A cluster randomised trial of staff education, regular sedation-analgesia quality feedback, and a sedation monitoring technology for improving sedation-analgesia quality for critically ill mechanically ventilated patients.

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ABSTRACT

Background

Optimum sedation of intensive care (ICU) patients requires the avoidance of pain, agitation, and unnecessary deep sedation, but achieving this is challenging. Excessive sedation can prolong ICU stay whereas light sedation may increase pain and frightening memories, which are commonly recalled by ICU survivors. We evaluated the effectiveness of three interventions that may improve sedation-analgesia quality: an online education programme; regular feedback of sedation-analgesia quality data; and use of a novel sedation-monitoring technology (Responsiveness Index, RI).

Methods

We did a cluster randomised trial in eight ICUs. These were randomly allocated to receive: education alone (two ICUs); education plus sedation-analgesia quality feedback (two ICUs); education plus RI monitoring technology (two ICUs); or all three interventions (two ICUs). A 45 week baseline period was followed by a 45 week intervention period, separated by an eight week implementation period in which the interventions were introduced. All mechanically ventilated patients were potentially eligible. We assessed patients' sedation-analgesia quality for each 12-hour nursing care period, and sedation-related adverse events (SRAEs) daily. Our primary outcome was the proportion of care periods with optimum sedation-analgesia, defined as free from excessive sedation, agitation, poor limb relaxation and poor ventilator synchronisation. Analysis used multilevel generalised linear mixed modelling to explore intervention effects in a single model taking clustering and patient level factors into account.

The trial is registered as Clinicaltrials.gov NCT01634451.

Findings

Between 1st June 2012 and 31st December 2014, we included 881 patients (9187 care periods) during the baseline period and 591 patients (6947 care periods) during the intervention period. During the baseline period optimum sedation-analgesia was present for 56·1% of care periods. We found a significant improvement in optimum sedation-analgesia with RI monitoring (OR 1·44 (95% CI: 1·07-1·95; p=0·017)) which was mainly due to increased periods free from excessive sedation (OR 1·59 (1·09-2·31)) and poor ventilator synchronisation (OR 1·55 (1·05-2·31)). However, more patients experienced SRAEs (RR 1·91 (1·02-3·58)). We found no improvement in overall optimum sedation-analgesia with education, but fewer patients experienced SRAEs (RR 0·56 (0·32-0·99)). The sedation-analgesia quality data feedback did not improve quality or safety. The statistical modelling predicted that for an average ICU patient a combination of responsiveness monitoring and online education increased the proportion of care periods with optimum sedation-analgesia by about 10% (from 61·6% to 72·3%) without increasing SRAEs.

Interpretation

Combining RI monitoring and online education has potential to improve sedation-analgesia quality and patient safety in mechanically ventilated ICU patients.

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INTRODUCTION

Deep sedation during mechanical ventilation in the intensive care unit (ICU) is associated with longer ICU stay, more infections, and higher mortality.[1] Strategies promoting lighter sedation can improve these outcomes but increase the risk of patient agitation and discomfort. Pain and frightening memories are widely reported by ICU survivors, and are associated with longer-term psychological problems, especially post-traumatic stress.[2-4] Guidelines recommend simultaneous avoidance of deep sedation, pain, and agitation, but changing staff behaviour to improve management is challenging.[3,5] Most previous trials have used protocols or daily sedation breaks, but the effectiveness of these interventions is uncertain and probably context specific.[6,7]

Sedation-analgesia management is a priority for improving ICU patient care.[8-10] Potential quality improvement strategies include staff education, regular feedback of sedation-analgesia quality data, and bedside sedation-monitoring technologies. Inadequate staff education is a known barrier to sedation-analgesia improvement,[11 12] and staff anxiety and increased workload from greater patient wakefulness may limit behaviour change.[5,13,14] Regular feedback of quality data has been successful in decreasing ICU-acquired infections, especially using process control methodology to track change over time.[15,16] However, the effectiveness of this approach has not been evaluated for improving sedation-analgesia quality. Although several bedside sedation-monitoring technologies exist, these have not previously been evaluated in large ICU effectiveness trials. Existing technologies were primarily developed to monitor depth of anaesthesia, their discriminant ability in the target sedation states during ICU care is limited, and they are only recommended in specific situations such as during neuromuscular paralysis. [3,17]

We developed three contrasting interventions that might improve sedation-analgesia quality in mechanically ventilated critically ill patients. First, an online evidence-based education resource; second, process feedback charts for tracking and regular feedback of sedation-analgesia quality; and third, a novel bedside technology designed to continuously monitor patients for possible deep sedation (Responsiveness Index (RI)).[18-22] We report a cluster randomised trial to evaluate the effectiveness of each of these interventions for improving sedation-analgesia quality in mechanically ventilated critically ill patients.

