Dexmedetomidine or clonidine-based sedation compared with propofol in critically ill patients: the A2B Randomized Clinical Trial

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Word Count: 3980

Abstract

Importance

Whether alpha2-agonist-based sedation reduces time to extubation in mechanically ventilated (MV) intensive care unit (ICU) patients, compared with propofol-based sedation, is uncertain.

Objective

To evaluate whether dexmedetomidine or clonidine-based sedation reduces duration of MV compared with propofol-based sedation.

Design, Setting, and Participants

Pragmatic open-label three-group trial; 1:1:1 randomization in 41 ICUs in the United Kingdom; recruitment occurred from December 2018 to October 2023. Participants were 1437 adults within 48 hours of starting MV who were receiving propofol ±opioid for sedation-analgesia and were expected to require ≥48 total hours of MV. The analysis population compared propofol (N=471), dexmedetomidine (N=457), and clonidine-based (N=476) sedation. Median time from intubation to randomization was 21.0 (Interquartile range (IQR): 13.2-31.3) hours.

Interventions

In all groups, bedside algorithms continuously targeted a Richmond Agitation Sedation Scale of -2 to +1 unless clinicians requested deeper sedation. In the intervention groups algorithms supported alpha2-agonist up-titration and propofol down-titration followed by sedation primarily with allocated alpha2-agonist. Supplemental propofol was permitted if required.

Main Outcomes and Measures

The primary outcome was time to successful extubation, analyzed allowing for death as a competing risk. Secondary outcomes included mortality, sedation quality, rates of delirium, and cardiovascular adverse events.

Results

Among patients in the analysis population (mean (SD) age: 59.2 (14.9) years; 901 (65%) male; mean (SD) APACHE II score 20.3 (8.2)), the sub-distribution hazard ratio (sHR) for time to successful extubation for dexmedetomidine versus propofol was 1.09 (95% CI: 0.96 to 1.25; P=.20) and for clonidine versus propofol was 1.05 (0.95 to 1.17; P=.34), with HR >1 favoring alpha2-agonist. Median (95% CI) hours from randomization to successful extubation for each group was: propofol 162 (136 – 170); dexmedetomidine 136 (117-150); and clonidine 146 (124 – 168). Pre-defined sub-group analyses found no interactions with age, sepsis status, median Sequential Organ Failure Score, or median PRE-DELIRIC delirium risk score. Among secondary outcomes, delirium rates were similar, but agitation occurred at higher rate than propofol with both alpha2-agonists (dexmedetomidine versus propofol risk ratio (95% confidence intervals) 1.54 (1.21-1.97); clonidine versus propofol 1.55 (1.22-1.97). Rates of severe bradycardia (rate <50/minute) were higher with both alpha2-agonists compared with propofol (dexmedetomidine versus propofol 1.62 (1.36-1.93); clonidine versus propofol 1.58 (1.33-1.88)). Mortality was similar over 180 days follow-up (dexmedetomidine versus propofol hazard ratio (95% confidence intervals) 0.98 (0.77-1.24); clonidine versus propofol 1.04 (0.82-1.31).

Conclusions and Relevance

In MV critically ill patients, neither dexmedetomidine nor clonidine-based sedation was superior to propofol in reducing time to successful extubation.

Trial registration

ClinicalTrials.gov: NCT03653832

408 words

Key Points

Question

Does primary sedation with the alpha2-agonists dexmedetomidine or clonidine decrease the time to successful extubation in mechanically ventilated critically ill patients, compared with propofol-based sedation.

Findings

In this pragmatic multi-centered three-group randomized trial including 1437 patients expected to require at least 48 hours of mechanical ventilation, neither dexmedetomidine or clonidine-based sedation decreased the time to successful extubation compared to propofol-based sedation (subdistribution hazard ratio: dexmedetomidine versus propofol 1.09; clonidine versus propofol 1.05).

Meaning

Among mechanically ventilated patients expected to require at least 48 hours of mechanical ventilation, neither dexmedetomidine or clonidine based sedation were superior to usual care with propofol based sedation.

Introduction

Most critically ill patients receiving mechanical ventilation (MV) require sedation. Propofol is the most widely used sedative medication[1], but some trials suggest the alpha2-agonist dexmedetomidine may reduce delirium and duration of MV[2-6]. However, evidence is inconclusive and a *post hoc* analysis of the SPICE III trial found heterogeneity of effects on survival according to patient age raising concerns about safety for some patients.[7-9]

Clonidine is an inexpensive alpha2-agonist with lower alpha2-receptor specificity and is widely used as an adjunct sedative in some countries.[10] There is no high-quality research evaluating clonidine compared to propofol or dexmedetomidine[11].

We conducted a pragmatic multicenter, open-label, randomized controlled trial comparing the effectiveness and safety of dexmedetomidine and clonidine-based sedation with propofol-based primary sedation for MV critically ill patients. Our primary hypothesis was that alpha2-agonist based sedation reduces time to successful extubation.

Methods

The trial protocol has been published[12], and is available in Supplement 1. Previous patients were involved in outcome choice, and assisted with trial conduct (section 1, Supplement 2). Ethical approval was from the Scotland A Research Ethics Committee (18/SS/0085). The funder and sponsor had no role in the design, conduct, analysis, or reporting of the trial. This trial followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. Enrolment was paused during the UK lockdown (March-August 2020) due to the SARS-CoV-2 pandemic.

Patient selection, consent and randomization

Eligible patients were receiving MV in the intensive care unit (ICU), aged ≥18 years, were sedated with propofol ± opioid post-intubation, were within 48 hours of starting MV, and at randomization were expected to require a further 24 hours of MV and a total of ≥48 hours. Exclusion criteria included: acute brain injury; neuromuscular paralysis; bradycardia <50 beats/minute for ≥60 minutes; and patients not expected to survive a further 24 hours (see section 2, Supplement 2).

