# Relative and bedside nurse assessment of comfort and communication during propofol, dexmedetomidine, or clonidine-based sedation: pre-planned analysis within the A2B RCT

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## Abstract

### Background

Optimising comfort and ability to communicate for mechanically ventilated (MV) intensive care (ICU) patients is a priority for clinicians, ICU patients and their relatives. Current usual care is propofol-based sedation plus an opioid analgesic. The alpha2-agonists dexmedetomidine and clonidine are potential alternative sedatives.

### Objective(s)

To explore whether nurses and relatives perceive patients sedated with dexmedetomidine and/or clonidine appear more awake, comfortable, and cooperative than patients receiving only propofol-based sedation.

### Design and methods

Sub-study within an open-label three-arm trial.

### Setting and participants

41 ICUs in the United Kingdom. 1437 adults receiving propofol ±opioid for sedation-analgesia within 48 hours of starting MV, expected to require ≥48 total hours of MV.

### Interventions

Light sedation was targeted in all patients unless clinicians requested deeper sedation. In intervention groups algorithms promoted alpha2-agonist up-titration and propofol down-titration followed by sedation primarily with allocated alpha2-agonist. Usual care was propofol-based sedation. Intervention continued until patients were successfully extubated (primary outcome), or other pre-defined end-points.

### Outcomes

For each 12-hours care period nurses responded to two 'yes/no' questions: *Is the patient able to communicate pain*? *Is the patient able to cooperate with care?* When the patients' personal legal representative visited, they were asked for 'yes/no' responses to three questions: *does the patient appear awake? Does the patient appear comfortable? Does the visitor feel they can communicate with the patient?*

Intervention versus propofol group responses were compared fitting a generalised linear mixed model, with results expressed as Odds Ratios (OR; 95% confidence intervals); ORs >1 indicated greater probability of a 'yes' response.

## Results

Nurse responses were available for >90% of trial patients (mean (SD) 12 (12) care periods per patient). Comparing dexmedetomidine versus propofol groups, the OR for a 'yes' response to *'communicate pain'* was 1.38 (1.08 to 1.75), and for clonidine versus propofol was 1.13 (0.89 to 1.43). For *'cooperate with care'* comparing dexmedetomidine versus propofol groups, OR was 1.14 (0.98 to 1.32), and for clonidine versus propofol 0.96 (0.83 to 1.12). Relative responses were available for 32-34% of trial patients across groups (mean (SD) 3 (3) days per patient). For the *'appear awake'* question, the dexmedetomidine versus propofol group OR was 1.48 (1.04 to 2.10), and clonidine versus propofol 1.35 (0.95 to 1.91). For *'appear comfortable'* the dexmedetomidine versus propofol group OR was 0.64 (0.38 to 1.09), and for clonidine versus propofol 0.78 (0.45 to 1.34). For the *'feel they can communicate'* comparison the dexmedetomidine versus propofol group OR was 1.00 (0.68 to 1.47), and for clonidine versus propofol 1.05 (0.71 to 1.54).

## Limitations

Interventions were unblinded, with risk of bias; missing data may not have been at random.

## Conclusions

Nurses perceived patients receiving dexmedetomidine-based sedation could better communicate pain than with propofol-based sedation, and relatives perceived patients appeared more awake. No differences for the other questions were found, or for the clonidine versus propofol comparisons, although some uncertainty remains due to the wide confidence intervals.

## Future work

Additional mixed methods research of sedation quality with different agents from staff and relative perspectives.

## Study registration:

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## Plain Language summary

Patients receiving intensive care (ICU) usually require sedation to keep them comfortable and pain free. The most widely used sedation is currently a drug called propofol. Two alternatives are the drugs dexmedetomidine and clonidine. Both are called 'alpha2-agonists' based on how they work.

The A2B trial was a large study comparing these three drugs for sedating patients during their ICU stay. The trial found no differences in the time spent on the breathing machine or in the ICU. There were no differences in rates of delirium or the quality of sedation measured using scoring systems, except patients who received the alpha2-agonists appeared to experience more agitation compared with propofol.

As part of the trial, we asked bedside nurses to answer 'yes' or 'no' to questions asking their opinion at the end of their nursing shift on whether patients appeared able to communicate pain and could cooperate with care. We also asked the patients' closest relatives' their 'yes/no' response to questions about whether they thought their relative appeared awake, comfortable, and whether they could communicate with the patient when visiting. We compared responses to each question for both alpha2-agonist groups with the propofol group.