METHODS

The trial was part of a research programme funded by the Chief Scientist's Office Scotland (CZH/3/3) and with unrestricted support from GE Healthcare (Development and Evaluation of Strategies to Improve Sedation practice in inTensive care; DESIST, ClinicalTrials.gov NCT01634451)

Design

We did a cluster randomised trial in eight Scottish ICUs that admit mixed medical-surgical critically ill patients, excluding specialist cardiac, neurosurgical, or paediatric patients. We collected sedation-analgesia quality and other outcome data in all ICUs for 45 weeks (baseline period). We then randomly allocated ICUs to implement up to three interventions over an eight week period: online education ("education"); sedation-analgesia quality feedback ("process feedback"); and sedation monitoring technology ("responsiveness monitoring"). There were four pre-defined intervention combinations: education alone (two ICUs); education plus process feedback (two ICUs); education plus responsiveness monitoring (two ICUs); or all three interventions (two ICUs). Data were then collected for a further 45 weeks (intervention period). In a single analytic model we used a before-after approach (baseline versus intervention) to assess the effectiveness of education, and a parallel group factorial analysis to assess the effectiveness of process feedback and responsiveness monitoring, adjusting for potential confounders and outcomes observed in the baseline period. We evaluated effectiveness in clusters (ICUs) by analysing outcomes both at the care period level (12-hour nursing shift) and summarised at patient level. A process evaluation was included to further assess the impact of each intervention and to better understand the results. A detailed description of the study design, methodology, and analysis plan have been previously published.[23]

Setting and Participants

We selected ICUs in Scotland from teaching (N=4) and district general hospitals (N=4) that admitted between 202 and 798 mechanically ventilated patients annually (see http://www.sicsag.scot.nhs.uk). We selected ICUs to represent a typical UK case-mix. Nurse-patient ratio was 1:1 for mechanically ventilated patients consistent with UK national

guidance, and pre-trial approaches to sedation-analgesia management in each ICU are described in the supplement (table S1). We aimed to study patients requiring at least 24-48 hours of mechanical ventilation. Although interventions were at the ICU level the Adults with Incapacity (Scotland) Act 2000 required us to obtain consent from a relative/welfare guardian to collect data and include patients in the analysis. All mechanically ventilated, intubated patients were potentially eligible if consent was obtained within 48 hours of starting mechanical ventilation. Exclusion criteria were patients: no longer mechanically ventilated when screened or expected to be extubated within 4 hours; where active therapy was being withdrawn; and where the responsible clinician declined permission. Detailed screening logs captured enrolment rates and reasons for non-inclusion throughout the trial. The study was approved by the Scotland A Research Ethics committee (11/SS/0065).

Trial Interventions

Education: We delivered a nine module education package through the National Health Service provider of web-based educational materials (LearnPro NHS: http://www.learnpro.co.uk). Modules covered topics relating to sedation, analgesia, agitation, sleep, and delirium management in the ICU and included inbuilt assessments. Nurses completed training during the eight week implementation period, but the education package was available throughout the intervention period; it can be viewed at http://packagemanager.learnprouk.com (username “desisttest”; password “welcome”).

Process feedback: We developed statistical process control charts that described rates of overall optimum sedation, agitation, excessive sedation, poor relaxation, poor ventilator synchronisation, and patients experiencing sedation-related adverse events (SRAEs) at sequential two month intervals.[16,18] The methodology for this has been previously published.[18] We provided sedation-analgesia quality reports to ICUs randomised to this intervention during the eight week implementation period, and then updated reports every two months during the intervention period using ongoing trial data. ICUs were provided with strategies to share data from the reports (including posters and slide-sets) and encouraged to integrate these into quality improvement and other activities. An example of a report is included in supplementary material.

Responsiveness monitoring: We introduced a novel technology, Responsiveness Index (RI), into practice during the implementation period in the ICUs randomised to this intervention. RI is a continuous measure of patient arousal based on facial electromyography (fEMG) collected via frontal electrodes. The RI was colour-coded to indicate low arousal (red colour), intermediate arousal (amber colour), and higher arousal (green colour). The algorithm,[20] clinical validation studies,[21,22] and a proof of concept trial[19] have been published previously. Low arousal occurs during deep sedation, but also during natural sleep, low levels of clinical stimulation, and as a result of illness related coma. In the trial RI monitoring was intended to support bedside decision-making by clinical staff. Continuous RI monitoring was encouraged for all enrolled sedated patients. We asked nurses to use red RI values as a trigger to review sedation, reduce sedative doses, and transition patients into the amber/green RI range.

Outcomes

Our primary outcome was the proportion of care periods with optimum sedation-analgesia. We defined a care period as a 12 hours nursing shift and assessed sedation-analgesia with a quality assessment tool (SQAT) developed and validated prior to the trial.[18] The SQAT was implemented into routine daily practice in all ICUs prior to the baseline period and completed by staff at the end of each care period throughout the trial. We defined optimum sedation-analgesia as a care period free from excessive sedation, agitation, poor ventilator synchronisation, and poor relaxation. Care periods with each of the four quality components were reported as secondary outcomes.

Secondary patient level outcomes were the numbers of care periods *within each patient* with overall optimum sedation-analgesia and with each quality component.

Additional data were collected by research staff. Safety outcomes were the proportion of days during mechanical ventilation on which a SRAE occurred (defined as unplanned removal of nasogastric tube, central line, arterial line or drain; unplanned extubation; staff injury; or patient injury) and the proportion of patients who experienced SRAEs. Secondary outcomes were sedative and analgesic drug use (expressed as propofol and alfentanil equivalents), the proportion of days on which high dose (≥4000mg) propofol was administered (as a secondary safety outcome for risk of propofol-infusion syndrome), and

the proportion of patients receiving haloperidol (the first-line antipsychotic used for delirium management). Duration of mechanical ventilation, ICU and hospital stay, and ICU and hospital mortality were also recorded.