Signed consent was obtained following consultation with surrogate decision-makers, with deferred consent if these were unavailable within 2 hours of confirming eligibility (see section 3, Supplement 2).

Randomization used a remote web-based system, allocating in a 1:1:1 ratio to the three groups using permuted blocks (randomly arranged sizes of 3, 6, 9, 12) stratified by center. The allocation sequence was computer-generated by an independent programmer and concealed and stored on a remote server. Randomization was done by local researchers.

Trial interventions, sedation targets, and weaning.

Intervention-group patients commenced intravenous infusion of open-label study drug using a weight-based dose regimen (see section 4, Supplement 2) within two hours post-randomization. Medical staff decided if deep sedation (RASS -4 or -5) was clinically indicated, and continued to do this on a daily basis. Clinical staff used group-specific algorithms to up-titrate alpha2-agonist and down-titrate propofol to transition patients to receive the allocated alpha2-agonist (see section 5, Supplement 2). The aim was principally alpha2-agonist based sedation, but propofol was permitted if the maximum alpha2-agonist

dose was reached or because of clinician concerns or dose-limiting side-effects. Starting and maximum dose was alpha2-agonist specific: dexmedetomidine 0.7micrograms/kg/hour (maximum 1.4micrograms/kg/hour); clonidine 1.0micrograms/kg/hour (maximum 2micrograms/kg/hour). Lower starting doses were recommended for patients with cardiovascular instability. Usual care was propofol-based sedation without specific dose-guidance. If deep sedation was not requested by medical staff, bedside algorithms indicated a sedation target Richmond Agitation and Sedation Scale (RASS) score of -2 to +1 (range: -5 (unresponsive) to +4 (combative)), with continuous titration to clinical status.[13] The choice and dosing of opioid for analgesia was determined by the clinical team according to usual care and clinical judgement. Other sedatives, especially benzodiazepines, were discouraged and recorded daily as 'rescue medications' consistent with international guidelines[14]. Guidance was provided for MV weaning, sedation discontinuation, and assessment of readiness for extubation for all groups (see section 6, Supplement 2), which represented 'best practice'. However, this was not tightly protocolized. Guidance for managing cardiovascular instability and other scenarios were provided, including pausing and/or decreasing alpha2-agonist dose (see sections 5 and 6, Supplement 2). Interventions continued until the patient was successfully extubated, died during MV, was transferred before extubation to a non-participating ICU, or until 28 days of MV.

Data were recorded by clinical staff within 12-hours nursing 'day' and 'night' shifts including: RASS score (recommended 4 hourly); delirium status (Confusion Assessment Method for ICU (CAM-ICU), 12 hourly[15]); and pain behaviour based on limb movement and ventilator compliance (Sedation Quality Assessment Tool (SQAT), 12 hourly[16]).

Trial Outcomes

The primary outcome was time from randomization to successful extubation, defined as extubation followed by 48 hours of spontaneous breathing without MV. For patients receiving non-invasive ventilation a 48 hours period of receiving no more than 5cmH2O continuous positive airways pressure was required to achieve the primary outcome (see also section 7, Supplement 2). Primary outcome was ascertained by unblinded local research teams.

Secondary outcomes included: all-cause 180 days mortality; ICU length of stay; time to first RASS score ≥-2; time to first day without agitation, unnecessary deep sedation, or a pain behaviour ('overall optimum sedation'); and rates of delirium/coma and delirium. Key safety outcomes recorded daily were rates of severe bradycardia (<50 beats/minute), cardiac arrhythmia, and cardiac arrest. Other pre-defined daily sedation-related adverse events (AEs) were also collected (see section 18, Supplement 2), and any other AEs and serious adverse events (SAEs) reported.

Longer-term patient-centred outcomes, collected by blinded research staff, were: Health-Related Quality of Life (EQ-5D-5L; 90, 180 days)[17]; anxiety and depression (HADS; 180 days)[18]; post-traumatic stress (IES-Revised; 180 days)[19]; and cognitive function (TMoCA; 180 days)[20]. Patient experience of ICU care was measured descriptively in four domains using the Intensive Care Experience Questionnaire (ICE-Q; 90 days)[21] (see section 8, Supplement 2). A detailed description of secondary outcomes is available in section 7, Supplement 2.

We recorded daily dosages of intravenous sedative and opioid medications, and rescue medications for agitation/delirium.

Clinical effectiveness outcomes are reported here; health economics, process evaluation, and additional patient-centered outcomes will be detailed in subsequent articles.

Statistical Methods

We used hierarchical testing to control overall type I error, while allowing sequential testing of several hypotheses. Stage 1 testing explored superiority of clonidine versus propofol (H1) and dexmedetomidine versus propofol (H2) each at 2.5% level. If H1 or H2 or both were significant, stage 2 testing planned to test clonidine versus dexmedetomidine for non-inferiority (H3) and/or dexmedetomidine versus clonidine for superiority (H4). Stage 3 was a superiority test of clonidine versus dexmedetomidine (H5), but was only planned if H3 was significant. Supplement 2, section 9 provides a detailed description of the testing strategy.

Using published data, we estimated that at seven days 53% of 'usual care' patients would be extubated and 14% would die prior to extubation[22]. We expected a heavily-skewed median duration of MV of around 7 days in the usual care group, and chose an overall mean difference of two days for superiority testing. This was consistent with effects observed in a contemporaneous systematic review[4], and corresponded to an assumed extubation rate of 63% in the dexmedetomidine or clonidine arms at 7 days and a hazard ratio (HR) of 1.37. Supplement 2, section 9 provides a detailed description of the sample size modelling.