We found that, overall, nurses thought patients sedated with dexmedetomidine were better able to communicate pain than with propofol, but found no difference between clonidine and propofol. There were no differences in the ability to cooperate with care. Relatives thought patients sedated with dexmedetomidine appeared more awake than with propofol. The difference for clonidine was smaller.

Despite finding no differences in clinical outcomes between the sedation approaches used in the A2B trial, both nurses and relatives may perceive differences in some aspects of sedation quality depending on the sedation medicine used.

Word count: 298

## Background

Achieving comfort, analgesia and enabling communication with intensive care unit (ICU) patients is a goal of optimum sedation.[1] The views of staff and relatives regarding the overall comfort of patients and their ability to cooperate with care have not previously been studied in trials of ICU sedation. Protocols to guide pain, agitation and delirium management typically use validated rating scales completed by bedside staff, such as the Richmond Agitation Sedation Scale (RASS),[2] Confusion Agitation Method for ICU (CAM-ICU),[3] and Behavioural Pain Scale (BPS).[4] These categorise patient status in order to prompt changes in treatment rather than reflecting the views of staff and relatives. Many patients recall pain, anxiety and discomfort following ICU discharge, with a high prevalence of frightening memories and long-term psychological morbidity.[5 6] The need for more holistic approaches to ensuring patient comfort has been highlighted by consensus groups and guidelines.[1 7]

The A2B trial was a randomised trial comparing ICU sedation based on propofol, dexmedetomidine, or clonidine for patients expected to require more than 48 hours of mechanical ventilation (MV).[8] The main results of the trial have been reported elsewhere.[9] Briefly, neither dexmedetomidine- or clonidine-based sedation decreased the primary outcome of time to successful extubation. Among secondary outcomes, neither alpha2-agonist improved rates of delirium, unnecessary deep sedation, or pain behaviours but both were associated with higher rates of patient agitation. Within the trial, we undertook a pre-planned exploration of the views of bedside nurses and relatives visiting patients regarding their perceptions of patient comfort and communication while receiving sedation with the allocated trial interventions. We hypothesised that nurses and relatives would perceive that the patients sedated with dexmedetomidine and/or clonidine were more awake, comfortable, and cooperative than patients receiving only propofol-based sedation. We report here the results of this analysis.

## Methods

### A2B trial overview:

The A2B trial protocol has been published.[8] Briefly, eligible patients were receiving MV in the ICU, aged ≥18 years, and were within 48 hours of starting MV and sedated with propofol. At randomisation they 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. Randomisation used a remote web-based system, allocating in a 1:1:1 ratio to the three groups using permuted blocks stratified by centre. Intervention-group patients commenced intravenous infusion

of open-label study drug using a weight-based dose regimen within two hours post-randomisation. Bedside nurses used group-specific algorithms to up-titrate alpha2-agonist and down-titrate propofol to transition patients to receive the allocated alpha2-agonist, with the aim of alpha2-agonist based sedation, supplemented with propofol if required. Usual care was propofol-based sedation without specific dose-guidance. For all groups bedside algorithms indicated a sedation target RASS score of -2 to +1 (range: -5 (unresponsive) to +4 (combative)), unless responsible clinicians requested deeper sedation for therapeutic reasons. The choice and dosing of opioid for analgesia was determined by the clinical team according to usual care and clinical judgement. For the majority of patients this was either fentanyl or alfentanil according to local prescribing policies. Other sedatives were discouraged and recorded as 'rescue medications' if required. Interventions continued until the patient was successfully extubated, died during MV, was transferred before extubation to a non-participating ICU, or until the end of 28 days of MV.

## Ethical approval:

The A2B trial received ethical approval from the Scotland A REC (Reference 18/SS/0085) on 21/08/2018. This exploratory analysis was part of the main protocol, and the relevant outcomes were included in the pre-specified Statistical Analysis Plan.[10] Ethical approval allowed any clinical nurse providing care during the trial to participate without additional written consent. For relatives, ethical approval was provided for the Personal Legal Representative (PerLegR) who had provided written consent for participation in the trial, usually the next-of-kin, to be approached to provide responses when they visited the patient. Assessments of relatives' views were therefore always the same individual for each patient. As the A2B trial included a deferred consent model when relatives were unavailable two hours after confirming eligibility, the PerLegR might have provided consent after starting the intervention.