Sample Size

We did not know the rates of optimum sedation-analgesia and intraclass correlation coefficients (ICC) when designing the trial. We therefore modelled sample size to detect a 25% increase in the proportion of care periods with optimum sedation-analgesia with each trial intervention (power 80%; 2-sided significance level 5%) assuming a 70% optimum sedation-analgesia rate during baseline. We estimated sample size using a range of ICC (0.04 to 0.13) and patient numbers enrolled per ICU in each period (66 to 250). We re-checked power during the baseline period based on recruitment rates in participating ICUs. Our target sample size was 1600 patients (100 per ICU in both baseline and intervention periods). We estimated this would require 98 weeks per ICU (45 weeks baseline; 8 weeks implementation; 45 weeks intervention).

Randomisation and allocation concealment

ICUs started the study in a staggered manner to enable research team support during implementation. Randomised allocation was revealed to ICUs at the end of the baseline period to ensure allocation concealment. Randomisation used computer-generated random permuted blocks, stratified according to recruitment start date ("early": first four ICUs; "late": last four ICUs), to help balance numbers recruited across randomised groups.

Blinding

ICU and research staff were unaware of the intervention allocation during baseline data collection. As the trial aimed to modify behaviour we could not blind clinicians during the intervention phase. Clinical and research staff collected raw trial data every day as part of routine practice, but analysis to generate all trial outcome measures was done remotely by a statistician concealed from group allocation. Patients lacked mental capacity during the intervention and were unaware of ICU allocation.

Analysis

A detailed trial analysis plan was agreed prior to database lock.[23] We evaluated the effect of each intervention using multilevel generalised linear mixed models to account for the nested structure of the data, namely: care period (level one), within admission (level two), within ICU (level three). We planned to fit a three-level multilevel model, but if the nature of the data meant this was not feasible an alternative two-level multilevel model with care period (level one) and admission (level two) was pre-specified. We used Markov Chain Monte Carlo methods for parameter estimation and reported ICCs at admission and ICU levels.

We pre-defined a two-stage approach to analysis. First, an odds ratio (with 95% confidence interval (CI)) was calculated for the baseline to intervention change within *each* ICU, recognising that intervention uptake might vary between ICUs. At a pre-planned meeting, these data were reviewed by the independent data monitoring committee (IDMC) together with a report of qualitative process evaluation data that summarised uptake and engagement with interventions (prepared by a researcher (KK) blinded to quantitative data). The IDMC decided whether effects observed within individual ICUs supported proceeding to the pre-defined main analysis, which was a pooled analysis summarising overall intervention effects in the study.

Our primary analysis was a multilevel logistic regression. Fixed effect independent variables at the ICU level were: time period (baseline or intervention), interventions (process feedback and responsiveness monitoring), and intervention by time period interaction. Fixed effect independent variables at admission level were: age, sex, and APACHE II score (a measure of illness severity). We tested for an interaction between the process feedback and responsiveness monitoring interventions. Intervention effects were presented as odds ratios (95% CI). We did a pre-planned sensitivity analysis using intervention data recorded in the final 30 weeks of the study to check for sustained effects 4-5 months post-implementation. A detailed description of the analytic approach and the models used for the secondary outcomes have been published previously.[23]

Analyses used STATA (StataCorp; www.stata.com), MLwiN (University of Bristol; www.bristol.ac.uk/cmm/software/mlwin) and SAS (www.sas.com) statistical software.

In order to provide an illustration of the clinical impact of the interventions, we used mean age, sex and APACHE II score from the baseline period and the average treatment effects

from education, education plus process feedback, and education plus responsiveness monitoring observed in the trial to estimate the changes in sedation-analgesia quality and safety for an average ICU patient.

Process evaluation

For education we recorded the proportion of nursing staff completing online training in each ICU. To assess changes in knowledge, nurses answered ten core knowledge questions prior to starting education and repeated this at least five months after the implementation phase. Mean change in core knowledge test score was measured using analysis of covariance, adjusting for the pre-intervention score. For sedation-analgesia quality feedback we recorded the number of reports provided to ICUs during the intervention period. For responsiveness monitoring we recorded the number of patients monitored, duration of monitoring, and patterns of hourly RI data recorded by nursing staff.

An inductive thematic analysis of focus group data and field work undertaken in all ICUs throughout the study was undertaken by an ethnographic researcher (KK) and checked by an independent qualitative researcher (JH) according to a pre-specified plan. These data enabled detailed understanding of variation in the fidelity and reach of the intervention and staff perceptions across the ICUs. A description of the process evaluation design has been previously published and further details provided in supplementary material.[23]

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit.

RESULTS

Between 1st June 2012 and 31st December 2014, 881 patients were included during the baseline period and 591 patients during the intervention period. A summary of recruitment, patient demographics, and numbers of care periods with primary outcome data available for each ICU is shown in figure 1. Data describing admission diagnostic categories, and

additional detail concerning screening/enrolment are provided in supplementary material (table S2 and S3).