The sample size was originally 1737, but was modified due to the recruitment impact of the SARS-CoV-2 pandemic to 1437 (479 patients per group). The reduced sample size maintained 99% power for the H1 and H2 tests. The only impact on the original power was for the non-inferiority comparison of clonidine versus dexmedetomidine (H3). If required, this had 80% power to conclude non-inferiority, using one-sided significance level of 4% (increased from 2.5% in the original sample size calculation), and using a non-inferiority

margin of one day (we estimated that this equates to survival probabilities of 63% and 57% in the dexmedetomidine and clonidine arms respectively at 7 days based on published data). The increased significance level of 4% for the non-inferiority comparison meant that the upper limit on the familywise type I error rate increased from 5% to 6.5%. Supplement 2, section 9 provides a detailed description of the sample size re-modelling due to the SARS-CoV-2 pandemic.

Analysis

All analyses were conducted in accordance with the pre-specified statistical analysis plan, available in Supplement 1.

For the primary outcome, as a first analysis, median estimates and 95% confidence intervals of time from randomization until successful extubation were computed within each treatment group using the simple Kaplan-Meier estimator with deaths treated as censored. A Fine and Gray proportional sub-distribution hazards regression model was then fitted to the primary outcome , including allocated treatment as a fixed effect, and adjusting for site, censoring withdrawals at the time of withdrawal.[23] Site was accounted for in the analysis by implementing the marginal model approach to the Fine and Gray method for clustered data[23]. This approach also addressed the potential competing risk of death. Results were reported as the sub-distribution HR (sHR) for each comparison and illustrated using cumulative incidence functions (see section 13, Supplement 2). Several sensitivity analyses were undertaken to assess the robustness of the primary analysis (see sections 10 and 14, Supplement 2). As a post-hoc analysis in response to reviewer comments, to compute absolute differences we calculated the difference in percentage of patients successfully extubated within 7 days by calculating a difference in cumulative incidence at 7 days post-

randomization based on the fitted Fine and Gray primary analysis model. Confidence intervals were computing using a non-parametric bootstrap method based on 1000 resamples.

Pre-specified subgroup analyses were performed defined by age (<64 versus ≥64 years); baseline PRE-DELIRIC delirium risk score (above/below median)[24]; baseline Sequential Organ Failure Assessment (SOFA) score (above/below median)[25]; and sepsis at enrolment. We calculated sHRs for dexmedetomidine and clonidine groups versus propofol and a p-value for interaction. We also fitted age as a continuous value in interaction analyses.

For mortality, Kaplan-Meier survival curves and a mixed effects partially proportional hazards regression analysis was used to analyse time to all-cause mortality. Post-hoc unadjusted risk differences were also calculated with 95% score confidence intervals (computed in R software version 4.4.1.)[26] using the "epiR" package[27] and checked using the "propCI" package[28] .

For post-randomization ICU length of stay, the same approach as for the primary outcome was used.

For sedation outcomes, time from randomization to the first 12-hours care period with RASS score of ≥-2 and the time to the first day achieving overall optimum sedation (no agitation, unnecessary deep sedation, or pain behaviour) were compared using the same method as for the primary outcome. Rates of agitation (defined as RASS +3/+4), pain (presence of either of the two pain behaviours), unnecessary deep sedation (defined as RASS -4/-5 without indication for deep sedation) and overall optimum sedation were also compared during seven days post-randomization using Poisson regression, calculating a rate ratio (RR).

A similar approach was used to compare rates of coma/delirium or delirium during ten days post-randomization. Sedation practice in the three groups, including daily use of sedative and opioid medications and the use of rescue medications, were reported descriptively.

The proportion of patients in each group experiencing an episode of severe bradycardia, cardiac arrhythmia and cardiac arrest during the intervention were described. The rates of these events were compared between the groups using Poisson regression, calculating a RR. Other pre-defined sedation-related AEs and reported AE/SAEs were reported descriptively.

Subgroup analyses for the mortality and cardiovascular safety outcomes were undertaken by age ≥64 versus <64 years, and also with age as a continuous variable.

A detailed description of analytic methods for all analyses, including the longer-term outcomes, is provided in Supplement 2, section 10. All analyses were undertaken using SAS version 9.4 (except where indicated above). Graphical plots in the main paper were generated using R software version 4.4.1.

Results

Patient characteristics

From December 2018 to October 2023, we randomized 1438 patients in 41 ICUs in the United Kingdom. Final follow-up was January 2024. One patient was randomized twice in error. The analysis population defined in the Statistical Analysis Plan comprised 1404 patients allocated to receive propofol (N = 471), dexmedetomidine (N = 457), or clonidine (N = 476) as primary sedative (figure 1). The reasons for excluding 34 patients was: duplicate randomization (1), no valid consent recorded (7), patient withdrew data (7), patients randomized in error (4), next-of-kin withdrew patient (1), and data omitted due to serious breach at single study site (14). Further details are available in section 11, Supplement 2. The median (interquartile range (IQR)) time from MV in the ICU to randomization was 21.0 (13.2-31.3) hours. Table 1 presents baseline characteristics of patients, which were well-balanced. At randomization, prior to commencing group-specific algorithms, 62% of patients were RASS -4/-5. For the sub-group analyses: 59% of patients were aged ≤64; median PRE-DELIRIC score was 73%; 66% of patients had sepsis; and median SOFA score was 8, with >75% of patients having severe cardiovascular dysfunction (SOFA 3 or 4).

Outcomes

Primary outcome

The sHR for time to successful extubation for dexmedetomidine versus propofol was 1.09 (95% CI: 0.96 to 1.25; P= .20) and for clonidine versus propofol was 1.05 (0.95 to 1.17; P= .34), with a HR>1 favoring alpha2-agonist. The median times to extubation are shown in table 2, and illustrated in Figure 2 with further information in Supplement 2, sections 12 and 13. There was no significant difference in the proportion of patients receiving MV seven

days post-randomization (table 2). Findings were supported by the pre-defined sensitivity analyses (section 14, Supplement 2). As neither H1 or H2 tests were significant the H3-H5 hypothesis testing was not undertaken, as pre-defined in the analysis plan.

