Randomized Trials to Reduce Clinical Uncertainty: Gold Standard or Fool's Gold?

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The late Professor Brian Kavanagh's 'future-gazing' closing plenary lecture at the 2018 World Federation of Pediatric Intensive and Critical Care Societies in Singapore was entitled *"The State of the Art, Paediatric Intensive Care in 2038."* He was engaging and compelling when he anticipated that we would '*look back in confusion at the status of randomized controlled trials as the primary form of evidence'*. His central point was that the complexity of critical illness is such that that random allocation of an intervention such as higher Positive End Expiratory Pressure (PEEP) in Acute Respiratory Distress Syndrome (ARDS) in a randomized controlled trial (RCT) underestimates the nuances of clinical practice. Heterogeneity in the response to an intervention – benefit in some, harm in others and no effect in some – often results in a negative trial.(1) This can occur when up to half of the participants may have benefited. He implied, charmingly as ever, that we would be foolish to conduct such RCTs without, at the very least, greater knowledge of the phenotypes of critical illness that predispose to this heterogeneity.

We loved the lecture but disagreed with his conclusions. Trials are indeed flawed, but they are still the best tool for determining causation. After all, we only know of the heterogeneity in response to PEEP in ARDS because variations in care were systematically recorded *in randomized trials*. Of course, critical illness is mind-bogglingly complex, but if we see a signal through all this noise of complexity it is highly likely to be robust. We choose to interpret Kavanagh's lecture as a challenge to do *better* clinical trials. Our community's approach to trials has matured in the 6 years since Brian's lecture. There are increasingly established collaborative research networks such as ANZIC-PSG, PALISI, PCCS-SG and PACCMAN (2–4) and the journal regularly includes content under the heading PCCM trials. More trials are being completed with sample sizes greater than those achieved in previous decades. Major PICU RCTs are appearing regularly in the highest impact general journals.(5–10)

Despite apparent successes we should reflect on Kavanagh's key concern – "heterogeneity may undermine the value of any observations". After all, many critical care trials show small or insignificant differences in outcomes. In fact, the problem may be even deeper - heterogeneity comes in many forms, including physiological, but also in the other elements of care that are not the primary focus of a trial. Different healthcare systems in different resource

settings vary widely in many factors, including but not limited to: admission thresholds, staffing, case-mix, length of stay and prevalence of co-morbidities. We not only need good RCTs, but we need them in a variety of healthcare settings. If a trial result from a high-resource setting is reproduced in a lower, or middle, income setting, this greatly increases the probability of the findings being robust.

In this context then, the trial by Maya and colleagues from Puducherry in India published in this issue of the Journal is of interest and potential importance (REF. PCCM 2024 Maya et al). The authors must be congratulated in completing an RCT of high flow nasal cannula (HFNC) versus nasal prong bubble continuous positive airway pressure (b-CPAP) in children with moderate to severe acute bronchiolitis, a significant undertaking in an under-resourced setting. The trial has a number of strengths: it was prospectively registered with an independent trial registry prior to commencing recruitment; it seeks to address a common area of clinical uncertainty; and the analysis is by intention-to-treat. One feature deserves especial mention: a very high proportion of the 128 eligible patients were randomised. This represents 92% of the eligible population – which is greatly in favour of the generalizability of the result. The fact that this was achieved with a prospective consent process is even more remarkable. The interventions were delivered unblinded – we do not consider this a weakness, but a necessary and pragmatic approach that assesses the real-world utility of the options that includes clinicians' prior beliefs about the devices.

Before reviewing the results, we do point out that the study had some weaknesses. It was completed in a single center – a strike against any result being more widely generalisable across the Indian Healthcare system. Oxygen saturation targets were high at >94% - greater than those demonstrated to be safe and effective in bronchiolitis in a large randomised controlled trial(11) which may distort the results. The primary outcome measure was open to observer interpretation. Failure of respiratory support was defined by the occurrence of one of the following: 1) a one-point increase in m-WCAS compared with baseline; 2) respiratory rate rise >10 breaths per minute compared with baseline; or 3) escalation in the technique of respiratory support, i.e., using any other modality than the primary intervention method. Part of the problem here is that the sampling time for the change in respiratory rate is not defined. In an unblinded trial this does risk a bias in reporting of the primary outcome.

The sample size calculation assumed that the success rate of HFNC would be 70% - nearly double that of b-CPAP of 40%. The justification for this proposed effect size is unclear. It is very ambitious at best given that the existing literature suggests a failure rate with CPAP that is half of that of HFNC in high resource comparisons with HFNC (12) and in that in the larger trials that do not focus solely on bronchiolitis, suggest only non-inferiority or indeed a signal in favour of CPAP (7, 8)

The results then almost exactly replicate the power calculation. There was a lower proportion of treatment failure in the HFNC versus b-CPAP group (14/59 vs 25/59; RR 0.56 [95%CI 0.32 – 0.97]; p=0.031). It is puzzling that there was no crossover reported from HFNC to b-CPAP, but still 9/59 in the HFNC group received non-invasive ventilation (NIV) (compared to 23/59 in the b-CPAP group). Unfortunately, NIV was not defined nor was the threshold for escalation to NIV apparently protocolized. This then is another possible entry point for bias – the authors describe a 'need for non-invasive ventilation' but we cannot exclude a differential threshold for NIV as a step-up from b-CPAP but two-steps up from HFNC.

We note that 5/59 in the HFNC group were subsequently intubated and ventilated compared to 2/59 in the b-CPAP group. Interestingly, duration of oxygen therapy and hospital stay were higher in the HFNC group compared to the b-CPAP group, highlighting that the apparent benefit of HFNC with regards to treatment failure reported by the authors may be offset by the risk of prolonged hospital stay. Of note, the comparative cost effectiveness of HFNC and b-CPAP may be influenced more by hospital length of stay than the rate of treatment failure. The value of the time to failure analysis is unclear.

So, what are we to do with these findings? First of all, despite some study weaknesses, it is clear that both HFNC and CPAP can be delivered effectively in this setting. There may be some advantages of HFNC, but these are visible predominantly against endpoints that we suspect are not high priorities for patients and their families, and may not compel clinicians to change practice. On the other hand, the CPAP technique used in this trial (indigenous bubble CPAP) may not be as effective as the CPAP used in previous trials, including from comparable health systems,(13, 14) which may explain the difference in treatment failure rates between the trials. Designing trials to give clear answers is hard – as Brian Kavanagh highlighted. Our group

has taken 20 years to increase its confidence in doing trials and still, in retrospect, regrets some design decisions on every one (2) We look forward to many more pragmatic trials from settings outside Europe, North America and Australasia – after all, that is where most of the critically ill children are. Maya and colleagues have made an important contribution in confirming that such studies are feasible. We hope we can continue to develop the methodologies to deliver high quality trials to reduce uncertainty on important clinical questions around the world.

We still have a long way to go to show that Brian was wrong about the value of randomised trials in pediatric critical care, but we suspect he would have been delighted to see the progress.

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