Our analysis of changes in sedation-analgesia quality in individual ICUs suggested variation in effects, with significant and potentially important changes between the baseline and intervention periods occurring in some ICUs. These are illustrated in supplementary material (figure S1). Our qualitative data suggested that this might be partly explained by differences in engagement with interventions between ICUs, including ICUs randomised to the same interventions. At the IDMC review members unanimously recommended undertaking the pooled main analysis to estimate overall effects from each intervention.

The baseline rates for overall optimum sedation-analgesia and for each of the sedation-analgesia quality components are shown in table 1. This showed that 56.1% of care periods had optimum sedation-analgesia prior to the interventions with relatively high rates of care periods free from unnecessary deep sedation (80·6%), agitation (90·1%), poor relaxation (82·7%), and poor ventilator synchronisation (89·2%).

Pooled raw data for the primary outcome prior to modelling indicating the number of patients and care periods available for analysis by phase and intervention are included in the supplementary material (table S4). These raw data suggested that there was no change (baseline to intervention) in rates of optimum sedation-analgesia associated with education or in the four ICUs that received process feedback, but an increase in optimum sedation-analgesia of 7·0% occurred in the ICUs randomised to responsiveness monitoring.

We found that ICU variance was small (ICC=0.003) suggesting a lack of clustering at ICU level, so we conducted multilevel modelling using a 2-level model. We also found no evidence for interaction between the process feedback and responsiveness monitoring interventions (p=0.08) so this interaction was excluded. The ICCs for all two-level analyses are shown in the supplementary material (table S5).

Results from modelling the effects of the interventions on the primary outcome and its components are summarised in figure 2. There was no statistically significant effect from education on overall optimum sedation-analgesia (OR 1.13 (95% CI: 0.86-1.48); p=0.392), but both days (RR 0.52 (0.30-0.92)) and patients (RR 0.56 (0.32-0.99)) with SRAEs decreased.

Responsiveness monitoring resulted in a significant improvement in optimum sedation-analgesia (OR 1.44 (1.07-1.95); p=0.017), which appeared to result from an increase in care periods free from excessive sedation (OR 1.59 (1.09-2.31)) and poor ventilator synchronisation (OR 1.55 (1.05-2.30)). Patient level analyses showed a similar pattern of findings (table 2A). In contrast, responsiveness monitoring appeared to increase patients experiencing SRAEs (RR 1.91 (1.02-3.58)). Process feedback demonstrated no beneficial effects on the optimum sedation-analgesia quality (OR 0.74 (0.54-1.00); p=0.052) or any secondary outcomes, and in the modelling there was a decrease in excessive sedation free care periods.

Other secondary outcomes are shown in tables 2B and 2C. We found no differences in average drug use per patient or length of mechanical ventilation, ICU or hospital stay, or mortality.

The effects we observed were similar in the sensitivity analysis restricted to data from the last 30 weeks of the intervention period (see table S6).

The predictions from modelling the effects of intervention combinations for an average ICU patient enrolled in the trial are shown in table 3. The modelling predicted that the combination of education and responsiveness monitoring resulted in a 10-11% improvement in the proportion of care periods with optimum sedation from 61.6% to 72.3%, mainly as a result of decreased deep sedation without an increase in SRAEs.

Process evaluation

Education: Most nurses completed the training during the implementation period (range 74% to 100% across the ICUs). Nursing knowledge increased from a mean pre-education score of 6.4 (SD 1.8) out of 10 by an average of 0.82 (95% CI: 0.65-0.98) adjusted for pre-education score (P<0.0001). The qualitative data suggested education was universally valued, considered comprehensive, and a useful resource especially for less experienced staff. Its impact appeared greatest on the awareness and management of agitation and delirium, and was perceived to increase nursing autonomy.

Process feedback: All four ICUs received the two-monthly sedation-analgesia quality reports as planned. However, qualitative data suggested process feedback was poorly understood and was sometimes disbelieved by staff especially when indicating poor sedation-analgesia quality. Process feedback had poor penetration within ICUs and was thought to lack relevance to daily bedside practice.

Responsiveness monitoring: Most enrolled patients were monitored (82% of enrolled patients; range 76% to 95% between the four ICUs). Monitoring initiation was delayed in many patients (median (1st, 3rd quartile) time between intubation and monitoring 21 hours (11, 34)), most likely while consent was obtained. The first RI value was red in most patients (59% overall; range 50-66% across ICUs) and remained red for a median 35% of monitored time (range 23 to 48% across ICUs). The median time to first achieving a green RI value was 9 hours (4, 23), suggesting nurses were not always acting on RI data or interventions to increase RI values were unsuccessful. The qualitative data suggested that many nurses found the technology a useful bedside prompt to review sedation management but views were mixed and some staff understood the monitor poorly, questioned its utility and validity, found its bedside presence intrusive, and did not alter their practice.

A more detailed summary of the process evaluation is presented in the supplement.

