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Article:
Masterson, J.A., Ritchie, I., Aitken, L.M. et al. (2026) Effect of intensive care unit sedation strategy on patient-reported experience: secondary mediation analysis of the A2B randomised controlled trial. Anaesthesia. ISSN: 0003-2409

https://doi.org/10.1111/anae.70437

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Original Article

Effect of intensive care unit sedation strategy on patient-reported experience: secondary mediation analysis of the A2B randomised controlled trial

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Summary

Introduction The optimal ICU sedation strategy to improve patient-reported experience is unknown. In a planned secondary analysis of the A2B randomised trial, we evaluated the effect of sedation strategy (dexmedetomidine, clonidine or propofol) on recalled patient experience at 90 days post-randomisation. Using mediation analyses, we explored plausible mediators of the relationship between sedation strategy and patient experience.

Methods We analysed data for all patients from A2B who completed the Intensive Care Experience Questionnaire (ICE-Q) at 90 days. The primary outcome was patient-recalled experience, measured by the four ICE-Q domain scores (awareness, frightening memories, recall, satisfaction). Sedation strategy effect was evaluated using linear regression, adjusting for potential confounders. Mediation analyses were conducted for duration of mechanical ventilation; ICU stay; and days with pain behaviour, agitation and coma/delirium.

Results Of 1404 patients included in the primary trial analysis, 1009 (71.9%) were alive at 90 days post-randomisation with ICE-Qs completed by 289/1009 (28.6%). Compared with propofol, dexmedetomidine sedation was associated with higher awareness of surroundings (median score 32 vs. 28, adjusted mean difference 3.6, 95%CI 1.0–6.2, p = 0.01), but clonidine sedation had no association (difference 2.4, 95%CI -0.2–5.0, p = 0.07). No associations were found with other ICE-Q domains. The contribution of the five potential mediators on the dexmedetomidine–awareness relationship was small.

Discussion Dexmedetomidine compared with propofol sedation strategy may be associated with increased recalled awareness of surroundings, which is considered a favourable indicator of ICU experience. Together with the primary A2B trial results, which showed no effect on ventilation duration, these hypothesis-generating findings in a subgroup of the A2B cohort do not support the use of dexmedetomidine over propofol based on patient-reported experience. Based on our findings, we advocate that a personalised approach to sedation strategies should continue to be used.

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Accepted: 29 May 2026
Keywords: critical care; ICU sedation; mediation analysis; patient reported outcome measures; randomised controlled trial
*The A2B trial investigators are listed in online Supporting Information Appendix S1.

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Introduction

Patient-centred approaches are fundamental to high-quality healthcare [1]. Comprehensive evaluation of interventions requires measurement beyond objective clinical outcomes and costs and should include patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs) [2]. Patient-reported experience measures are designed to capture patient perception of care processes, offering insights distinct from clinical outcomes and PROMs. Interventions that measure, report and act on PREMs are associated with improved patient safety and clinical effectiveness [3].

In ICU settings, patient experience has been studied primarily through qualitative methods [4–6], with limited quantitative research on patient-reported experience, including its determinants and relationship with outcomes. Patient-reported experience is associated with post-ICU psychological sequelae [7, 8]; this is important given the high prevalence of anxiety, depression and post-traumatic stress disorder in ICU survivors [9–12]. Typical ICU sedation and analgesia strategies comprise intravenous sedative and opioid infusions [13]. There is a plausible link between sedation and analgesia practices; the associated incidence of pain, agitation, coma and delirium; patient-reported experience; and subsequent post-ICU psychological sequelae. Exploration of these issues in heterogeneous ICU populations, however, is challenging.

The A2B randomised controlled trial evaluated two α-2 agonist-based sedation strategies against propofol-based (GABA-agonist) sedation [14]. The trial collected information on potential causative and mediating factors that might link baseline characteristics and ICU treatments to patient experience of their admission. Patient experience was measured with the Intensive Care Experience Questionnaire (ICE-Q) among ICU survivors [15]. We undertook a secondary data analysis of the A2B trial dataset. Our main objective was to explore if any of the three sedation strategies were associated with patient experience recalled 90 days post-randomisation. Secondary objectives were to explore plausible mediators of the relationship between treatment allocation and patient experience domains and to identify other factors associated with patient experience of ICU care.

Methods

The A2B study received ethical approval from the Scotland A Research Ethics Committee. This was a prespecified secondary analysis of the A2B trial, a pragmatic multicentre, open-label, randomised controlled trial comparing effectiveness and safety of dexmedetomidine and clonidine-based sedation with propofol-based primary sedation (further information in online Supporting Information, Appendix S2) [14]. Full details of trial design, population and protocol have been published [16]. This analysis was restricted to patients who provided data for at least one domain of the ICE-Q domain. This study is reported in line with the Guideline for Reporting Mediation Analyses of Randomized Trials and Observational Studies Short Form [17].