## Assessment and data collection:

All patients were assessed while receiving their allocated sedation intervention from randomisation until either primary outcome (successful extubation), death prior to primary outcome, transfer to another ICU before extubation, or 28 days post-randomisation without achieving the primary outcome. Caring nurse data collection was based on 12-hours nursing shifts. The nurse was asked to complete a 'nursing shift' form that included: whether a clinical request for deep sedation was made; regular RASS scores (suggested four hourly); a CAM-ICU score (once per shift); and assessments of two behavioural pain ratings based on ventilator compliance and upper limb movement. These outcomes contributed to outcomes reported for the main trial publication. At the end of each nursing care period ('day shift' and 'night shift') nurses were also asked to respond to two binary 'yes/no' questions about their view of the patient's comfort and cooperation during that

shift, namely: *Is the patient able to communicate pain*? And, *Is the patient able to cooperate with care?*

For relative assessments, when the PerLegR visited and agreed to provide an opinion, they were asked to provide the caring nurse with a binary 'yes/no' response to three questions, namely: *does the patient appear awake to the visitor? Does the patient appear comfortable to the visitor?* And, *does the visitor feel they can communicate with the patient?* The bedside nurse recorded responses on the daily shift forms. Data recorded on daily shift forms were entered onto the trial database by local research staff.

## Patient and Public Involvement (PPI)

The decision to include the views of visiting relatives was strongly supported by a PPI group who helped develop the trial funding proposal and subsequently contributed to protocol design. The choice and wording of questions put to relatives was informed by a group of ICU survivors and their relatives. A lay co-applicant, Mr Bob Glen, was part of the Trial Management Group throughout the trial and reviewed information materials. An independent PPI representative was a member of the Trial Steering Committee. Mr Glen reviewed and approved the final manuscript, and is a co-author.

## Equality, Diversity and Inclusion (EDI)

The trial inclusion/exclusion criteria had no limitations based on gender, LGBTQ preference, ethnicity, social status or geographical location. Children were excluded, but are usually managed in different ICUs from adults, experience a different spectrum of illness, and are typically studied in paediatric-centric ICU trials.

## Blinding

Clinical staff were not blinded to group allocation, as they were managing sedation and titrating the allocated sedatives. Relatives were not formally blinded as part of the trial. We did not record whether relatives had asked or been told which group the patient was allocated to.

## Trial registration

The A2B trial registration is NCT03653832.

## Analysis

### *Analysis population*

The analysis population comprised all randomised patients in whom nursing and/or relative responses were recorded at least once during the intervention period (and who were not excluded for another reason from the pre-defined overall trial analysis population).[9] We described the

numbers of patients in whom data were available and the mean (Standard Deviation, SD) number of days on which responses were available from nurses and from relatives.

### *Statistical analyses*

Baseline characteristics for patients included in the trial have been published previously.[9] For the present analysis, we summarised relevant baseline data for those patients included in the analysis of nursing responses and visiting relative responses. We calculated the mean (SD) numbers of days with available data for each question, and mean (SD) proportion of care periods with 'yes' responses to the questions.

We analysed outcomes by fitting a generalised linear mixed model with a logit link function, using all available data. Site was included as a random effect in the model and treatment group as a fixed effect. For these outcomes, which were measured in multiple care periods, a random effect for participant (nested within site) was also included. Results were expressed as the odds ratio (OR) for each of dexmedetomidine and clonidine versus propofol-based sedation, with corresponding 95% confidence interval (CI). A higher OR indicated a greater probability of a 'yes' response to the question analysed.

We recognised that these assessments were most relevant when the patient was either not comatose due to their illness, or concurrent sedation level during the nursing shift was at RASS -3 or higher, indicating patients who were not comatose. In sensitivity analysis, we therefore summarised data when the highest RASS score during the concurrent nursing shift was -3 or higher, and repeated the same generalised linear mixed model analysis restricted to responses for nursing shifts in which a RASS score of -3 or above was recorded.

All analyses were undertaken using SAS version 9.4.

## Results

From December 2018 to October 2023, we randomized 1438 patients in 41 ICUs in the United Kingdom. One patient was randomised twice in error. The pre-defined overall trial analysis population comprised 1404 patients allocated to receive propofol (N = 471), dexmedetomidine (N = 457), or clonidine (N = 476) as primary sedative. The numbers of patients and proportions of the overall analysis population in whom data were available for this analysis are summarised in table 1.

A summary of baseline characteristics for the populations analysed is shown in table 2. Patients included in both the bedside nurse assessments and visiting relative assessments were similar to the published overall trial population. There were no clinically relevant differences between the three

groups, or between the sub-group for whom visiting relative assessments were available compared with bedside nursing assessments.

### Bedside nurse response to questions

A summary of the bedside nurse responses to the questions is shown in table 3.