DISCUSSION

We found that optimum sedation-analgesia, meaning a patient was free from deep sedation, agitation, poor relaxation and poor ventilator synchronisation, was improved after implementing responsiveness monitoring technology. This intervention decreased the proportion of care periods with deep sedation and poor ventilator synchronisation, but increased SRAEs. A web-based education intervention did not affect overall optimum sedation-analgesia quality, but decreased SRAEs. The regular feedback of sedation-analgesia quality data did not improve outcomes or safety. Using statistical modelling, we estimated that the implementation of the education and responsiveness monitoring combination increased the absolute proportion of time with optimum sedation-analgesia by about ten percentage points for an average ICU patient without increasing SRAEs.

The most effective intervention, the responsiveness technology, was a continuous objective bedside alert to the possibility of deep sedation. Responsiveness Index is not linearly related to clinical sedation scores which was why we used it to assist decision-making rather than link values to strict protocols.[21] Sedation-analgesia quality improved mainly by decreasing deep sedation, consistent with the monitoring concept.[19-21] Our process evaluation found that monitoring was not started for >20 hours in more than half of patients and that red values occurred for prolonged periods despite guidance to review and decrease sedation. There was variable reach and penetration of the technology within ICUs consistent with delays in technology adoption. It is possible that greater improvements to sedation-analgesia quality with responsiveness monitoring might therefore be achieved with more education, experience and confidence in the technology and the use of decision-making protocols directly linked to RI data. The increase in SRAEs following introduction of responsiveness monitoring may have occurred because less time was spent with deep sedation. Concerns regarding agitation and adverse events are known to affect the willingness of nurses to decrease sedation.[13,14] Our data suggest responsiveness monitoring successfully changed the behaviour of bedside staff, although further work is required to maximise its uptake and clinical effectiveness.

The education intervention did not improve sedation-analgesia quality, but was associated with an almost 50% relative reduction in SRAE rates compared to baseline. This result was surprising, but is clinically important because adverse events may directly contribute to patient complications. Inadequate education and training are known barriers to sedation-analgesia improvement, and are difficult to overcome given the high staff numbers and turnover in many ICUs.[11,12] Specifically, increasing wakefulness through strategies such as daily sedation breaks is perceived to increase patient agitation, workload and nurse anxiety.[5,13,14] The management of pain, agitation and delirium was a strong focus of the education intervention and the process evaluation indicated that these elements were most positively perceived by staff, resulting in improved knowledge which was retained over time. Although this part of the analysis used a before-after approach, and it is possible that temporal trends contributed to the findings, the demonstration of improved knowledge, reduced SRAEs and the low cost of this intervention support its widespread implementation.

Process feedback did not improve any of the study outcomes and deep sedation appeared to increase over time. The modelling highlighted that the greatest improvements occurred in those ICUs not randomised to receive process feedback, especially those in which responsiveness monitoring was implemented. There did not appear to be any interaction between process feedback and responsiveness monitoring either statistically or in qualitative data from the process evaluation. The reach and fidelity of process feedback among staff was limited and it did not seem to impact bedside practice. We did not pre-define how the data should be used by ICUs and despite local meetings and champions it was poorly understood and lacked credibility with staff. Process control charts may be useful for tracking sedation-analgesia quality over time in response to sequential quality improvement initiatives, but our data suggest they are not effective in isolation.

The reasons that education and process feedback had no effect on the sedation-analgesia quality outcome were informed by our mixed-methods process evaluation. Quality improvement theory emphasises the need for interventions that engage staff in change especially in complex healthcare environments such as ICUs.[15] Although we included strategies to support implementation, staff perceived process feedback as too remote from the bedside and lacked relevance to individual patient management. In most ICUs staff did not appear to feel ownership of data, and often disbelieved "negative" findings. Education was positively perceived and improved knowledge, but it is possible that this was insufficient to change behaviours consistently and could have been limited by factors such as support from senior clinicians or perceived effect on workload. Although ICU-level effects on the sedation-analgesia quality outcome did not occur, the reduction in SRAEs suggested some behaviour change did occur. Responsiveness may have been more effective because it was present at the bedside and provided objective evidence to support clinical decision-making, thereby alleviating individual responsibility. Alternatively, the data may also have challenged clinicians resistant to change because the data were visible to colleagues. These mechanisms were supported by the process evaluation, which also suggested greater benefit might be possible with greater engagement with the technology.

Our primary outcome was the first integrated sedation-analgesia quality measure to include freedom from deep sedation, agitation, pain/discomfort, and poor ventilator synchronisation. Previous trials have used length of stay outcomes rather than patient

comfort.[6,7,24-26] In some of these trials the control groups were more deeply sedated than is current practice which may have inflated treatment effects, emphasising the importance of context and concurrent process evaluation in trials of complex healthcare interventions.[27] We chose sedation-analgesia quality as our primary outcome because this is important to patients, as highlighted in a recent UK public/professional priority setting partnership.[8] Baseline period data in our trial showed that freedom from excessive sedation was already present for 81% of care periods, suggesting the ICUs were already using a practice more consistent with evidence-based guidelines.[3] This is another possible explanation for the relatively small absolute treatment effects we observed. We found no differences in length of ventilation or ICU stay, but our trial was not powered for these outcomes and the baseline practice decreased the plausibility of a large effect on these outcomes. The improvements in sedation-analgesia and patient safety associated with education and responsiveness monitoring are potentially clinically relevant, especially if greater uptake than achieved in the trial were achieved through improved implementation strategies.