The primary outcome was recalled patient experience of ICU care, measured at 90 days post-randomisation using the ICE-Q [15]. Of 31 listed items, 24 contribute to four domains, each with an independent score: awareness of surroundings (9 items, score range 9–45, higher score indicates greater awareness); frightening memories (6 items, range 6–35, higher indicates more frightening memories); recall (5 items, range 5–25, higher indicates greater recall of ICU stay); and satisfaction (4 items, range 4–20, higher indicates greater satisfaction) (online Supporting Information Table S1). In contrast with intra-operative awareness, ICE-Q `awareness of surroundings´ refers to the ability to recall the ICU environment and interact purposefully during care, which is considered a favourable indicator of ICU experience, rather than distressing conscious recall.

The ICE-Q uses 5-point Likert scales of degree of agreement (`strongly agree´ to `strongly disagree´) or degrees of frequency (`all of the time´ to `never´) (see online Supporting Information Appendix S2 for detail about its development and validation). Patients were first contacted by post. If they did not reply by post, they were contacted by telephone (maximum three attempts) and offered the option to complete the questionnaire during the telephone call [16]. To facilitate comparison between domains, each domain score was reported using its original denominator as well as scaled to a common denominator of 5 by dividing the unscaled score by the number of items within the domain. To further aid clinical interpretation, each scaled domain score was dichotomised to facilitate reporting of positive patient experience: 4–5 for awareness, recall, satisfaction (compared with 1–3 which represents neutral or negative experience); and 1–2 for frightening (compared with 3–5 which represents neutral or negative experience). In the absence of research establishing the minimum important difference of ICE-Q scores, we relied on an established distribution-based approach to provide an indicative estimate (online Supporting Information Appendix S2) [18]. For the awareness of the surroundings domain, the minimum important difference was 2.06.

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The primary exposure was treatment allocation (dexmedetomidine, clonidine, propofol). Baseline characteristics presented for descriptive purposes were demographics and pre-morbid factors (age, sex, functional comorbidity index [19]); recalled pre-morbid health-related quality of life (5-level EuroQol 5 dimensions (EQ-5D-5L)); acute illness-related factors (admission type: medical, surgical, trauma); baseline sepsis status (based on clinician judgement); APACHE 2 score; total Sequential Organ Failure Assessment (SOFA) score (excluding neurological score) at randomisation; and delirium risk (Prediction of Delirium in ICU patients (PRE-DELIRIC) score) [20].

After clinical consultation, we selected five predefined potential mediators of treatment effect on patient experience available in the trial dataset: duration of mechanical ventilation (primary trial outcome); duration of ICU stay; days with pain behaviour (poor limb relaxation and/or poor synchronisation with mechanical ventilation, as adapted from the Sedation Quality Assessment Tool) [16, 21]; days with agitation (Richmond Agitation-Sedation Scale (RASS) +3 or +4); and days in a coma (RASS -4 or -5 for > 8 h) or delirium (captured using the Confusion Assessment Method-ICU (CAM-ICU)). Days in a coma or delirium were analysed as a composite outcome to avoid bias from missing delirium assessments in patients who were deeply sedated, for whom validated delirium screening tools cannot be applied.

Individual ICE-Q questions and domain scores were visualised using stacked bar charts and forest plots. Univariable and multivariable linear regression was used to evaluate the association between treatment allocation and each of the four ICE-Q domain scores, reporting a mean difference in ICE-Q as the primary estimate. The latter estimates the treatment effect at a population level (aligning with the research question) whereas reporting group medians and quartiles provide the most accurate descriptive representation of the distribution. Potential confounders were limited to those available within the trial dataset and guided by clinical expertise from the trial steering group to include age; functional comorbidity index; recalled pre-critical illness EQ-5D-5L; admission type; APACHE 2 score; and PRE-DELIRIC score. Variable selection was based on causal directed acyclic graphs to underpin the analytical approach for modelling and mediation analyses (Fig. 1 and online Supporting Information Figure S1).

Mediation analysis facilitates an understanding of mechanisms by which an intervention produces its effect [22–24]. We conducted mediation analyses to evaluate the direct and indirect effects of treatment allocation on outcomes via potential mediators using linear regression.

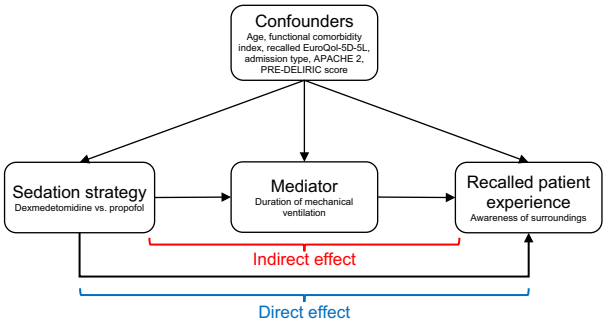


Figure 1 Conceptual directed acyclic graph representing causal framework underpinning mediation analysis for one combination of intervention, mediator and outcome. This illustrates the relationships between sedation strategy (dexmedetomidine vs. propofol comparison) and recalled patient experience showing the hypothesised direct and indirect pathways and the confounders included in the analysis. PRE-DELIRIC: Prediction of Delirium in ICU patients score.

