Co-ordinated multidisciplinary intervention to reduce time to successful extubation for children on mechanical ventilation: the SANDWICH cluster stepped-wedge RCT

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GlaxoSmithKline (Brentford, UK), Boehringer Ingelheim (Ingelheim am Rhein, Germany), Bayer (Leverkusen, Germany), Novartis (Basel, Switzerland) and Eli Lilly (Indianapolis, IN, USA) and from sitting on a Data Monitoring and Ethics Committee for a trial undertaken by Vir Biotechnology (San Francisco, CA, USA). In addition, his institution has received funds from grants from the NIHR, Wellcome Trust, Innovate-UK, the Medical Research Council and the Northern Ireland Health and Social Care Research and Development Division. He has a patent issued to his institution for a treatment for acute respiratory distress syndrome and is a Director of Research for the Intensive Care Society (2009–20) and NIHR EME Programme Director (2019 to present).

Disclaimer: This report contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

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Scientific summary

The SANDWICH cluster stepped-wedge RCT

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Scientific summary

Background

Approximately 20,000 children are admitted to UK paediatric intensive care units each year, and two-thirds receive mechanical ventilation. Although mechanical ventilation improves survival, it can lead to complications; therefore, weaning should be carried out as soon as the patient is able to maintain spontaneous breathing. Children receiving mechanical ventilation require sedative therapy. Therefore, during the ventilator weaning process, sedation requires optimisation because oversedation can result in a protracted weaning time.

A meta-analysis of 17 trials that evaluated protocolised weaning from mechanical ventilation in adult intensive care units reported that weaning protocols reduced the duration of mechanical ventilation by 26% in comparison with no protocol, and without adverse effects. By contrast, there have been fewer clinical trials of protocolised weaning in children. Three small trials (Foronda FK, Troster EJ, Farias JA, Barbas CS, Ferraro AA, Faria LS, *et al.* The impact of daily evaluation and spontaneous breathing test on the duration of pediatric mechanical ventilation: a randomized controlled trial. *Crit Care Med* 2011;**39**:2526–33; Jouvet PA, Payen V, Gauvin F, Emeriaud G, Lacroix J. Weaning children from mechanical ventilation with a computer-driven protocol: a pilot trial. *Intensive Care Med* 2013;**39**:919–25; Maloney C. Computerized Weaning of Childhood Respiratory Failure. PhD thesis. Salt Lake City, UT: University of Utah; 2007) conducted in the Americas ($n = 321$ children) were included in a Cochrane review (Blackwood B, Murray M, Chisakuta A, Cardwell CR, O'Halloran P. Protocolized versus non-protocolized weaning for reducing the duration of invasive mechanical ventilation in critically ill paediatric patients. *Cochrane Database Syst Rev* 2013;**7**:CD009082). The larger of these trials ($n = 294$) reported an average of a 32-hour reduction in duration of mechanical ventilation in the protocol group. The review concluded that the evidence was inadequate to show if protocolised weaning caused children benefit or harm.

In view of the limited generalisability of previous trials to the UK setting and the recognised importance of the clinical issue to the paediatric critical care community, the National Institute for Health Research Heath Technology Assessment programme issued a commissioned call for a study to identify the efficacy of protocolised weaning in children. The aim of this study, therefore, was to evaluate a ventilation liberation intervention in a pragmatic trial to answer the question, 'Does this intervention work under usual conditions?'.

Objectives

The objectives were to determine both in critically ill children anticipated to have a prolonged duration of mechanical ventilation and in all children whether or not the intervention influenced ventilation and clinical outcomes, caused additional harm, was cost-effective and was acceptable to staff delivering care. Anticipated prolonged ventilation was defined using historical data from the national Paediatric Intensive Care Audit Network database. Diagnostic codes associated with invasive ventilation of ≤ 24 hours were categorised as 'short'. All other diagnostic codes were categorised as 'prolonged'.

Methods

Design

A pragmatic, stepped-wedge, cluster randomised clinical trial with a cost-effectiveness and process evaluation was conducted. The trial incorporated 22 4-week periods. All clusters started data collection

simultaneously and were randomised sequentially to transition from the control to the training period, and subsequently to the intervention period. Clusters were non-blinded.