We used a cluster randomised design to compare the three interventions. This was efficient, enabled incorporation of baseline and intervention data from each ICU and a concurrent comparison of the effectiveness of the interventions. However, our trial has limitations. We could not blind clinical staff, which increased the risk of performance bias. We tried to minimise this by making relevant data recording part of routine care, analysing it remotely, concealing outcomes from staff (except when communicated as part of the process feedback intervention), and collecting a large volume of outcome data over a prolonged period. A sensitivity analysis undertaken using data collected >15 weeks after implementing interventions showed similar results suggesting sustained effects. The requirement for consent from a surrogate decision-maker was unavoidable within the Scottish legal/ethical system but increased the possibility of enrolment bias. We minimised this by randomising entire clusters and using the same consent process throughout the trial. This enriched the study population with patients requiring longer term ventilation, in whom the plausibility for effectiveness was highest. For example, the median duration of mechanical ventilation in the study population was 4 days compared to 2 days for all mechanically ventilated patients in participating ICUs (based on ICU audit data; see http://www.sicsag.scot.nhs.uk). Although we adjusted for relevant patient-level factors we cannot exclude the possibility of

unmeasured confounding variables. We also included a relatively small number of ICUs, especially for exploring several interventions, and it is impossible to exclude some temporal effect on the evaluation of online education with the design used. Variation between ICUs at baseline and differences in uptake and implementation of the interventions, which was suggested by the qualitative process evaluation, could also have been important. These issues are difficult to avoid in pragmatic cluster trials, but modelling enabled an estimation of overall effects. Our study illustrates the importance of a process evaluation in trials of complex healthcare interventions, to provide explanatory data to understand the effects observed.[27]

In conclusion, we have shown that continuous responsiveness monitoring can improve overall optimum sedation-analgesia quality in mechanically ventilated critically ill patients and that online staff education can decrease SRAEs. These interventions appear to have beneficial effects on staff behaviours in relation to sedation-analgesia and combining them may improve sedation-analgesia quality and patient safety in ICUs.

Contributors

TSW: Secured funding; literature search; protocol design; study management; data collection; data analysis; data interpretation; writing manuscript; approved final manuscript
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PP: Secured funding; study management; approved final manuscript

SC: protocol design; study management; data collection; approved final manuscript

TQ: protocol design; study management; data collection; approved final manuscript

JR: protocol design; study management; data collection; approved final manuscript

MMcD: protocol design; study management; data collection; approved final manuscript

AD: protocol design; study management; data collection; approved final manuscript

JR: protocol design; study management; data collection; approved final manuscript

JR: protocol design; study management; data collection; approved final manuscript

CJW: Secured funding; protocol design; study management; data analysis; data interpretation; writing manuscript; approved final manuscript

Declaration of interests

TSW received funding from GE Healthcare, who developed Responsiveness Index monitoring in collaboration with Edinburgh University, through unrestricted grants to Edinburgh University to undertake this work and studies preceding the trial during development of Responsiveness Index monitoring.

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560

561 **Research in context**

562 **Evidence before this study**

563 We searched Pubmed, Medline and the Cochrane Database of Systematic Reviews database
564 without language or date restrictions for published research that evaluated interventions to
565 improve sedation and analgesia quality for mechanically ventilated intensive care patients.
566 We also searched recently published guidelines relevant to sedation and analgesia
567 management. The most recent search was done on January 27th 2016. Published trials focus
568 on avoidance of deep sedation rather than integrated measures of sedation depth, pain,
569 and agitation. Recent research with patients suggests optimising overall comfort is
570 important, and observational research indicates pain and discomfort are prevalent. The
571 primary outcome for most randomised trials was length of mechanical ventilation or ICU
572 stay rather than patient-focussed outcomes. Two recent Cochrane reviews summarised
573 existing RCT evidence. Aitken found that evidence supporting protocol-driven sedation did
574 not support effectiveness for reducing duration of ventilation or ICU stay. Burry did not find
575 strong evidence to support daily sedation interruptions for reducing duration of ventilation
576 or ICU stay. Both studies highlighted the importance of the context and setting for
577 understanding the generalisability of trial results. Although some sedation-monitoring
578 technologies exist, they are largely designed for depth of anaesthesia monitoring and their
579 discriminant value is limited for ICU sedation. Existing technologies have not been tested in
580 large randomised trials.

Added value of this study

This cluster randomised trial evaluated the effects of three differing interventions that might improve sedation-analgesia quality in mechanically ventilated patients: an online educational programme for staff, the regular feedback of data about ongoing sedation-analgesia quality, and a novel sedation-monitoring technology (Responsiveness Index) developed as a continuous alert for possible deep sedation. The study used sedation-analgesia quality as the primary outcome, whose components were the absence of unnecessary deep sedation, agitation, and two discomfort behaviours (poor relaxation and poor synchronisation with the ventilator). An embedded process evaluation showed variation in the reach and uptake of the interventions between ICUs, despite clear implementation strategies. Despite this, we found that the Responsiveness Index monitoring was most effective at increasing rates of optimum sedation, mainly by decreasing deep sedation and poor ventilator synchronisation. We found that education did not change the primary outcome but improved patient safety by decreasing sedation-related adverse events. Regular feedback of sedation-analgesia quality data alone did not improve quality.