Separate mediation models were developed for each exposure (dexmedetomidine and clonidine were evaluated separately, each using propofol as the control), each of the four ICE-Q domain scores and each of the five mediators. Details on assumptions that underpin the mediation analyses are reported in online Supporting Information Appendix S2. All analyses were performed using Stata version 18.5 (StataCorp, College Station, TX, USA).

We undertook a complete case analysis. To explore response bias, we evaluated differences between those with and without missing data by comparing characteristics of patients alive at 90 days post-randomisation with sufficient data (`responders´, defined as patients who answered all questions that pertained to at least one ICE-Q domain) vs. ICE-Q non-responders. We undertook quantitative bias analysis to evaluate the impact of non-response on our primary findings [25]. Specifically, we applied inverse probability of attrition weighting to adjust for differential response rates. To estimate the probability of response, we fitted a logistic regression model using baseline covariates hypothesised to be associated with attrition (online Supporting Information Appendix S2). We then used the inverse of these predicted probabilities as weights. Inverse probability of attrition weighting re-weights the responder sample to approximate the characteristics of the full target population, including non-responders, thereby reducing bias introduced by attrition.

Results

Of 1404 patients recruited to the A2B trial and included in the primary analysis, 1009 (71.9%) were alive at 90 days

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post-randomisation. Of these, 289 (28.6%) completed questions in at least one domain of the ICE-Q (responders); the remainder were classified as non-responders (720, 71.4%) (Fig. 2). Patient demographics and clinical variables are shown in Table 1 and patient characteristics stratified by ICE-Q response and vital status at 90 days are detailed in online Supporting Information Table S2. Responders and non-responders were similar across most characteristics, including comorbidity prevalence (responders vs. non-responders, ≥ 1 comorbidity 219/289, 75.8% vs. 516/720, 73.3%); admission type (medical 170/289, 58.8% vs. 417/720, 57.9%); and severity of illness (median (IQR [range]) APACHE 2 score 18 (14–24 [0–48]) vs. 19 (14–24 [0–70])). However, responders tended to be older (median (IQR [range]) 62 (52–71 [20–88]) y vs. 58 (47–68 [18–92] y)). Duration of mechanical ventilation (trial primary outcome) was also similar between groups (median (IQR [range]) 5 (2–9 [0–185]) d vs. 4 (2–10 [0–183]) d).

The primary outcome, median (IQR [range]) ICE-Q domain scores, scaled for comparison purposes so that each was scored 1–5 were frightening experiences 3.2 (2.5–3.7 [1.0–5.0]); awareness of surroundings 3.3 (2.8–3.9 [1.0–5.0]); recall of experiences 2.6 (2.0–3.0 [1.0–4.0]); and satisfaction with care 3.8 (3.3–4.3 [2.0–5.0]) (see online Supporting Information Table S3 for unscaled domain scores). Responses to the individual questions contributing to ICE-Q domains are in Figure 3 and stratified by treatment allocation in online Supporting Information Figure S2. Using the dichotomised domain score to aid interpretability, patients reported most positive experience in the satisfaction with care domain (score 4/5, 121/282, 43%), followed by awareness of surroundings (score 4/5, 58/267, 22%) and frightening experiences (score 1/2, 41/281, 15%). In contrast, there were low levels of positive experience in the recall of experiences domain (score 4/5, 9/276, 3%).

In univariable analyses, treatment allocation was not associated with three patient experience domains: frightening experiences; recall of experiences; or satisfaction with care (online Supporting Information Figure S3 and Table S4). However, treatment with