'*Is the patient able to communicate pain*?' The mean proportion of days with 'yes' response was: dexmedetomidine 39%; clonidine 35%; and propofol 33%. Comparing the dexmedetomidine with propofol group the OR for a 'yes' response was: 1.38 (95% confidence interval 1.08 to 1.75); for the clonidine with propofol group comparison the OR for a 'yes' response was 1.13 (95% CI 0.89 to 1.43). Restricting the analysis to days with RASS -3 or above the mean proportion of days was: dexmedetomidine 44%; clonidine 40%; and propofol 37%. Comparing the dexmedetomidine with propofol group the OR for a 'yes' response was: 1.37 (95% confidence interval (CI) 1.07 to 1.74); for the clonidine with propofol group comparison the OR for a 'yes' response was 1.09 (0.86 to 1.38).

'*Is the patient able to cooperate with care?* The mean proportion of days was: dexmedetomidine 42%; clonidine 38%; and propofol 38%. Comparing the dexmedetomidine with propofol group the OR for a 'yes' response was: 1.14 (95% CI 0.98 to 1.32); for the clonidine with propofol group comparison the OR for a 'yes' response was 0.96 (95% CI 0.83 to 1.12). Restricting the analysis to days with RASS -3 or above the mean proportion of days was: dexmedetomidine 46%; clonidine 42%; and propofol 42%. Comparing the dexmedetomidine with propofol group the OR for a 'yes' response was: 1.11 (0.95 to 1.30); for the clonidine with propofol group comparison the OR for a 'yes' response was 0.94 (0.80 to 1.09).

### Visiting relative responses to questions

A summary of the visiting relative responses to the questions is shown in table 4.

'*Does the patient appear awake to the visitor?*' The mean proportion of days was: dexmedetomidine 53%; clonidine 50%; and propofol 44%. Comparing the dexmedetomidine with propofol group the OR for a 'yes' response was: 1.48 (95% CI 1.04 to 2.10).; for the clonidine with propofol group comparison the OR for a 'yes' response was 1.35 (0.95 to 1.91). Restricting the analysis to days with RASS -3 or above the mean proportion of days was: dexmedetomidine 56%; clonidine 54%; and propofol 49%. Comparing the dexmedetomidine with propofol group the OR for a 'yes' response was: 1.31 (95% CI 0.93 to 1.85); for the clonidine with propofol group comparison the OR for a 'yes' response was 1.25 (0.89 to 1.77).

*'Does the patient appear comfortable to the visitor?'* The mean proportion of days was: dexmedetomidine 88%; clonidine 90%; and propofol 93%. Comparing the dexmedetomidine with

propofol group the OR for a 'yes' response was: 0.64 (0.38 to 1.09); for the clonidine with propofol group comparison the OR for a 'yes' response was 0.78 (0.45 to 1.34). Restricting the analysis to days with RASS -3 or above the mean proportion of days was: dexmedetomidine 89%; clonidine 91%; and propofol 93%. Comparing the dexmedetomidine with propofol group the OR for a 'yes' response was: 0.58 (0.33 to 1.02); for the clonidine with propofol group comparison the OR for a 'yes' response was 0.70 (0.39 to 1.25).

*'Does the visitor feel they can communicate with the patient?'* The mean proportion of days was: dexmedetomidine 54%; clonidine 52%; and propofol 52%. Comparing the dexmedetomidine with propofol group the OR for a 'yes' response was: 1.00 (0.68 to 1.47); for the clonidine with propofol group comparison the OR for a 'yes' response was 1.05 (0.71 to 1.54). Restricting the analysis to days with RASS -3 or above the mean proportion of days was: dexmedetomidine 56%; clonidine 54%; and propofol 57%. Comparing the dexmedetomidine with propofol group the OR for a 'yes' response was: 0.87 (0.59 to 1.30); for the clonidine with propofol group comparison the OR for a 'yes' response was 0.96 (0.64 to 1.42).