The trial was sponsored by Queen's University Belfast, Belfast, UK. Ethics approval was granted by the National Research Ethics Committee East Midlands. The trial was co-ordinated by the Northern Ireland Clinical Trials Unit and was managed by a Trial Management Group. Independent oversight was provided through a Trial Steering Committee and a Data Monitoring Committee.

Setting and participants

Trial sites were hospitals that had paediatric intensive care units. Children were eligible as trial participants if they were invasively mechanically ventilated, and were excluded if they were admitted with a tracheostomy in situ, they were not expected to survive, their treatment was being withdrawn or their parents/guardians opted out.

Interventions

The intervention incorporated co-ordinated multidisciplinary care in sedation and ventilation weaning. The core components included (1) assessment of sedation levels, (2) review of sedation and ventilation requirements during a multidisciplinary ward round, (3) assessment of a child's readiness for ventilator liberation using a checklist and (4) a spontaneous breathing trial to test extubation readiness.

Usual care generally included slow reductions in ventilator support to very low levels prior to extubation. Sedation levels were measured, but scores were not discussed during ward rounds. Weaning was led by consultant intensivists with little engagement of nurses or other medical staff.

Outcomes

The primary outcome was the duration of invasive mechanical ventilation from the initiation of ventilation to the first successful extubation. Secondary outcomes were total duration of invasive mechanical ventilation (all invasive ventilation periods), incidence and duration of post-extubation non-invasive ventilation, intensive care and hospital length of stay, incidence of successful extubation, number of unplanned extubations, reintubation, tracheostomy insertion, post-extubation stridor, adverse events, and intensive care and hospital mortality. Primary and secondary outcomes were reported for the prolonged ventilation cohort and all children. The primary cost-effectiveness outcome was the cost per respiratory complication avoided at 28 days.

Statistical analysis

The original estimated sample size calculation to detect a 1-day difference, and assuming recruitment of 13–15 intensive care units, was between 11,024 and 14,310 patients. Following the internal pilot study, sample size parameters were re-estimated using a more recent and appropriate Paediatric Intensive Care Audit Network data set (years 2014–16 for the 18 participating units only). The revised sample size calculation indicated that an estimated sample size of 9520 patient admissions would provide 80–87% power to detect a 1-day difference.

All analyses were conducted by intention to treat following a prespecified statistical analysis plan. For the primary and time-to-event secondary outcomes, Cox proportional hazards models were used with a frailty term for clustering by intensive care unit. Outcomes were censored at the date of transitioning from the control to the training period, discharge to another hospital, 90 days, death and receiving a tracheostomy. An absolute measure of effect was derived by computing the median of the model-based prediction of survival duration at all 22 time periods, for both the intervention and the usual-care conditions, and the difference between the two, and by summarising the extent of variability using the interquartile range over the 22 time periods. Binary secondary outcomes were analysed using mixed-effects binomial regression with a log-link to estimate the adjusted relative risk (aRR), and a binomial model with identity link to estimate the adjusted risk difference, with estimation using the restricted maximum likelihood approach. All mixed models included cluster as a random

effect assuming an exchangeable correlation structure and used the Kenward and Roger small-sample correction to correct the potential inflation of the type I error rate owing to small number of clusters. In the case of non-convergence of binomial linear mixed models to estimate risk differences, marginal estimates of risk differences using generalised estimating equations, assuming an independent correlation structure, with a Fay and Graubard small-sample correction on standard errors, with 95% confidence intervals (CIs) derived from a *z*-distribution, were reported. In the case of non-convergence of the binomial model with a log-link, a Poisson model with robust standard errors was fitted. For continuous outcomes, similar-models were used with an identity link and assuming a normal distribution, but checking for normality assumptions and making transformations where necessary.

A secondary prespecified analysis of the primary outcome was conducted that adjusted for additional covariates: age, severity of illness, respiratory versus other diagnostic grouping, type of admission (planned/unplanned) and reason for admission (surgical/medical). A prespecified exploratory subgroup analysis of the primary outcome was conducted using interaction models and 99% confidence intervals for size of unit, adherence to the intervention, type of admission to unit and reason for admission. An extensive series of sensitivity analyses was conducted to consider robustness of assumed modelling structures.

Results

Recruitment took place from 5 February 2018 to 14 October 2019 across 17 hospitals (18 paediatric intensive care units). In total, 10,495 admissions were analysed: 4849 in the control period and 5646 in the intervention period. There were 8843 (84%) admissions in the prolonged ventilation cohort: 4155 and 4688, respectively, in the control and intervention periods. Patient characteristics were broadly similar at baseline.