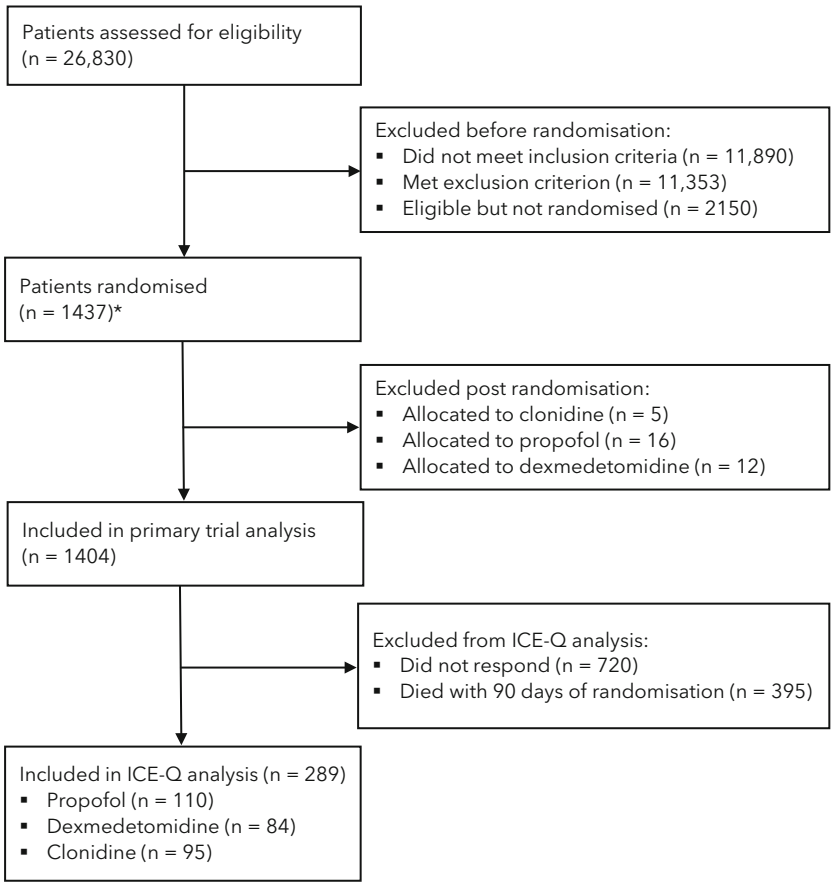


Figure 2 Study population derivation. ICE-Q, Intensive Care Experience Questionnaire. *Note 1438 patients were randomised, but one patient was randomised twice in error.

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Table 1 Baseline characteristics of patients who completed at least one ICE questionnaire stratified by treatment allocation. Values are median (IQR [range]) or number (proportion).

	Dexmedetomidine n = 84	Clonidine n = 95	Propofol (standard care) n = 110
Age; y	62 (52–71 [20–92])	62 (54–70 [18–86])	62 (51–71 [19–90])
Sex; male	48 (57%)	60 (63%)	69 (63%)
Admission Functional Co-Morbidity Index*			
0	22 (26%)	16 (17%)	32 (29%)
1	23 (27%)	29 (31%)	25 (23%)
2	15 (18%)	23 (24%)	24 (22%)
3+	24 (29%)	27 (28%)	29 (26%)
Recalled EuroQol-5D-5L at baseline**	0.86 (0.69–0.99 [-0.30–1.00])	0.83 (0.69–0.99 [-0.30–1.00])	0.78 (0.54–0.99 [-0.50–1.00])
Admission type			
Medical	52 (62%)	55 (58%)	63 (57%)
Surgical (atraumatic)	29 (35%)	33 (35%)	36 (33%)
Trauma	3 (4%)	7 (7%)	11 (10%)
Planned admission			
Planned	11 (13.1%)	7 (7%)	12 (11%)
Unplanned	73 (86.9%)	88 (97%)	98 (89%)
Delirium risk (PRE-DELIRIC score)#	66 (48–82 [7–100])	76 (62–88 [7100])	69 (44–81 [4–100])
APACHE 2 score	18 (13–23 [0–39])	19 (14–25 [0–60])	18 (14–24 [0–70])
Total sequential organ failure assessment score##	8 (6–9 [0–17])	8 (6–10 [1–16])	7 (6–10 [1–16])
Sedative and opioid use before randomisation			
Propofol	84 (100%)	94 (99%)	110 (100%)
Midazolam	3 (4%)	7 (7%)	6 (6%)
Clonidine	3 (4%)	2 (2%)	2 (2%)
Dexmedetomidine	0	1 (1%)	0
Fentanyl	21 (25%)	22 (23%)	30 (27%)
Alfentanil	43 (51%)	56 (59%)	64 (58%)
Morphine	4 (5%)	5 (5%)	4 (4%)
Remifentanil	15 (18%)	15 (16%)	12 (11%)
Diazepam	1 (1%)	0	1 (<1%)

*Functional Comorbidity Index comprises long-term conditions which are associated with physical function rather than mortality-focused measures such as the Charlson Comorbidity Index. See Lee et al. [17] for more details.
**EQ5DL was patient-reported, preferentially, but where a patient was unable to complete, this questionnaire was judged and completed by surrogate individual.
#Risk of delirium missing data: dexmedetomidine 9 (11%); clonidine 17 (18%); propofol 25 (23%); total 51 (18%).
##Total SOFA missing data: dexmedetomidine 5 (6%); clonidine 4 (4%); propofol 2 (2%); total 11 (4%).

dexmedetomidine compared with propofol was associated with a significantly higher score in the awareness of surroundings domain, indicating a more positive experience (32 (27–36 [9–42]) vs. 28 (22–34 [11–45]); mean difference 2.7, 95%CI 0.4–5.0, p = 0.02), which exceeded the minimum important difference threshold. After adjustment for potential confounders, the association of dexmedetomidine with a higher awareness of surroundings domain score persisted (mean difference 3.6, 95%CI 1.0–6.2, p = 0.01) (online Supporting Information Figure S4 and Table S5), which was greater than the minimum important difference. Using the dichotomised domain score (4 or 5), 20/79 (25%) patients allocated to the dexmedetomidine group had a positive experience in relation to awareness of surroundings compared with 18/96 (19%) in those allocated to the propofol group.