Table 1: Proportion of patients in the overall trial analysis population contributing data to each of the bedside nurse and visiting relative questions.

| **Question** | **Proportion of analysis population (Number)** | | |
|---|---|---|---|
| | **Propofol** | **Dexmedetomidine** | **Clonidine** |
| **Bedside Nurse** | | | |
| *Is the patient able to communicate pain*? | 97% (457) | 94% (430) | 95% (452) |
| *Is the patient able to cooperate with care* | 93% (438) | 90% (413), | 92% (438). |
| **Visiting Relative** | | | |
| *Does the patient appear awake to the visitor?* | 34% (162) | 32% (148) | 34% (164) |
| *Does the patient appear comfortable to the visitor?* | 33% (156) | 32% (147) | 34% (160) |
| *Does the visitor feel they can communicate with the patient?'* | 33% (157) | 33% (150) | 33% (158) |

Table 2: Comparison of patients' baseline characteristics for the patients in whom: bedside nurse assessments of patients' comfort and communication were recorded, and visiting relative assessments of comfort and ability to communicate were recorded.

| | **Bedside nurse assessments** | | | |
|---|---|---|---|---|
| **Variable** | **Dexmedetomidine group (N = 456)** | **Clonidine group (N = 476)** | **Propofol (N = 471)** | **Overall cohort (N = 1403)** |
| **Age mean (SD))** | 59 (15) | 60 (15) | 60 (15) | 60 (15) |
| **Male number (%)** | 283 (66) | 297 (66) | 295 (65) | 875 (65) |
| **Admission APACHE II score mean (SD)** | 20 (8) | 20 (8) | 21 (9) | 20 (8) |
| **Admission FCI mean (SD)** | 1.6 (1.5) | 1.7 (1.4) | 1.6 (1.5) | 1.6 (1.4) |
| **Sepsis at baseline number (%)** | 282 (66) | 296 (66) | 300 (66) | 878 (66) |
| **Diagnostic category number (%)**<br>**Medical**<br>**Surgical**<br>**Unavailable** | <br><br>268 (62)<br>130 (30)<br>32 (7) | <br><br>270 (60)<br>140 (31)<br>42 (9) | <br><br>285 (62)<br>141 (31)<br>31 (7) | <br><br>823 (62)<br>411 (31)<br>105 (8) |
| | | | | |
| | **Visiting relative assessments** | | | |
| | **Dexmedetomidine group (N = 153)** | **Clonidine group (N = 168)** | **Propofol (N = 164)** | **Overall cohort (N = 485)** |
| **Age mean (SD)** | 60 (14) | 61 (14) | 60 (15) | 60 (15) |
| **Male Number (%)** | 95 (62) | 100 (60) | 108 (66) | 303 (63) |

| | | | | |
|---|---|---|---|---|
| **Admission APACHE II score mean (SD)** | 20 (9) | 20 (7) | 21 (8) | 20 (8) |
| **Admission FCI mean (SD)** | 1.7 (1.5) | 1.9 (1.4) | 1.6 (1.5) | 1.7 (1.5) |
| **Sepsis at baseline number (%)** | 104 (68) | 111 (66) | 114 (70) | 329 (68) |
| **Diagnostic category number (%)** | | | | |
| **Medical** | 103 (67) | 105 (63) | 110 (67) | 318 (66) |
| **Surgical** | 41 (27) | 52 (31) | 43 (26) | 136 (28) |
| **Unavailable** | 9 (6) | 11 (7) | 11 (7) | 31 (6) |

FCI, Functional Co-morbidity index

Table 3: Bedside nurses' assessments of ability to communicate pain and cooperate with care.

| Outcome | All available care periods included | | | | | Care periods restricted to RASS score -3 or greater | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Ability to communicate pain** | **Dexmedetomidine (N = 430)** | **Clonidine (N = 452)** | **Propofol (N = 457)** | **Overall (N = 1339)** | | **Dexmedetomidine (N = 418)** | **Clonidine (N = 434)** | **Propofol (N = 439)** | **Overall (N = 1291)** |
| Number of care periods for which patient was able to communicate pain Number (percentage) | 319 (74) | 315 (70) | 313 (69) | 947 (71) | | 316 (76) | 313 (72) | 309 (70) | 938 (73) |
| Number of care periods per patient during follow-up for which communication of pain data were available Mean (SD) | 12 (12) | 12 (11) | 12 (12) | 12 (12) | | 10 (10) | 11 (11) | 11 (11) | 10 (11) |
| Number of care periods per patient during follow-up for which patient able to communicate pain Mean (SD) | 5 (8) | 4 (7) | 4 (8) | 5 (7) | | 5 (8) | 4 (7) | 5 (8) | 5 (7) |
| Percentage of care periods per patient during follow-up for which patient was able to communicate pain Mean (SD) | 39% (35) | 35% (33) | 33% (33) | 36% (34) | | 44% (36) | 40% (35) | 37% (35) | 40% (35) |

