 patients to reduce intubation or death. The meta-trial pooled individual patient-level data from six independent randomized controlled trials with harmonized eligibility criteria, randomization procedures and outcomes. In total, 1126 COVID-19 patients with hypoxemic respiratory failure from six countries were randomised. 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 ignoring additional problems that treatment effects across components may be unequal in magnitude and importance. However, here the two components are reasonable and clinically meaningful - awake prone positioning reduced treatment failure (hazard ratio 0·78, 95% confidence interval [95%CI] 0·65; 0·93), primarily driven by a reduction in intubation (hazard ratio 0·75 (CI%95 0·62; 0·91), compared to usual care, with strong overlap between the components (around ¾ of deaths preceded by intubation).

This novel meta-trial study design has several notable strengths. It is more efficient, being cheaper and quicker to initiate than a single multinational trial[9]. This is particularly important during a pandemic, and the authors deserve praise for their innovation and organisation to rapidly answer this important clinical question. The study was necessarily 'open' (unblinded). In addition, potential bias in primary outcome assessment was minimised, using a composite of all-

cause mortality (completely objective) and need for intubation, by standardising the potentially subjective criteria for intubation. The study employed a group sequential design, using a Kim-DeMets alpha spending function to provide overall control of finding a treatment effective if in truth it is ineffective, scheduling 4 interim analyses permitting early stopping. The study did indeed terminate for benefit at the third scheduled interim analysis, planned for n=600 with mature primary outcomes (which, with a 60-70% event rate would be triggered at ~400 primary events observed. However, the actual 3rd interim analysis used 929 patients, with an observed event rate of just 45% (~400 events). So, the analysis took place roughly on schedule in 'information-time' (driven by events), which is what matters statistically. By study close, the final analysis included 1126 participants. This illustrates the challenges of successfully implementing such adaptive designs, where recruitment and event rates may well deviate from assumptions, necessitating corrective actions. Here, there was additional heterogeneity of 6 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' (usually determined in earlier Phase II efficacy studies, with different prone sessions randomised). The target duration varied between trials, but the overall protocol goal was to maintain prone positioning as long as possible, ideally 16 hours 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. This is why 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. First, 27% who proned >8 hours had low treatment failure (17% vs. 48% in those proned <8 hours vs. 46% overall control). Secondly, given no statistical heterogeneity in overall effect (6 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% all patients]. The largest effect (Mexico; RR 0·78, 95%CI 0·63; 0·96) had the highest prone duration (9±3·2 hours), whereas lower effects in France (RR 0·97, 95%CI 0·77; 1·23) and USA (RR 0·92, 95%CI 0·68; 1·26) had lower durations (2·9±2·9 and 4·4±4·7 hours, respectively).

Does wide variation in awake prone positioning duration reflect different patient populations, sociocultural factors, or institutional factors that modify ability to prone, or center ability to adhere to study protocols? While longer prone duration might better avoid intubation, alternatively prone duration may 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 encouragement, prompting and repositioning support. Most observational studies have also found that few could lie prone for >8 hours.[3] A pilot feasibility trial reported intolerance by 2/3 patients of a standardized prone positioning intervention, deemed not feasible by most nursing staff.[10] 96% in the meta-trial were in intensive/intermediate care units, and not on general medical wards with less favourable nursing-to-patient ratios. Future studies should identify effective strategies to optimize prone duration at the hospital, nursing unit, and patient-level.

These findings may 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 (e.g., on general wards or those with do-not-intubate goals of care). The number needed to treat with awake prone positioning to prevent one intubation was 14[8], impressive for such a safe intervention in a high acuity population. Caution is needed however: the fragility index[11] is 5, meaning that if only 5 fewer control patients had treatment failure, the results are 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 likely utility of awake prone positioning for averting intubation, which will reassure those already using it and may persuade naysayers that tummy time is probably worth a try.

**Conflicts of interest.**

Jason Weatherald is co-principal investigator of the CORONA trial (NCT04402879)

John Norrie declares no relevant conflicts of interest.

Ken Kuljit S. Parhar is co-principal investigator of the CORONA trial (NCT04402879).

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