Among the potential confounders in univariable analyses, there were several significant associations (online Supporting Information Figure S3 and Table S4). However, in multivariable modelling, only sex remained significantly associated with two of the four ICE-Q domain scores (online Supporting Information Figure S4 and Table S5): women

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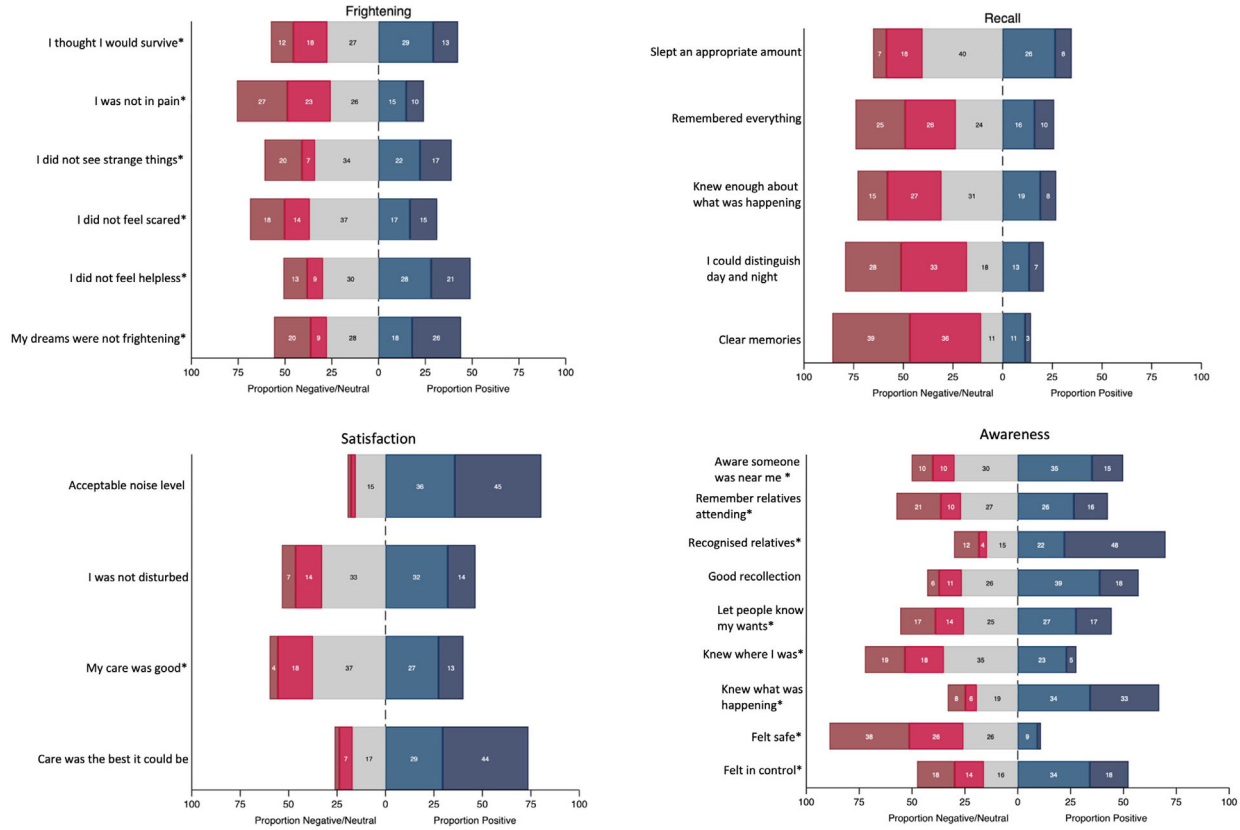


Figure 3 Distribution of responses to individual ICE-Q questions by domain. *Indicates where a score has been inverted from the original questionnaire for consistency in the figure. A score of 5 denotes a positive experience and a score of 1 denotes a strongly negative experience for all domains. Note the descriptors of each ICE-Q question have been modified to reflect the score reversal and a score of 1 denotes a strongly negative experience for all domains. Brown, strongly negative; red, negative; grey, neutral; blue, positive; dark blue, strongly positive.

recalled significantly worse frightening experiences and worse satisfaction than men.