Secondary outcomes

Mortality and ICU length of stay:

The HR for mortality during 180 days post-randomization for dexmedetomidine versus propofol was 0.98 (0.77 to 1.24) and clonidine versus propofol was 1.04 (0.82 to 1.31) (table 2 and section 15, Supplement 2). There were no differences in time to ICU discharge among surviving patients (table 2 and section 16, Supplement 2).

Sedation practice:

The median number of 12-hours nursing shifts to first achieve a RASS ≥-2 was 2 for all three groups and the median time to the first day without any unnecessary deep sedation, agitation or pain behaviours was 3 days for all three groups (table 2). However, over the seven days post-randomization rates of agitation were higher with both dexmedetomidine and clonidine compared to propofol (Rate Ratio (RR): Dexmedetomidine versus propofol: 1.54 (1.21 to 1.97); clonidine versus propofol: 1.55 (1.22 to 1.97)). Over the same period rates of pain behaviours, unnecessary deep sedation, and overall optimum sedation were similar (see section 17, Supplement 2).

During days 2-14 post-randomization, documented clinician request for deep sedation among patients receiving the interventions ranged from 12-26% for dexmedetomidine; 13-28% for clonidine; and 12-29% for propofol. The target RASS score of ≥-2 was achieved in >75% of patients on most days in all three groups (figure 3). In the propofol group, patients received propofol on a median 4 (IQR 2-8) days, and during days 2-7 post-randomization median daily propofol dose was 22-26 mg/kg/day. In the alpha2-agonist groups up-titration

occurred as intended over 24 hours post-randomization. In the dexmedetomidine group, patients received dexmedetomidine on a median (IQR) 4 (2-7) days at a median dose ranging from 9-15 micrograms/kg/24 hours over days 2-7. Patients also received propofol on 77% of days; the median daily dose ranged from 4-7 mg/kg/24 hours. In the clonidine group, patients received clonidine on a median (IQR) 4 (2-7) days at a median dose ranging from 15-22 micrograms/kg/24 hours over days 2-7. Patients also received propofol on 76% of days; the median daily dose ranged from 8-10 mg/kg/24 hours. For further description of sedation practice see section 20, Supplement 2.

Alfentanil (54%) and fentanyl (28%) were the most frequently used analgesics at baseline. Subsequent daily doses of analgesics were similar between the groups. The proportions of patients that received rescue medication for agitation were: propofol 38%, dexmedetomidine 31%, and clonidine 34%. For further details of analgesia and rescue medication use see sections 20 and 21, Supplement 2).

Delirium and coma:

There was no difference in delirium or coma rates with dexmedetomidine and clonidine compared to the propofol group (dexmedetomidine versus propofol RR (95% confidence intervals) 0.95 (0.88 to 1.02); clonidine versus propofol RR 0.98 (0.91 to 1.05). There was also no difference in delirium rates: (dexmedetomidine versus propofol RR, 0.96 (0.84 to 1.10); clonidine versus propofol RR 1.03 (0.91 to 1.18). For further information see section 17, Supplement 2.

Safety:

The prevalence of severe bradycardia during the intervention was higher in the dexmedetomidine group (33%) and clonidine group (33%) than the propofol group (20%).

The RRs during the intervention period were: dexmedetomidine versus propofol 1.62 (95% CI: 1.36 to 1.93) and clonidine versus propofol 1.58 (1.33 to 1.88). Prevalence and rates of cardiac arrhythmias and cardiac arrest are shown in section 19, Supplement 2. Prevalence and rates were similar in all groups, except for a higher rate of cardiac arrhythmias reported with dexmedetomidine versus propofol (RR 1.27 (1.15 to 1.40)). More patients had SAEs and AEs reported in the dexmedetomidine group than the propofol or clonidine group (Table 2). Other pre-defined sedation-related AEs collected daily, including severe hypotension, were similar between groups (section 18, Supplement 2).

Long-term outcomes:

For patients completing long-term follow-up there were no clinically important differences in the quality of life or psychological outcomes between the groups (Table 2). Responses to the patient experience questionnaire are summarized in section 8, Supplement 2.

Subgroup analyses

For the primary outcome, there was no significant interaction with any of the four pre-defined subgroup analyses (figure 4). A weak interaction with age (when considered as a continuous variable) was observed for dexmedetomidine versus propofol suggesting reduced benefit on time to extubation with increasing age (HR 0.90 per 10-year increment (95% CI: 0.82 to 0.99); section 14, Supplement 2). For mortality, no interactions with age were found for either dexmedetomidine or clonidine compared with propofol (section 15, Supplement 2).

There were no interactions between age <64 versus ≥64 and rates of severe bradycardia for either alpha2-agonist, but the clonidine association with severe bradycardia lessened with increased age per 10-year increments. For dexmedetomidine, rates of cardiac arrhythmia

appeared higher among younger patients. Conversely, for clonidine rates appeared lower among younger patients. Further details are provided in section 19, Supplement 2.

Discussion

We found that dexmedetomidine and clonidine were not superior to propofol-based sedation for reducing time to successful extubation in critically ill patients, when introduced within 48 hours of initiating MV. We found no evidence of improved sedation quality or less delirium, and rates of agitation and severe bradycardia were higher in both alpha2-agonist groups.

Our findings were consistent in sensitivity analyses, and pre-defined sub-group analyses found no interactions with baseline organ failure severity, delirium risk, or the presence of sepsis with either alpha2-agonist. Given the SPICE III trial findings[7], we explored interactions with age for the primary outcome, mortality, and cardiovascular AEs. Several interactions between age and the primary outcome, severe bradycardia and cardiac arrhythmias, but not mortality, were found. However, these should be interpreted with caution as secondary analyses.