Implications of all the available evidence

Our findings suggest that using continuous Responsiveness Index monitoring can help decrease deep sedation and improve overall optimum sedation. Combining this with system level staff education may enable ICUs to decrease deep sedation while maintaining patient safety. This approach might overcome some of the barriers to changing sedation practice in ICUs. A trial designed to determine whether Responsiveness Index monitoring can improve outcomes such as length of stay and cost-effectiveness in addition to sedation-analgesia quality is justified

TABLES

Table 1: Total number of care periods with data available on each sedation-analgesia quality measure during baseline period for all eight participating ICUs, along with the number and percentage of care periods with optimum sedation-analgesia and each component of the primary outcome.

Sedation-Analgesia Quality Measure	Total number of evaluable care periods	Number of care periods with measure	% of care periods with measure
Primary Outcome			
Optimum Sedation	9187	5150	56·1
Components of Primary Outcome			
Free from Excessive Sedation	9319	7510	80·6
Free from Agitation	9274	8360	90·1
Free from Poor Relaxation	9362	7744	82·7
Free from Poor Synchronisation	9335	8331	89·2

Table 2A: Estimates of effects of each intervention on the sedation-analgesia quality measures at patient level. A rate ratio (RR) >1 indicates an increase in the outcome with the intervention (improvement).

		Education	Process Feedback	Responsiveness Monitoring
Sedation-Analgesia Quality Outcomes at Patient Level				
Optimum Sedation	RR (95% CI)	1·02 (0·92-1·13)	0·90 (0·80-1·01)	**1·17 (1·04-1·31)**
Free from Excessive Sedation	RR (95% CI)	1·02 (0·96-1·08)	**0·90 (0·84-0·97)**	**1·09 (1·01-1·17)**
Free from Agitation	RR (95% CI)	1·02 (0·96-1·08)	1·02 (0·95-1·09)	0·98 (0·91-1·05)
Free from Poor Relaxation	RR (95% CI)	0·98 (0·92-1·04)	0·98 (0·91-1·05)	1·05 (0·98-1·13)
Free from Poor Synchronisation	RR (95% CI)	1·00 (0·95-1·07)	0·99 (0·92-1·06)	1·04 (0·97-1·11)

Note: Outcomes with statistically significant intervention effects (95% confidence intervals (CIs) do not overlap 1) are highlighted in bold. Results are from generalised linear model with log link and negative binomial error distribution for number of DESIST care periods with an outcomes present for each patient, using the total number of DESIST care periods with valid data for that outcome for each patient as an offset. Adjusted for age, sex and APACHE II score.

Table 2B: Estimates of effects of each intervention on the sedative and analgesic drug use outcomes. A ratio of geometric means (RoGM) or odds ratio (OR) <1 indicates a decrease in the outcome with the intervention (improvement).

		Education	Process Feedback	Responsiveness Monitoring
Sedative and Analgesic Drug Use				
Propofol Equivalents Used (mg)	RoGM (95% CI)	1·09 (0·85-1·40)	1·01 (0·77-1·34)	1·01 (0·76-1·34)
Alfentanil Equivalents Used (mg)	RoGM (95% CI)	1·06 (0·83-1·35)	1·05 (0·80-1·38)	1·18 (0·90-1·55)
Day on which ≥4000mg Propofol (or equivalents) Administered	OR (95% CI)	**0·43 (0·22-0·86)**	**2·45 (1·11-5·42)**	1·11 (0·52-2·38)
Patient Received Haloperidol	OR (95% CI)	1·18 (0·74-1·89)	0·95 (0·56-1·63)	1·14 (0·68-1·91)

Note: Outcomes with statistically significant intervention effects (95% confidence intervals (CIs) do not overlap 1) are highlighted in bold. Results are from normal linear model for log-transformed propofol and alfentanil equivalents, mulitlevel generalised linear model with logit link for day on which ≥4000mg propofol (or equivalents) administered, and generalised linear model with logit link for patient received haloperidol. Adjusted for age, sex and APACHE II score.

Table 2C: Estimates of effects of each intervention on patient outcomes. For mortality outcomes an odds ratio (OR) <1 indicates a reduction in mortality with the intervention (improvement). For the time to event outcomes a hazard ratio (HR) >1 indicates an increased risk of the event with the intervention (improvement), which corresponds to a shorter duration of mechanical ventilation, ICU stay, or hospital stay.