In mediation analyses for the effect of dexmedetomidine on the ICE-Q awareness of surroundings domain, a small proportion of the effect could be explained by each of variables evaluated (Table 2). For the three mediators that did not show competitive mediation (i.e. opposite directions of direct and indirect effect), the proportion of the total effect mediated by each mediator was number of days with pain 10.2%; number of days with coma/delirium 13.2%; number of days with agitation 1.0%. This indicates that the effect of dexmedetomidine on improved awareness is not explained by less pain, coma or agitation. Similarly, analyses for clonidine showed a small proportion of the total effect mediated by any of the mediators. Results of mediation analyses for the other ICE-Q domains are in online Supporting Information Tables S6–S8. In the quantitative bias and sensitivity analysis, reweighting the responder population to allow for non-response using inverse probability of attrition weighting did not materially alter the primary findings (online Supporting Information Tables S9–S13 and Figures S5 and S6).

Discussion

This secondary analysis of data from the A2B randomised controlled trial evaluated factors associated with patient-reported experience 90 days post-randomisation and potential mediating pathways. Patients reported the most positive experience in the satisfaction with care domain and least positive experience in the recall of experience domain. Allocation to dexmedetomidine was associated with a more positive experience of environmental awareness compared with propofol-based sedation. However, the mechanisms driving this association were largely unexplained by the mediators assessed, given that delirium or coma days mediated only a modest proportion of the total effect. More work is required to understand the longer term impacts of patient experience on outcomes. We recommend that personalised approaches to sedation should continue to remain standard practice.

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Table 2 Mediation analysis of the effect of sedation strategy on the awareness of surroundings domain of ICE-Q score. The effect of each intervention on the outcome is decomposed into its direct effect on the outcome and into its indirect effect which goes through the mediator to impact on the outcome. For example, dexmedetomidine (vs. propofol) increases the awareness of surroundings domain score by 3.38. Only 13.2% of its effect is mediated indirectly through the number of days with delirium or coma (mediator) and the remaining 86.8% of the effect occurs directly on the outcome. A negative proportion can occur when competitive mediation is present. This means that the direct effect and indirect effect act in opposite directions on the outcome.

Mediator	Dexmedetomidine (vs. propofol)			Clonidine (vs. propofol)		
	Coefficient (95%CI)	% of total effect	p value	Coefficient (95%CI)	% of total effect	p value
Mechanical ventilation						
Indirect effect	0.00 (-0.13–0.12)	-0.1%	0.94	-0.11 (-0.35–0.13)	-4.6%	0.36
Direct effect	3.61 (1.03–6.18)	100.1%	0.01	2.53 (0.06–5.01)	104.6%	0.05
Total effect	3.60 (1.04–6.16)		0.01	2.42 (-0.08–4.92)		0.06
Duration of ICU stay; days						
Indirect effect	-0.05 (-0.30–0.21)	-1.3%	0.71	-0.11 (-0.39–0.18)	-4.6%	0.45
Direct effect	3.63 (1.08–6.19)	101.3%	0.01	2.51 (0.04–4.98)	104.6%	0.05
Total effect	3.58 (1.02–6.15)		0.01	2.40 (-0.11–4.91)		0.06
Days with delirium or coma						
Indirect effect	0.45 (-0.26–1.16)	13.2%	0.22	0.16 (-0.26–0.57)	7.2%	0.46
Direct effect	2.94 (0.38–5.50)	86.8%	0.03	1.99 (-0.50–4.47)	92.8%	0.12
Total effect	3.38 (0.80–5.97)		0.01	2.14 (-0.37–4.65)		0.10
Days with agitation						
Indirect effect	0.03 (-0.25–0.32)	1.0%	0.81	0.00 (-0.08–0.08)	0.2%	0.91
Direct effect	3.57 (0.99–6.15)	99.0%	0.01	2.41 (-0.10–4.92)	99.8%	0.06
Total effect	3.60 (1.03–6.18)		0.01	2.41 (-0.09–4.92)		0.06
Days with pain						
Indirect effect	0.34 (-0.45–1.13)	10.2%	0.40	-0.27 (-0.65–0.11)	-12.8%	0.17
Direct effect	2.99 (0.34–5.65)	89.8%	0.03	2.36 (-0.15–4.87)	112.8%	0.07
Total effect	3.33 (0.72–5.95)		0.01	2.09 (-0.47–4.65)		0.11

To our knowledge, we present the first comparison of patient-reported experience between sedation strategies using a validated, standardised instrument. Patient-reported experience plays a critical role in evaluation and improvement of healthcare quality and is not captured by clinical outcomes or PROMs [26, 27]. As health systems increasingly prioritise value-based and person-centred care, patient-reported experience has become an essential component of performance assessment and a key driver of meaningful patient-aligned improvement [28].