| **Ability to cooperate with care** | **Dexmedetomidine (N = 413)** | **Clonidine (N = 438)** | **Propofol (N = 438)** | **Overall (N = 1289)** | | **Dexmedetomidine (N = 401)** | **Clonidine (N = 419)** | **Propofol (N = 420)** | **Overall (N = 1240)** |
|---|---|---|---|---|---|---|---|---|---|
| Number of care periods for which patient was able to cooperate with care Number (percentage) | 329 (80) | 325 (74) | 329 (75) | 983 (76) | | 319 (80) | 319 (76) | 319 (76) | 957 (77) |
| Number of care periods per patient during follow-up for which cooperation with care data were available Mean (SD) | 11 (10) | 11 (11) | 11 (11) | 11 (10) | | 9 (9) | 10 (10) | 9 (10) | 9 (10) |
| Number of care periods per patient during follow-up for which patient able to cooperate with care Mean (SD) | 5 (7) | 4 (7) | 5 (7) | 5 (7) | | 5 (6) | 4 (7) | 5 (7) | 5 (7) |
| Percentage of care periods per patient during follow-up for which patient was able to cooperate with care Mean (SD) | 42% (33) | 38% (33) | 38% (33) | 39% (33) | | 46% (35) | 42% (34) | 42% (34) | 43% (34) |

Table 4: Visiting relative assessments of whether patient appears awake, seems comfortable, and whether they feel able to communicate with patient.

| **Outcome** | **All available days included** | | | | | **Days restricted to RASS score -3 or greater** | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Patient appears awake to the visiting relative** | **Dexmedetomidine (N = 148)** | **Clonidine (N = 164)** | **Propofol (N = 162)** | **Overall (N = 474)** | | **Dexmedetomidine (N = 144)** | **Clonidine (N = 158)** | **Propofol (N = 151)** | **Overall (N = 453)** |
| Number of days recorded on which patient appeared awake to the visitor Number (percentage) | 109 (74) | 108 (66) | 100 (62) | 317 (67) | | 107 (74) | 108 (68) | 99 (66) | 314 (69) |
| Number of days during follow-up for which data available regarding whether patient appears awake to the visitor visiting relative Mean (SD) | 3 (3) | 3 (3) | 3 (3) | 3 (3) | | 3 (3) | 3 (3) | 3 (3) | 3 (3) |
| Number of days during follow-up on which patient appears awake to the visitor visiting relative Mean (SD) | 2 (2) | 2 (2) | 1 (2) | 2 (2) | | 2 (2) | 2 (2) | 2 (2) | 2 (2) |
| Percentage of days during follow-up for which patient appears awake to the visiting relative Mean (SD) | 53% (40) | 50% (42) | 44% (41) | 49% (41) | | 56% (40) | 54% (42) | 49% (41) | 53% (41) |

| **Patient seems comfortable to the visitor** | Dexmedetomidine (N = 147) | Clonidine (N = 160) | Propofol (N = 156) | Overall (N = 463) | | Dexmedetomidine (N = 143) | Clonidine (N = 154) | Propofol (N = 145) | Overall (N = 442) |
|---|---|---|---|---|---|---|---|---|---|
| Number of days recorded on which patient appeared comfortable to the visitor Number (percentage) | 140 (95) | 153 (96) | 152 (97) | 445 (96) | | 137 (96) | 148 (96) | 141 (97) | 426 (96) |
| Number of days during follow-up for which data available regarding whether patient appears comfortable to the visitor visiting relative Mean (SD) | 3 (3) | 3 (3) | 3 (3) | 3 (3) | | 3 (3) | 3 (3) | 3 (3) | 3 (3) |
| Number of days during follow-up on which patient appeared comfortable to the visitor Mean (SD) | 3 (2) | 3 (3) | 3 (3) | 3 (3) | | 3 (2) | 2 (3) | 3 (3) | 3 (3) |
| Percentage of days during follow-up on which patient appeared comfortable to the visitor Mean (SD) | 88% (26) | 90% (24) | 93% (19) | 90% (23) | | 89% (25) | 91% (23) | 93% (20) | 91% (23) |
| **Visiting relative feels they can communicate with the patient** | **Dexmedetomidine (N = 150)** | **Clonidine (N = 158)** | **Propofol (N = 157)** | **Overall (N = 465)** | | **Dexmedetomidine (N = 146)** | **Clonidine (N = 151)** | **Propofol (N = 147)** | **Overall (N = 444)** |
| Number of days for which the visitor feels they can communicate | 107 (71) | 102 (65) | 104 (66) | 313 (67) | | 107 (73) | 100 (66) | 102 (69) | 309 (70) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| with the patient Number (percentage) | | | | | | | | | |
| Number of days during follow-up for which data available regarding whether relative feels able to communicate with patient Mean (SD) | 3 (3) | 3 (3) | 3 (3) | 3 (3) | | 3 (2) | 3 (3) | 3 (3) | 3 (3) |
| Number of days during follow-up for which the visitor feels they can communicate with the patient Mean (SD) | 2 (2) | 2 (2) | 2 (3) | 2 (2) | | 2 (2) | 2 (2) | 2 (3) | 2 (2) |
| Percentage of days during follow-up for which the visitor feels they can communicate with the patient Mean (SD) | 54% (41) | 52% (44) | 52% (42) | 52% (42) | | 56% (41) | 54% (44) | 57% (43) | 56% (42) |