		Education	Process Feedback	Responsiveness Monitoring
Mortality				
ICU	OR (95% CI)	1·19 (0·73-1·93)	1·33 (0·77-2·29)	0·78 (0·46-1·35)
Hospital	OR (95% CI)	1·08 (0·68-1·72)	1·08 (0·65-1·81)	0·82 (0·50-1·37)
Time-To-Event Outcomes				
Cessation of Mechanical Ventilation	HR (95% CI)	0·92 (0·76-1·12)	1·00 (0·80-1·24)	0·87 (0·70-1·08)
Discharge from ICU	HR (95% CI)	0·89 (0·71-1·11)	0·98 (0·77-1·26)	0·92 (0·71-1·17)
Discharge from Hospital	HR (95% CI)	0·88 (0·70-1·11)	1·15 (0·89-1·48)	1·03 (0·79-1·33)

Note: Outcomes with statistically significant intervention effects (95% confidence intervals (CIs) do not overlap 1) are highlighted in bold. Results are from generalised linear model with logit link for ICU and hospital mortality and a Cox proportional hazards model for time to event outcomes (durations of mechanical ventilation, ICU and hospital stay). Adjusted for age, sex and APACHE II score. The proportional hazards assumption was assessed by testing for a non-zero slope over time on the basis of Schoenfeld residuals.

Table 3: Predicted percentages from modelling effects of intervention(s) on sedation-analgesia quality measures at care period level and sedation-related adverse event (SRAE) outcomes.

	Baseline	Education	Education + Process Feedback	Education + Responsiveness Monitoring
Sedation-Analgesia Quality Measure at Care Period Level				
Primary Outcome				
Optimum Sedation	61·6%	64·4%	57·1%	72·3%
Components of Primary Outcome				
Free from Excessive Sedation	85·5%	86·5%	80·6%	91·0%
Free from Agitation	97·3%	97·6%	98·1%	97·2%
Free from Poor Relaxation	90·3%	88·6%	88·4%	90·7%
Free from Poor Synchronisation	94·5%	94·8%	94·3%	96·6%
Sedation-Related Adverse Events				
Day on which a SRAE Occurred	2·0%	1·1%	1·1%	1·9%
Patient Experienced a SRAE	17·6%	10·7%	12·1%	18·6%

Note: Predictions are for the average ICU patient enrolled in the study (age 60 years, 60% male, APACHE II score 22).

Figure 1: Modified CONSORT diagram to show the flow of patients included in each ICU during the baseline and intervention periods of the study, together with characteristics of the patients. Further detailed screening data are included in the supplementary material (Table S3).

Figure 2: Estimates of effects of each intervention, odds ratios (OR) and 95% confidence intervals, on sedation-analgesia quality measures at care period level and sedation-related adverse event (SRAE) outcomes. For the sedation-analgesia quality measures an OR >1 indicates an increase in the outcome with the intervention (improvement); for the SRAE outcomes an OR <1 indicates a decrease in the outcome with the intervention (improvement).

Note: Results are from multilevel generalised linear model with logit link for sedation-analgesia quality measures and SRAE at day level, and generalised linear model with logit link for SRAE at patient level. Adjusted for age, sex, and APACHE II score.

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Figure 1

			ICU 1	ICU2	ICU 3	ICU 4	ICU 5	ICU 6	ICU 7	ICU 8
45 WEEKS	**BASELINE PERIOD**									
	Screened	(N)	1225	483	1015	408	374	282	722	315
	Eligible	(N)	206	190	453	274	135	141	223	106
	Consented	(N (%))	120 (58)	98 (52)	236 (52)	103 (38)	108 (80)	61 (43)	92 (41)	74 (70)
	Excluded	(N)	2	0	0	1	1	0	5	2
	Primary outcome data available	(N (%))	113 (96)	91 (93)	232 (98)	101 (99)	104 (97)	61 (100)	78 (90)	67 (93)
	Age	(mean (SD))	59 (16)	61 (16)	59 (16)	58 (17)	64 (17)	58 (14)	60 (14)	59 (15)
	Male	(%)	67	52	61	67	54	57	66	61
	APACHE II score	(mean (SD))	22 (8)	21 (8)	23 (7)	24 (7)	20 (7)	24 (8)	24 (8)	23 (8)
	Care periods with primary outcome data	(N)	1401	1127	2350	1407	717	559	923	703
8 WEEKS	**IMPLEMENTATION PERIOD**		**Education**		**Education + Process Feedback**		**Education + Responsiveness Monitoring**		**Education + Process Feedback + Responsiveness Monitoring**	
45 WEEKS	**INTERVENTION PERIOD**		**ICU 1**	**ICU2**	**ICU 3**	**ICU 4**	**ICU 5**	**ICU 6**	**ICU 7**	**ICU 8**
	Screened	(N)	1105	369	944	345	244	191	394	209
	Eligible	(N)	118	120	306	163	90	81	201	63
	Consented	(N (%))	65 (55)	58 (48)	170 (56)	55 (34)	62 (69)	28 (35)	116 (58)	44 (70)
	Excluded	(N)	0	0	2	1	0	0	4	0
	Primary outcome data available	(N (%))	64 (99)	56 (97)	167 (99)	52 (97)	61 (98)	28 (100)	107 (96)	42 (96)
	Age	(mean (SD))	60 (17)	60 (15)	59 (15)	59 (18)	67 (14)	65 (12)	58 (14)	56 (18)
	Male	(%)	54	53	67	52	60	46	56	73
	APACHE II score	(mean (SD))	20 (7)	21 (7)	22 (8)	24 (7)	20 (7)	26 (6)	23 (8)	24 (8)
	Care periods with primary outcome data	(N)	841	589	2149	510	511	281	1383	683

Figure 2