Measurement of ICU experience is challenging because patients are often sedated; lack capacity; or experience delirium, which impairs cognition and perception. The ICE-Q is one of few validated tools for ICU survivors, developed from empirical work that shows adequate psychometric performance, and it captures wide-ranging aspects of experience compared with narrower tools such as the Intensive Care Unit Environmental Scale [29] and the Intensive Care Unit Memory Tool [30]. The four ICE-Q domains highlight how well staff communicate; address psychological needs; involve patients/families in decision-making; and provide co-ordinated care. Because patients in ICU often experience vulnerability, uncertainty and interactions with multiple professionals, systematic measurement offers valuable insight into human and relational factors that shape trust, safety and recovery.

We found that patients assigned to dexmedetomidine reported more positive experiences related to awareness of surroundings. This domain includes nine questions (online Supporting Information Table S1), and we observed improvements across all nine elements, suggesting consistency (online Supporting Information Figure S7). This consistency strengthens the validity of the finding by confirming that dexmedetomidine provides a genuine, coherent treatment effect on the underlying construct of patient awareness, rather than isolated benefits on individual elements.

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The association between dexmedetomidine and improved awareness of surroundings is biologically plausible and aligns with postulated sedation mechanisms. High α-2-receptor specificity promotes light sedation with patients more arousable, co-operative and interactive [31], to potentially promote clearer cognition than GABA-agonists, even at comparable sedation levels [32, 33]. Systematic reviews also suggest that dexmedetomidine reduces delirium, potentially increasing environmental engagement during sedation [34]. However, we found no differences in deep sedation, delirium or optimum sedation rates between groups. Lower α-2-receptor specificity for clonidine might explain its lack of association; patients allocated to the clonidine group also received higher concurrent propofol doses in the trial [14]. The limited mediation effect of the evaluated variables suggests that other unmeasured factors may be mediating the effect of dexmedetomidine on awareness, such as improved orientation through environmental cues or enhanced family interaction. Such nuanced mechanisms are difficult to capture objectively in trial contexts.

Patients randomised to an α-2 agonist sedation strategy received adjunctive propofol during their ICU admission, which might have influenced patient experience and recall. This issue is explored in detail in the main trial [14] and process evaluation publications [35]. Propofol infusion supported safe sedation when α-2 agonists were limited by adverse effects including severe bradycardia or where agitation required supplementary sedation. The embedded qualitative process evaluation found that continued low-dose propofol use reflected limited staff confidence with α-2 agonists; dose-limiting adverse-effects, for example, severe bradycardia; and the need for a `propofol safety net´ for agitation. Importantly, however, reported median propofol infusion rates in the first 5 days post-randomisation were substantially lower in patients allocated to the dexmedetomidine/clonidine groups compared with propofol usual-care group (dexmedetomidine: 0.21–0.29 $mg.kg.h^{-1}$; clonidine 0.33–0.38 $mg.kg.h^{-1}$; propofol 0.83–1.08 $mg.kg.h^{-1}$) [14].

Our study has several strengths. The A2B trial minimised bias through randomisation with allocation concealment and ICE-Qs were administered prospectively by researchers unaware of treatment allocation. We constructed a directed acyclic graph to guide analyses, develop mediation analyses that appropriately considered confounding and temporality. However, our study also has important limitations. First, although sample size was large relative to other ICU patient experience studies, ICE-Q follow-up was obtained for only 29% of survivors. Although responders had similar characteristics to non-responders, we took further steps to mitigate the impact of non-response. We adjusted analyses for confounders to reduce the potential bias in exposure-outcome association due to non-response (a form of collider bias) and accounted for potential confounding in the mediation analysis. However, confounder selection was restricted to variables available in the trial dataset. For example, the presence of unmeasured pre-existing strong social support could influence the mediator (e.g. days with pain behaviour), the outcome and the likelihood of non-response through greater family presence during ICU stay and follow-up. We undertook quantitative bias analysis as a sensitivity analysis to evaluate the impact of non-response, which did not show substantial deviation from the primary findings. Nonetheless, non-response bias cannot be fully excluded given the high attrition (> 70%) and potential residual confounding. If non-response was strongly linked to poor patient-reported experience and not captured by variables included in the quantitative bias analysis, bias may persist. The study was relatively underpowered to identify associations and mediating pathways with precision, which may miss small but clinically meaningful effects. Finally, ICE-Q was measured at 90 days post-randomisation; although the optimal timing for assessing ICU experience is uncertain, recall bias or attribution to other care periods cannot be ruled out.