Clinical effectiveness

Primary outcome

The intervention resulted in a significantly shorter duration of invasive mechanical ventilation before successful extubation in the prolonged ventilation cohort {adjusted median difference −6.1 hours [interquartile range (IQR) −8.2 to −5.3 hours]; adjusted hazard ratio [aHR] for extubation 1.11, 95% CI 1.02 to 1.20, $p = 0.02$; and in all children, adjusted median difference−7.1 hours [IQR −9.6 to −5.3 hours]; aHR 1.11, 95% CI 1.03 to 1.20, $p = 0.01$}.

Secondary outcomes

In the prolonged ventilation cohort, there was a higher incidence of successful extubation in the intervention period (aRR 1.01, 95% CI 1.00 to 1.02, $p = 0.03$; percentage point difference 0.95, 95% CI −0.07 to 1.97) and shorter total duration of invasive mechanical ventilation (aHR 1.09, 95% CI 1.00 to 1.18, $p = 0.06$; adjusted median difference −0.2 days, 95% CI −0.25 to −0.18 days). There was a higher incidence of post-extubation use of non-invasive ventilation in the intervention period (aRR 1.22, 95% CI 1.01 to 1.49, $p = 0.04$; percentage point difference 9.42, 95% CI 4.30 to 14.54), but no statistically significant difference in duration of non-invasive ventilation (aHR 0.91, 95% CI 0.72 to 1.15, $p = 0.43$; adjusted median difference 0.22 days, IQR 0.18 to 0.29 days) or intensive care length of stay (aHR 0.97, 95% CI 0.90 to 1.06, $p = 0.53$; adjusted median difference 0 days, IQR 0 days). Hospital length of stay was significantly longer in the intervention period (aHR 0.89, 95% CI 0.81 to 0.97, $p = 0.01$; adjusted median difference 0.91 days, 95% CI 0.84 to 0.97 days). There was a higher incidence of unplanned extubation in the intervention period (aRR 1.62, 95% CI 1.05 to 2.51, $p = 0.03$; percentage point difference 0.98, 95% CI −0.32 to 2.27), but no statistically significant difference in reintubation (aRR 1.10, 95% CI 0.89 to 1.36, $p = 0.38$; percentage point difference 0.83, 95% CI −1.70 to 3.37) or other patient safety outcomes, including tracheostomy insertion, post-extubation stridor, mortality or adverse events.

In all children, there was no evidence of an effect on the incidence of successful extubation (aRR 1.01, 95% CI 1.00 to 1.02, $p = 0.07$; percentage point difference 0.87, 95% CI −0.14 to 1.89), but the total duration of invasive ventilation was shorter (aHR 1.09, 95% CI 1.01 to 1.18, $p = 0.03$; adjusted median difference −0.28 days, IQR −0.33 to −0.20 days). There was a statistically significant difference in the incidence of post-extubation use of non-invasive ventilation (aRR 1.22, 95% CI 1.01 to 1.49, $p = 0.04$; percentage point difference 8.19, 95% CI 3.53 to 12.84), but no evidence of a difference in duration of non-invasive ventilation (aHR 0.95, 95% CI 0.75 to 1.19, $p = 0.67$; adjusted median difference 0.12 days, IQR 0.10 to 0.16 days). Intensive care length of stay was not significantly different (aHR 0.99, 95% CI 0.92 to 1.07, $p = 0.83$; adjusted median difference 0 days, IQR 0 days), but hospital length of stay was significantly longer in the intervention period (aHR 0.91, 95% CI 0.84 to 0.99, $p = 0.02$; adjusted median difference 0.59 days, IQR 0.41 to 0.79 days). The incidence of unplanned extubation was higher in the intervention period (aRR 1.58, 95% CI 1.05 to 2.37, $p = 0.03$; percentage point difference 0.85, 95% CI −0.36 to 2.07), but with no statistically significant difference in the risk of reintubation (aRR 1.09, 95% CI 0.89 to 1.33, $p = 0.42$; percentage point difference −0.11, 95% CI −3.16 to 2.94) or other patient safety outcomes, including tracheostomy insertion, post-extubation stridor, mortality or adverse events.