We observed 60% higher rates of severe bradycardia with both alpha2-agonists. This occurred in a third of patients, which is substantially higher than reported in previous trials. A possible explanation is the daily recording of cardiovascular safety events in our trial, compared with non-systematic recording in previous trials.[7,29] Higher rates of cardiac arrhythmia were also reported with dexmedetomidine, but not clonidine, and occurred more frequently in younger patients. Whether these cardiovascular adverse effects directly impact clinical outcomes is uncertain and merit further study, but they likely limited dose-escalation and might explain the continued use of propofol in many patients.

Sedation is a complex intervention involving medications, guidelines, clinician behaviours, and organisational culture.[30,31] In our pragmatic trial clinicians implemented group-specific

algorithms, adapted to individual patient needs and dose-limiting effects. Treatment allocation was well-maintained, with low rates of cross-over to alpha2 agonists in the propofol group as rescue medication. The quality of sedation achieved appeared similar with all three groups, with the exception of agitation which occurred at 55% higher rate with both alpha2-agonists. Clinician request for deep sedation occurred on 25-30% of days in all groups, similar to rates in the SPICE III trial[7]. This might reflect resistance to lighter sedation in clinical practice, although the median time to achieving the RASS target of ≥-2 was within 24 hours for all groups, and around 75% of patients achieved this target on most study days. Overall, patients also had high illness severity, which may have influenced clinician choice of deeper sedation for some patients. The higher observed rates of agitation with alpha2-agonists was surprising, given rescue medication use was similar. This might reflect less clinician experience using alpha2-agonists for primary sedation.

Most intervention group patients continued to receive some propofol. Median daily doses were generally small, at 25-30% of those used in the propofol group, indicating they were used as adjunct sedatives. Several factors may explain this. First, high rates of shock in the trial population and the significantly higher observed rates of severe bradycardia with both alpha2-agonists likely limited dosing, with propofol required to achieve sedation targets. Second, the higher rates of observed agitation may have required supplemental propofol, especially given benzodiazepine use was avoided consistent with guidelines[14]. Third, the SARS-CoV-2 pandemic had a major impact on staff numbers and experience during trial conduct, and nurses may have lacked confidence using alpha2-agonists alone.

The use of opioid analgesia, which was at clinical discretion, was similar between the groups despite the analgesic properties of alpha2-agonists. Pain behaviours were reported on 35-

45% of days in all groups, with no between-group differences, indicating the importance of balancing light sedation with adequate analgesia. We found no reduction in delirium despite a high delirium risk and prevalence. This finding is consistent with the lack of significant effects in other recent trials[7,29].

Our trial adds to the uncertainty about the clinical effectiveness of dexmedetomidine as a primary sedative[2,3,6,7,29]. A caution exists for dexmedetomidine use in younger patients, because higher mortality was found in the SPICE III trial[7,32]. Fifty-nine percent of patients in our trial were aged ≤64. We found no interactions between mortality and age, but these were secondary analyses. If dexmedetomidine causes harm this could be dose-related and the clinical judgement allowed in our trial might have decreased dose-related toxicity[9,32,33].

The most recent international practice guideline recommends only using dexmedetomidine 'when desirable effects are valued over undesirable effects'[34]. Ours is the first large trial of clonidine-based sedation. Our findings do not support the routine early use of either dexmedetomidine- or clonidine-based sedation strategies as an alternative to propofol.

Strengths of our trial include the broad population studied and pragmatic design, which increases generalizability. The primary outcome was relevant to clinicians and patients, and we described sedation, delirium and safety outcomes in detail. Sedation practice was comprehensively described, we systematically recorded important adverse effects, and primary outcome completeness was >95%. We met most expert recommendations recently described for sedation trial design and conduct.[35]

Limitations

Our trial has important limitations. First, the intervention was unblinded and the primary outcome measured by unblinded researchers, which could have resulted in bias. Second, although clear separation in treatment exposure was achieved, the continued use of low dose propofol in the alpha2-agonist groups may have influenced outcomes. Third, best practice for sedation targets, weaning of MV, and the use of analgesia were encouraged, but could not be tightly controlled. We cannot exclude different effects if these were more tightly protocolized. Fourth, although our trial had high statistical power for the chosen minimum clinically important difference, we cannot exclude smaller effects on the primary outcome with certainty. Fifth, our findings cannot be extrapolated to all critically ill patients, for example those with less severe illness, or excluded groups such as cardiac surgery and brain injury.

Conclusions

In conclusion, we found that dexmedetomidine and clonidine-based sedation did not reduce time to extubation when compared with propofol. There were no beneficial effects on a range of other patient-centered outcomes, and rates of severe bradycardia and agitation were significantly higher.

Tables

Table 1: Baseline characteristics for the analysis population.

	Study group			
Characteristic	**Propofol (N = 471)**	**Dexmedetomidine (N = 457)**	**Clonidine (N = 476**	**Overall (n = 1404)**
Age (years)[1] Mean (SD)	59.2 (15.2)	58.8 (14.8)	59.6 (14.5)	59.2 (14.9)
18-64 (Number (%))	268 (56.4)	287 (62.9)	272 (57.6)	827 (58.9)
65-84 (Number (%))	203 (42.7%)	164 (36.0)	193 (40.9)	560 (39.9)
≥85 (Number (%))	4 (0.8)	5 (1.1)	7 (1.5)	16 (1.1)
Sex[2]				
Male (Number (%))	303 (64.6)	292 (65.0)	306 (65.2)	901 (65.0)
Female (Number (%))	166 (35.4)	157 (35.0)	163 (34.8%)	486 (35.0)
Estimated weight (kg) Mean (SD)[2]	81.7 (22.0)	81.7 (21.8)	83.6 (22.8)	82.4 (22.2)
Admission Functional Co-morbidity Index (Number (%))[2]				
0	119 (25.4)	121 (26.9)	115 (24.3)	355 (25.6)
1	122 (26.0)	123 (27.4)	134 (25.7)	379 (27.3)
2	120 (25.5)	97 (21.6)	103 (25.3)	320 (23.1)
≥3	108 (23.0)	108 (24.0)	117 (24.7)	333 (24.0)
APACHE II score[3] Mean (SD)	20.8 (8.5)	20.0 (8.0)	20.3 (8.1)	20.3 (8.2)
Time from start of Mechanical ventilation in ICU to randomization (hours)[4] Median (IQR)	21.0 (13.4-30.5)	20.7 (12.9-31.4)	21.0 (13.3-32.1)	21.0 (13.2-31.3)
Sequential Organ Failure Assessment (SOFA) score[2] Median (IQR)				
Respiratory	3 (2-3)	3 (2-3)	3 (2-3)	3 (2-3)
Cardiovascular	4 (3-4)	4 (3-4)	4 (3-4)	4 (3-4)
Coagulation	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)