## Discussion

In this pre-planned analysis of the A2B trial[9] we found that, overall, bedside nurses felt patients were able to communicate pain in a mean 36% of care periods. Comparing each alpha2-agonist to propofol-based sedation, dexmedetomidine was associated with greater probability of being able to communicate pain; the probability for clonidine was similar to propofol-based sedation. Overall, bedside nurses felt patients were able to cooperate with care for a mean 39% of care periods, with no significant differences between either dexmedetomidine or clonidine and propofol. Overall, visiting relatives felt patients appeared awake for a mean of 49% of days they visited. Comparison of dexmedetomidine and clonidine to propofol-based sedation suggested effects that favoured both alpha2-agonists compared with propofol, but the confidence interval only excluded a null effect for the dexmedetomidine to propofol comparison. Relatives felt patients appeared comfortable for a mean of 90% of days they visited. There were no marked differences between groups, but the observed effects and confidence intervals indicated a trend towards greater perceived comfort with propofol. Finally, relatives felt they could communicate with patients on a mean of 52% of days they visited, with no apparent differences between the groups.

To our knowledge, this is the first exploration of nurses' and relatives' perceptions of patient comfort and ability to communicate during ICU sedation. Embedding this sub-study within a randomised trial enabled direct comparison between sedation with the three strategies. The proportion of trial patients (>90%) and numbers of care periods with data (mean 11-12 care periods, equating to 6 days) was high for the bedside nurse responses. Given the study occurred in 41 ICUs over 5 years, with data recorded by nurses providing clinical care, it is likely that several thousand different nurses contributed opinions. The study therefore has high validity for representing nurse opinions, based on the questions asked. Approximately a third of patients had opinions from visiting relatives, and for a smaller number of days per patient (mean 3 days). The smaller sample resulted from several factors. First, the ethics committee approval only allowed the relative who had provided consent for each participant in the trial to provide views, which restricted data to days on which they visited. Second, the COVID19 pandemic had an extended effect on relative visiting behaviours during much of the trial. Despite this, we obtained views from 474 different relatives distributed evenly across the three groups. The patients in whom relative responses were available had similar baseline characteristics to the overall trial cohort, suggesting inclusion bias was unlikely.

Guidelines recommend the clinical assessment of sedation state, pain status, and cognition using validated scales designed to have high discriminative ability and inter-rater consistency.[7] As such they do not reflect nurses' personal views and nurse preferences. These can be discordant with guidelines, for example in relation to performing sedation breaks and/or maintaining wakefulness,

and because of concerns about patient comfort, distress and safety. [11-13]Factors such as personal beliefs and previous experiences, for example adverse events, are also potentially important,[11-14] and practices such as increasing overnight sedation to promote sleep and safety are common.[15] Our approach sought nurse and relative views based on their personal opinion, providing novel insights into sedation quality from these perspectives. This is relevant to understanding sedation practice and clinician preferences, given the complex interplay of factors involved in sedation delivery.[11 14]

Dexmedetomidine aims to achieve light sedation where patients are readily roused, more cooperative, and interactive when stimulated.[7] This may be mediated by clearer cognition and reduced delirium.[16-18] Analgesic properties also potentially contribute to patient comfort. These benefits underpinned our hypothesis that nurse and relative views would demonstrate superiority compared with propofol. In the A2B trial, patients first achieved the target RASS of -2 after a median 24 hours in all three groups, and on around 75% of intervention days, demonstrating that attempts were made to maintain light sedation.[9] This was also reflected in the high proportion of care periods available for analyses restricted to RASS score -3 or greater. Our findings are consistent with the proposed benefits of dexmedetomidine in relation to nurse communication and relative perceptions of wakefulness, although confidence intervals were wide. The lesser effect with clonidine is consistent with its much lower alpha2-receptor selectivity. In the trial, we found no differences between the groups in rates of unnecessary deep sedation, delirium or pain behaviours, but agitation occurred at a 50% higher rate in both alpha2-agonist groups compared with propofol.[9] This might explain why nurses reported no significant differences in the ability to cooperate with care, and relatives reported no significant differences in perceived ability to communicate. Relative assessment of comfort may have had a ceiling effect, as mean proportions were 88-93% across the groups. The trend to greater perception of comfort with propofol compared to both alpha2-agonists was unexpected, but might be explained by the greater agitation rates with alpha2-agonists. For all questions the confidence intervals from the modelling included a wide range of potentially important differences between the groups, perhaps reflecting the sample size available for analysis, diversity of views from nurses and relatives, and differences between individual patients.