Process evaluation

A total of 1865 out of 2247 eligible clinical staff members completed online training within 8 weeks. The median and IQR of training completion was 85% (IQR 80–90%). Across paediatric intensive care units, the intervention reached a high proportion of patients [82% (IQR 77–89%)]. Adherence to the intervention components across the units was high for sedation assessment [83% (IQR 82–91%)], setting targets at ward round for sedation level [85% (IQR 63–89%)] and ventilation support [90% (IQR 81–96%)]. Adherence was moderate for daily screening of readiness for a spontaneous breathing trial [74% (IQR 66–83%)] and lower for undertaking a spontaneous breathing trial when criteria were met [40% (IQR 31–51%)]. Reasons for non-progression to a spontaneous breathing trial were airway protection (24.5%), low consciousness (14.7%), expected return to theatre (13.9%), high haemodynamic support (9.9%) and non-adherence (9.7%).

Post-trial interviews with 193 staff provided a narrative explanation of the acceptability and potential sustainability of the intervention. Generally, adherence to sedation assessment and daily screening for readiness for a spontaneous breathing trial was high because these processes fitted easily with routine care. The adherence to setting targets on ward rounds and progressing to a spontaneous breathing trial was lower owing to ward round time pressures and buy in from medical staff. Afternoon and evening extubation following a successful breathing trial was influenced by established practice and limited experienced cover at night.

Overall, the intervention enhanced nurses' understanding, confidence and autonomy of the process of ventilator weaning. Conducting the daily screening gave bedside nurses a designated role in ventilator weaning for the first time; this was described as driving rather than conducting the weaning process. There was widespread awareness of the intervention having improved multidisciplinary communication and collaboration. This was as a result of the requirement to discuss weaning plans and the shared language provided by the trial.

External factors driving implementation were the dedicated SANDWICH nurses and local unit champions, support and buy-in from managers and senior staff, and a positive culture of embracing changes. Implementation was hindered by long-established hospital and unit organisational and patient care routines.

Cost-effectiveness

There was a higher mean difference in total respiratory complications per patient in the intervention period (control 0.41 vs. intervention 0.50; mean difference 0.10, 95% CI 0.03 to 0.16). The mean hospital cost was higher in the intervention period, but this was not significantly different (control £23,031.26 vs. intervention £23,926.58; mean difference £894.32, 95% CI −£634.33 to £2422.97). The estimated cost of delivering the intervention was £34.73 per patient and was added to the hospital cost to generate total costs.

The economic evaluation showed that the control period was associated with lower, but not statistically significant, total costs (cost difference: mean £929.05, 95% CI –£516.54 to £2374.64) and significantly fewer respiratory complications (mean difference in complications avoided –0.10, 95% CI –0.16 to –0.03). A post hoc sensitivity analysis was conducted to account for unplanned extubations that were not followed by a reintubation within 48 hours and the use of non-invasive ventilation, as these may not be viewed as complications. The difference in complication rate was no longer statistically significant (mean difference –0.03, 95% CI –0.08 to 0.02), although the change did not affect the incremental cost-effectiveness ratio owing to the higher costs associated with the intervention patients.

Conclusions

The intervention led to a small reduction in time to successful extubation. The effect may be explained by engagement of bedside nurses in screening: providing feedback to the medical team may have prompted earlier consideration of readiness for discontinuation, resulting in a shortening of ventilator time. The small effect size may be because the population enrolled was broad, which resulted in heterogeneity in the treatment effect, which may have diluted the overall effect. The increased risk of unplanned extubation without a difference in reintubation rates may account for the greater use of non-invasive ventilation after extubation. We did not identify a statistically significant effect of the intervention on the length of stay in the intensive care unit, but the hospital stay was longer. From a safety perspective, there was no difference in the number of adverse events or harms across the control and intervention periods. The economic evaluation indicated that the intervention was associated with higher hospital costs and a low probability of being cost-effective. This probably reflects the larger number of unplanned extubations and post-extubation non-invasive ventilation use observed in the intervention arm.

Implications for health care

The clinical importance of the beneficial reduction in duration of invasive ventilation should be considered alongside the higher rates of unplanned extubation and post-extubation non-invasive ventilation and longer hospital stay.

Recommendations for research

Future work should explore the intervention sustainability, the effect on a more homogeneous population, and the association between earlier extubation and use of non-invasive ventilation.

Trial registration

This trial is registered as ISRCTN16998143.

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