Renal	1 (0-3)	1 (0-3)	1 (0-2)	1 (0-3)
Liver	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
Total (excluding neurologic score)	8 (7-10)	8 (6-10)	8 (7-10)	8 (7-10)
Lactate (mmol/L)[5] Mean (SD)	1.6 (1.6)	1.7 (1.4)	1.7 (1.5)	1.7 (1.5)
Type of ICU admission[2]				
Medical Planned	9 (2)	10 (2)	6 (1)	25 (2)
Medical Unplanned	286 (61)	271 (60)	275 (59)	832 (60)
Surgical Planned	27 (6)	23 (5)	30 (6)	80 (6)
Surgical Unplanned	117 (25)	112 (25)	116 (25)	345 (25)
Trauma Planned	2 (0)	5 (1)	2 (0)	9 (1)
Trauma Unplanned	28 (6)	28 (6)	40 (9)	96 (7)
Primary ICU admission diagnosis (system)				
Cardiovascular	19 (5)	27 (6)	29 (7)	75 (6)
Respiratory	158 38)	155 (36)	158 (36)	469 (37)
Gastrointestinal	112 (27)	120 (28)	108 (24)	340 (27)
Neurological	16 (4)	15 (4)	13 (3)	44 (3)
Other	111 (27)	110 (26)	133 (30)	354 (28)
Missing	55 (13)	30 (7)	35 (8)	120 (9)
Sepsis status Number (%) with sepsis[2]	308 (65.7)	297 (66.1)	303 (64.6)	908 (65.5)
Risk of delirium (PRE-DELIRIC score; percent)[5] Median (IQR)	72 (51-87)	73 (53-85)	74 (55-86)	73 (53-86)
Richmond Agitation-Sedation Scale (RASS) score prior to randomization[2] Number (percentage)				
-5	90 (19.2)	89 (19.8)	95 (20.3)	274 (19.8)
-4	195 (41.6)	180 (40.1)	206 (43.9)	581 (41.9)
-3	119 (25.4)	112 (24.9)	108 (23.0)	339 (24.4)

-2	44 (9.4)	36 (8.0)	39 (8.3)	119 (8.6)
-1	11 (2.4)	14 (3.1)	14 (3.0)	39 (2.8)
0	4 (0.9)	7 (1.6)	4 (1)	15 (1.1)
+1	3 (1)	5 (1.1)	0 (0)	8 (1)
+2 to +4	3 (1)	6 (2)	3 (1)	12 (1)
Confusion-Assessment Method for the intensive care unit (CAM-ICU) status prior to randomization[5] Number (percentage)				
Coma (unable to assess)	364 (78.7)	339 (76.9)	369 (79.9)	1072 (78.5)
Positive	39 (8.4)	48 (10.9)	42 (9.1)	129 (9.5)
Negative	59 (12.8)	54 (12.2)	51 (11.0)	164 (12.0)
Sedative and Opioid Use prior to randomization[6] Number (percentage)				
Propofol	466 (100)	447 (100)	464 (99)	1377 (100)
Midazolam	28 (6)	17 (4)	28 (6)	73 (5)
Clonidine	6 (1)	11 (2)	7 (1)	24 (2)
Dexmedetomidine	3 (1)	5 (1)	3 (1)	11 (1)
Fentanyl	132 (28)	116 (26)	144 (31)	392 (28)
Alfentanil	248 (53)	250 (56)	252 (54)	750 (54)
Morphine	25 (5)	23 (5)	22 (5)	69 (5)
Remifentanil	63 (13)	60 (13)	63 (13)	186 (13)

Abbreviations and meaning:
Functional Comorbidity Index: score counts comorbidities from a list of 18 co-morbidities. Scores range from 0 (no comorbidity) to maximum 18 co-morbidities.
APACHE II score: illness severity scoring system that predicts hospital mortality from demographics, co-morbidities, and acute physiology during first 24 hours in ICU. Score ranges from 0 to 71. Scores equate to low (0-10), moderate (11-20), high (21-30), and very high (31 and above) risk of hospital mortality.
Sequential Organ Failure Assessment (SOFA) score: scores each of six organ failures from 0 (no organ failure) to 4 (severe organ failure). Neurological score is often omitted in non-neurological populations receiving sedation as in the A2B trial. The maximum total SOFA score possible in the A2B trial was 20. Higher scores associated with greater risk of death in ICU.
Sepsis status: Sepsis status (yes/no) at enrolment was based on clinical assessment.