Strengths of this sub-study include the randomised design, large sample size especially for the nurse data, and pragmatic real-world context. Patients were also closely involved throughout the design, data collection, analysis, and interpretation of the data. Our analytic approach included modelling that maximised use of available data with adjustment for site and multiple observations within participants. However, our study has limitations. Data were not available on every day, with only a third of patients contributing relative data. The populations with data were similar to the overall trial, but we cannot exclude some inclusion or response bias. Group allocation was not blinded,

which might have influenced subjective responses, especially among bedside nurses. Although sedation was randomised, most patients in the alpha2-agonist groups also received some propofol, at around a third of usual care dose, which meant the responses did not reflect sedation with alpha2-agonists alone in most cases. The majority of patients also received opioid infusions at the discretion of clinical teams.

Future research should further investigate the differences in perceived sedation quality from carer and relative perspective with different drugs and sedation strategies, potentially using opinion-based tools as in this study and/or qualitative methods. To investigate whether differences translate into improvements in clinical or patient-centred outcomes, the relationship between improved communication or wakefulness and changes in care decisions (e.g. earlier weaning or mobilization), or family satisfaction could be explored.

In conclusion, although the A2B trial found no significant differences in objective measures of sedation status (RASS score), delirium (CAM-ICU scores), or pain behaviours this sub-study suggested that nurses may perceive patients receiving dexmedetomidine as better able to communicate pain compared with propofol. There did not appear to be perceived differences in ability to cooperate with care for either alpha2-agonist versus propofol. Visiting relatives perceived patients appeared more awake with dexmedetomidine compared with propofol. Perceptions of comfort and ability to communicate were not notably different between groups, although confidence intervals did not rule out large effect sizes. Given the primary and other key clinical outcomes in the A2B trial were not superior with dexmedetomidine or clonidine compared to propofol, the implications of these findings for optimising ICU sedation are uncertain and reflect the complexity of ICU sedation practice.

## Acknowledgements

The A2B trial investigators, who all contributed to the data presented in this analysis, are listed in Appendix 1

## CRediT Statement

Timothy Walsh: conceptualisation (lead), formal analysis (supporting), funding acquisition (lead), investigation (equal), methodology (equal), administration (equal), supervision (lead), visualisation (equal), writing – original draft (lead), reviewing and editing (equal)

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## Disclosure of interest statement

Timothy Walsh declares receiving a grant from NIHR EME Board as a Co-applicant and a grant from NIHR Programme Board as a Co-applicant. Neither grant related to this work, and funding was to the University of Edinburgh. Christopher Weir declares membership of several boards: HS&DR Commissioned - Board Member (31/07/2013 to 01/03/2016); HS&DR Commissioned R&R (Bird) Sub Board (31/07/2013 to 01/05/2016); HS&DR Funding Committee Member (31/07/2013 to 31/01/2018); and EME - Funding Committee Member (01/07/2018 to 01/07/2022). Richard Parker declares membership of the HS&DR Board (31/07/2013 to 31/05/2018). Cathrine McKenzie declares being in receipt of an NIHR Senior Clinical Practitioner Research Award, and an NIHR Wessex Applied Research Collaborative Research Enhancement Award.

## Data-sharing statement

De-identified participant data will be made available to researchers if their proposal for use is within the agreed uses for which participants provided consent, the proposal is approved by the trial team, and any agreements are in place for data-sharing. A data dictionary for the trial data will be made available. All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation

## Patient Data Statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data is used.

## Ethics statement

The A2B trial received ethical approval from the Scotland A REC (18/SS/0085) on 21/08/2018.

## Information Governance statement

The University of Edinburgh an NHS Lothian (Co-sponsors) are committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679.

Under the Data Protection legislation, the University of Edinburgh is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here (https://data-protection.ed.ac.uk/contact). The University of Edinburgh is also the Data Processor

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