The implications of our findings for clinical practice are uncertain. The A2B trial did not show improvement in important clinical outcomes and identified potential harm with α-2-agonists, including 60% higher rates of severe bradycardia and 55% higher agitation [14]. Health economic analysis also found no incremental cost-effectiveness, concluding that sedative drug costs should not influence clinician choice [36]. Two recent guidelines recommend dexmedetomidine ``*when desirable effects are valued over undesirable effect*´´ [37] or ``*where light sedation and/or a reduction in delirium are of highest priority*´´ [38]. Our data suggest that dexmedetomidine may improve at one validated domain of patient experience but not others. Notably, there was no significant difference in frightening memories, which are associated with long-term psychological morbidity and quality of life [39, 40]. However, the awareness of surroundings domain has been associated with reduced duration of hospital stay and depression in the original ICE-Q validation study [15]. Furthermore, some individuals or clinicians may prioritise awareness over other outcomes, for example, to support family interaction.

Further research is needed to determine whether recall of ICU experience, particularly awareness of surroundings, lies on a causal pathway to long-term psychological

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sequelae such as post-traumatic stress disorder or other wellbeing measures and which experience domains matter most to patients. The smallest ICE-Q score change that patients find meaningful has yet to be established, reflecting similar gaps in other PREMs. Although we used distribution-based methods to contextualise score differences, anchor-based approaches are generally considered the optimal approach and should be prioritised in future work. Any consideration of dexmedetomidine use based on patient experience must be balanced against the full range of outcomes required before intervention adoption, including safety, clinical endpoints, PROMs and PREMs. The sex-related differences in frightening experiences and satisfaction observed in this study are consistent with broader evidence that female patients report more psychological distress, more frightening experiences and lower satisfaction with hospital care compared with male patients [41, 42]. Further research is required to clarify the mechanisms driving sex differences in patient experiences of ICU and to inform the development of targeted interventions that better address the specific needs of women during and after critical illness.

In conclusion, our study establishes that dexmedetomidine compared with propofol was associated with improved patient-reported awareness of surroundings during ICU care. However, only a small proportion of this effect was explained by clinically plausible mediators. Taken together with the primary A2B trial findings that show no superiority of dexmedetomidine over propofol, these hypothesis-generating results do not support routine preference for dexmedetomidine based on patient-reported experience alone. We recommend that personalised approaches to sedation should therefore remain standard practice.

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Acknowledgements

This study was registered at ClinicalTrials.gov (NCT03653832). This study was supported by the National Institute for Health and Care Research, after a commissioned call from officials at the Health Technology Assessment programme. The National Institute for Health and Care Research had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication. CM reports receiving a senior clinical practitioner research award from the National Institute for Health and Care Research and receiving personal fees from Pharmaceutical Press for serving as Editor-in-Chief of *Critical Illness*. NL reports being the director of research and intensive care society chair for the Scottish Intensive Care Society Audit Group, Public Health Scotland. Data are unable to be publicly shared due to the risk to individual patient privacy. However, a subset of trial patients agreed for their data to be made available for use in future research. Once a fully anonymised dataset is made available from the trial investigators, approved researchers can gain access to this dataset by applying to Edinburgh Clinical Trials Unit. Statistical code is not available. No other competing interests declared.

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Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1. A2B trial investigators.

Appendix S2. Supplementary methods.

Table S1. Domains and individual questions used in the ICE-Q questionnaire to assess patient-reported experience of intensive care.

Table S2. Baseline characteristics and mediators for patients stratified by response to any ICE questionnaire and vital status at 90 days.

Table S3. Mediator and outcome variables stratified by treatment allocation.

Table S4. Univariable association between ICE questionnaire domains and treatment allocation, covariates and potential mediators.

Table S5. Multivariable association between ICE questionnaire domains and treatment allocation and covariates.

Tables S6–S8. Mediation analysis of effect of sedation strategy on the frightening, satisfaction and recall domains of ICE-Q score.

Table S9. Multivariable association between ICE questionnaire domains and treatment allocation and covariates adjusted using inverse probability of attrition weighting in quantitative bias analyses to evaluate non-response bias.

Tables S10–S13. Mediation analyses of effect of sedation strategy on the awareness of surroundings, frightening, satisfaction and recall domains of ICE-Q score adjusted using inverse probability of attrition weighting in quantitative bias analyses to evaluate non-response bias.

Figure S1. Directed acyclic graphs showing the causal framework underpinning the mediation analysis.

Figure S2. Distribution of responses to individual ICE-Q questions by domain stratified by treatment allocation.

Figure S3. Univariable association between covariates and each ICE-Q domain

Figure S4. Multivariable association between covariates and each ICE-Q domain.

Figure S5. Univariable associations between covariates and each ICE-Q domain adjusted using inverse probability of attrition weighting in quantitative bias analyses to evaluate non-response bias.

Figure S6. Multivariable associations between covariates and each ICE-Q domain adjusted using inverse probability of attrition weighting in quantitative bias analyses to evaluate non-response bias.

Figure S7. Number of patients needing to be treated with dexmedetomidine compared with propofol to achieve a positive experience in nine items which constitute the awareness of surroundings domains.

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