PRE-DELIRIC score: a score comprising 10 risk factors for delirium available within 24 hours of ICU admission. The score provides an estimated percentage risk of delirium from 0-100% with 0-20% low risk; 20-40% moderate risk; 40-60% high risk; and >60% very risk.
Richmond Agitation-Sedation Scale (RASS): assesses patient sedation status based on observation, voice, and physical stimulation and categorises to a status on a ten-point scale from deep sedation (-5) to severe agitation (+4).
Confusion-Assessment Method for the intensive care unit (CAM-ICU): a method for diagnosing delirium in ICU patients based on sedation status (RASS score), attention assessment, and disorganised thinking. The score was modified to allow clinicians to judge if they could assess delirium when RASS was -3. If unable to assess this was categorised as coma for analysis. CAM-ICU generates three possible states: coma (unable to assess), delirium positive, or delirium negative.

Footnotes
[1]Based on data from 1403 patients: propofol group 475 patients; dexmedetomidine group 456 patients; clonidine group 472 patients.
[2]Based on data from 1387 patients: propofol group 469 patients; dexmedetomidine group 449 patients; clonidine group 469 patients.
[3]Based on data from 1383 patients: propofol group 467 patients; dexmedetomidine group 449 patients; clonidine group 467 patients.
[4]Based on data from 1404 patients: propofol group 471 patients; dexmedetomidine group 457 patients; clonidine group 476 patients.
[5]Based on data from 1381 patients: propofol group 468 patients; dexmedetomidine group 445 patients; clonidine group 468 patients.
[6]Based on data from 1381 patients: propofol group 467 patients; dexmedetomidine group 447 patients; clonidine group 467 patients.

Table 2: Primary and secondary outcomes. Absolute differences for the primary outcome within seven days post-randomization are estimated from the difference in cumulative incidence at 7 days (see: methods, analysis section for details).

	Group			**Absolute differences**		**Relative differences**	
	Propofol (N = 471)	**Dexmedetomidine (N = 457)**	**Clonidine (N = 476)**	**Dexmedetomidine versus propofol comparison**	**Clonidine versus propofol comparison**	**Dexmedetomidine versus propofol comparison**	**Clonidine versus propofol comparison**
Primary outcome				Difference in percentage of patients successfully extubated within 7 days (95% CI)^	Difference in percentage of patients successfully extubated within 7 days (95% CI)^	Hazard Ratio (95% CI)	Hazard ratio (95% CI)
Time to successful extubation (in hours post-randomization) Median (95% CI)	162 (136 – 170)	136 (117-150)	146 (124 – 168)	3.13% (-2.33 to 8.43%)	1.77% (-3.25 to 6.90%)	1.09 (0.96 to 1.25) P = .20	1.05 (0.95 to 1.17) P = .34
Secondary outcomes							
Mortality				Unadjusted Risk difference (95% CI)	Unadjusted Risk difference (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
ICU mortality Number (%)	105/467 (22)	96/454 (21)	103/472 (22)	-1.34% (-6.67 to 4.01%)	-0.66% (-5.98 to 4.66%)	0.95 (0.72 to 1.26)	0.98 (0.74 to 1.28)
90 days mortality Number (%)	135/471 (29)	122/457 (27)	138/476 (29)	-1.97% (-7.71 to 3.80%)	0.33% (-5.44 to 6.09%)	0.95 (0.74 to 1.21)	1.03 (0.82 to 1.31)
180 days mortality Number (%)	141/471 (30)	132/457 (29)	145/476 (30)	-1.05% (-6.91 to 4.81%)	0.53% (-5.32 to 6.37%)	0.98 (0.77 to 1.24)	1.04 (0.82 to 1.31)
Time from randomization to ICU discharge Days (median (95% CI))	12 (11 to 13)	11 (10 to 12)	12 (10 to 13)			Hazard Ratio (95% CI) 1.05 (0.92 to 1.19)	Hazard Ratio (95% CI) 1.01 (0.91 to 1.12)
Time to optimizing sedation post-randomization							
Number of 12 hours nursing shifts from randomization to first RASS score of -2 or greater Median (95% CI)	2 (2-2)	2 (2-2)	2 (2-2)			Hazard Ratio (95% CI) 1.06 (0.96 to 1.17)	Hazard Ratio (95% CI) 1.06 (0.97 to 1.16)
Number of days from randomization to first day with overall optimum sedation (no recorded agitation, unnecessary deep sedation or pain behaviour) Median (95% CI)	3 (2-3)	3 (3-4)	3 (3-4)			Hazard Ratio (95% CI) 0.94 (0.83 to 1.07)	Hazard Ratio (95% CI) 0.95 (0.82 to 1.10)

Patients with ≥1 Adverse Event (AE) and/or Serious Adverse Events reported (SAE)							
AEs (Number, %)	16 (3.4%)	47 (10.3%)	26 (5.5%)				
SAEs (Number, %)	4 (0.8%)	20 (4.4%)	12 (2.5%)				
Long-term patient-centered outcomes							
90 days post-randomization				Mean difference (95% CI)	Mean difference (95% CI)		
EuroQol (EQ 5D-5L) Visual Analogue Scale score[1] Mean (SD)	63 (23)	68 (18)	60 (21)	4.99 (-0.64 to 10.63)	-2.13 (-7.58 to 3.32)		
EuroQol (EQ-5D-5L) DSU index score (excluding deaths)[2] Mean (SD)	0.54 (0.33)	0.59 (0.29)	0.57 (0.28)	0.05 (-0.04 to 0.13)	0.02 (-0.06 to 0.10)		
180 days post-randomization				Mean difference (95% CI)	Mean difference (95% CI)		
Hospital Anxiety and Depression Scale (HADS)[3] Mean (SD)	14.8 (9.5)	13.4 (9.9)	13.6 (9.6)	-1.41 (-4.49 to 1.68)	-1.18 (-4.14 to 1.79)		
Impact of Events Scale – Revised (IES-R)[4] Mean (SD)	30.6 (24.9)	24.6 (20.8)	22.7 (21.7)	-6.06 (-13.80 to 1.69)	-7.97 (-15.45 to -0.49)		
Telephone Montreal Cognitive Assessment tool (T-MOCA)[5] Mean (SD)	16.3 (4.0)	16.5 (3.5)	17.0 (3.3)	0.16 (-1.09 to 1.40)	0.66 (-0.63 to 1.96)		
EuroQol (EQ 5D-5L) Visual Analogue Scale score[6] Mean (SD)	66 (23)	68 (23)	67 (20)	0.82 (-6.00 to 7.64)	0.28 (-6.22 to 6.79)		
EuroQol (EQ-5D-5L) DSU index score[7] Mean (SD)	0.54 (0.34)	0.61 (0.35)	0.61 (0.29)	0.06 (-0.04 to 0.17)	0.07 (-0.03 to 0.166)		

Footnotes

Hazard ratios (HRs) and rate ratios (RRs) are presented for alpha2-agonist:propofol.

Risk differences and mean differences are presented for alpha2-agonist minus propofol.

AE, Adverse Event defined as any untoward medical occurrence not included in pre-defined secondary outcome reporting. New/deteriorating organ function, new infections, procedure complications, co-prescribed medication reactions, and additional procedures, eg surgery, did not require reporting routinely. Reporting at discretion of local research team during ICU stay only. See also Supplement 1.

SAE, Serious Adverse Event defined as an AE (as defined above) that was life-threatening, result in prolonged hospitalisation, significant disability or incapacity, during ICU stay. Reported at local research team discretion. All SAEs were reported to the sponsor within 24 hours, reviewed by the chief investigator, and an agreed categorisation as unrelated, possibly related, expected and unexpected made. See also Supplement 1.

EuroQol (EQ 5D-5L) Visual Analogue Scale: ranges from 0 to 100, where 0 is worst and 100 is the best possible health state. Minimum clinically important difference around 7 points.

EuroQol (EQ-5D-5L) DSU index score: a health utility score ranging from -0.59 to 1 where a score of 1 represents best possible health state. Scores can include death (value 0) and health states worse than death (negative score). Only survivor scores included here.

Hospital Anxiety and Depression Scale (HADS): Combined anxiety and depression subscales range from 0 to 42 (0-21 for each sub-scale), higher scores indicate greater anxiety and/or depression. 0-14 (Normal), 15-20 (Mild), 21-30 (Moderate), 31-42 (Severe) symptoms; scores ≥21 are likely cases. Minimum clinically important difference 2-5 points.

Impact of Events Scale – Revised (IES-R): the IES-R ranges from 0 to 88, with higher scores indicating greater post-traumatic stress and a score ≥33 indicative of likely presence of Post-Traumatic Stress Disorder. Minimum clinically important difference around 9 points.

Telephone Montreal Cognitive Assessment tool (T-MOCA): maximum score of 22 with higher scores indicating cognitive impairment. Suggested cut-off of ≥17 to diagnose mild cognitive impairment. Minimum clinically important difference 1-2 points.

[1]Based on data from 318 surviving patients who completed questionnaires: propofol group 120 patients; dexmedetomidine group 93 patients; clonidine group 105 patients.
[2]Based on data from 313 surviving patients who completed questionnaires: propofol group 118 patients; dexmedetomidine group 92 patients; clonidine group 103 patients.
[3]Based on data from 234 surviving patients who completed questionnaires: propofol group 85 patients; dexmedetomidine group 69 patients; clonidine group 80 patients.
[4]Based on data from 204 surviving patients who completed questionnaires: propofol group 71 patients; dexmedetomidine group 62 patients; clonidine group 71 patients.
[5]Based on data from 187 surviving patients who completed questionnaires: propofol group 63 patients; dexmedetomidine group 67 patients; clonidine group 57 patients.
[6]Based on data from 245 surviving patients who completed questionnaires: propofol group 90 patients; dexmedetomidine group 71 patients; clonidine group 84 patients.
[7]Based on data from 240 surviving patients who completed questionnaires: propofol group 88 patients; dexmedetomidine group 69 patients; clonidine group 83 patients.

Figure Legends

Figure 1: Screening, randomization and follow-up.

Footnotes:

[a]One patient in the clonidine-based sedation group was randomized twice in error.

[b]Other reasons for meeting an exclusion criteria were: Guillain-Barre Syndrome (57), myasthenia gravis (41), home ventilation (32), pregnancy (36), allergy to IMP (4), untreated heart block (66), prisoners (81), previously enrolled in the trial (49), unknown reason (307).

[c]Other reasons for not randomizing were: lack of interpreter (27), death prior to randomization (7), randomization system unavailable (4), 'other' not specified (574).

[d]Reasons for exclusion from the analysis population were: no valid consent recorded (7), patient withdrew data (7), patients randomized in error (4), next-of-kin withdrew patient (1), and data omitted due to serious breach at single study site (14).

Figure 2: Cumulative incidence plot for time to successful extubation in days post-randomization for the three study groups. Numbers of patients at risk* are shown in 5 days intervals from randomization until 25 days post-randomization.

Footnote: There were initially 456 patients at risk in the Dexmedetomidine arm rather than 457 because information on ultimate extubation status was not available for one patient (see: supplement 2, section 12, table e12).

Figure 3: Box-and-whisker plots showing the highest RASS score achieved on each study day for the fourteen days post-randomization in each group, for patients who had not yet achieved the primary outcome. The Number of patients with clinical Request for Deep Sedation (NRDS) is shown for each day, together with the total number of patients still receiving the intervention.

Figure 4: Subgroup plot for subgroup analyses on the primary outcome, time to successful extubation, showing the sub-distribution hazard ratios (sHRs) on the log-scale. The number of successful extubation events and sample size in each group are also shown. A sub-distribution HR >1 favors the alpha2-agonist compared with propofol-based sedation. For the SOFA score sub-group analysis, the median population total SOFA score (excluding neurologic score) was 8. For the PRE-DELIRIC delirium risk prediction score, the median trial population score was 73%.

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