Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Dexmedetomidine Added to Standard Care on Ventilator-Free Time in Patients With Agitated Delirium
A Randomized Clinical Trial

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IMPORTANCE Effective therapy has not been established for patients with agitated delirium receiving mechanical ventilation.

OBJECTIVE To determine the effectiveness of dexmedetomidine when added to standard care in patients with agitated delirium receiving mechanical ventilation.

DESIGN, SETTING, AND PARTICIPANTS The Dexmedetomidine to Lessen ICU Agitation (DahLIA) study was a double-blind, placebo-controlled, parallel-group randomized clinical trial involving 74 adult patients in whom extubation was considered inappropriate because of the severity of agitation and delirium. The study was conducted at 15 intensive care units in Australia and New Zealand from May 2011 until December 2013. Patients with advanced dementia or traumatic brain injury were excluded.

INTERVENTIONS Bedside nursing staff administered dexmedetomidine (or placebo) initially at a rate of 0.5 μg/kg/h and then titrated to rates between 0 and 1.5 μg/kg/h to achieve physician-prescribed sedation goals. The study drug or placebo was continued until no longer required or up to 7 days. All other care was at the discretion of the treating physician.

MAIN OUTCOMES AND MEASURES Ventilator-free hours in the 7 days following randomization. There were 21 reported secondary outcomes that were defined a priori.

RESULTS Of the 74 randomized patients (median age, 57 years; 18 [24%] women), 2 withdrew consent later and 1 was found to have been randomized incorrectly, leaving 39 patients in the dexmedetomidine group and 32 patients in the placebo group for analysis. Dexmedetomidine increased ventilator-free hours at 7 days compared with placebo (median, 144.8 hours vs 127.5 hours, respectively; median difference between groups, 17.0 hours [95% CI, 4.0 to 33.2 hours]; $P = .01$). Among the 21 a priori secondary outcomes, none were significantly worse with dexmedetomidine, and several showed statistically significant benefit, including reduced time to extubation (median, 21.9 hours vs 44.3 hours with placebo; median difference between groups, 19.5 hours [95% CI, 5.3 to 31.1 hours]; $P < .001$) and accelerated resolution of delirium (median, 23.3 hours vs 40.0 hours; median difference between groups, 16.0 hours [95% CI, 3.0 to 28.0 hours]; $P = .01$). Using hierarchical Cox modeling to adjust for imbalanced baseline characteristics, allocation to dexmedetomidine was significantly associated with earlier extubation (hazard ratio, 0.47 [95% CI, 0.27-0.82]; $P = .007$).

CONCLUSIONS AND RELEVANCE Among patients with agitated delirium receiving mechanical ventilation in the intensive care unit, the addition of dexmedetomidine to standard care compared with standard care alone (placebo) resulted in more ventilator-free hours at 7 days. The findings support the use of dexmedetomidine in patients such as these.

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The incidence of delirium in critically ill patients is high.[1,2] Delirium is associated with increased mortality[3] and decreased long-term cognitive function.[4,5] Agitated delirium is particularly problematic in patients receiving mechanical ventilation because it increases the risk of self-extubation and removal of other essential medical devices.[6] Identification of an agent that shortens the duration of established delirium would be an important therapeutic advance.

Dexmedetomidine, a sedative α_2-agonist, is theoretically an attractive treatment for patients with agitated delirium in the intensive care unit (ICU) because unlike other sedatives, it induces a calm yet rousable state with preserved respiratory drive, thereby allowing it to be continued after extubation.[7] However, to our knowledge, no trial has compared dexmedetomidine with placebo for the treatment of patients receiving mechanical ventilation who would be candidates for extubation based on respiratory, cardiovascular, and metabolic criteria but who remain intubated because of severe agitated delirium. Accordingly, we tested the hypothesis that dexmedetomidine, when added to all other elements of standard care, would result in shorter duration of delirium and earlier extubation in such patients.

Methods

The Dexmedetomidine to Lessen ICU Agitation (DahLIA) study was a double-blind, parallel-group, placebo-controlled multicenter randomized trial in which intubated ICU patients were allocated randomly 1:1 to receive dexmedetomidine or saline as a treatment for agitated delirium. No other aspect of patient care was constrained, with the exception that clonidine was prohibited due to its potential interaction with dexmedetomidine.

The trial was conducted between May 9, 2011, and December 23, 2013, in the ICUs of 15 hospitals in Australia and New Zealand, 14 of which are mixed medical-surgical units (7 tertiary academic and 7 metropolitan) and 1 of which admits primarily postoperative cardiac surgical patients. The trial protocol, which contains the statistical analysis plan, appears in Supplement 1. The trial protocol was approved by the Austin Hospital human research ethics committee and, where required, by individual hospital ethics committees.

Consent was sought from the person responsible for the patient. In some jurisdictions, if this person could not be contacted, the patient could be enrolled in anticipation of retrospective consent. In other jurisdictions, eligible patients were enrolled when the treating clinician considered participation to be in the patient's best interest; however, patients were not included if relatives indicated that the patient would not wish to participate.

Once the patient had recovered sufficiently, all had the opportunity to provide fully informed consent to the use of data and ongoing study participation. Either the patient or person responsible could withdraw consent at any stage. A data and safety monitoring committee reviewed all adverse effects. There was no interim analysis.

Adult patients (aged ≥18 years) were eligible for the study if, in the opinion of their treating physician, they continued to require mechanical ventilation only because their degree of agitation was so severe as to make lessening their sedation and extubation unsafe. These criteria were quantified objectively by requiring that the patient should meet all of these additional criteria during the 4 hours prior to randomization: (1) need for mechanical restraint, antipsychotic or sedative medication, or both restraint and medication; (2) have Confusion Assessment Method for the ICU (CAM-ICU)[8] results that indicated presence of delirium; and (3) have a Motor Activity Assessment Scale (MAAS) score[9] of 5 or greater, confirming psychomotor agitation.

Patients were excluded if they (1) were pregnant or breastfeeding, (2) had dementia that required professional nursing care, (3) had a head injury as the cause of their altered mental state, (4) were already receiving dexmedetomidine or clonidine for sedation, (5) had been enrolled previously in the study, or (6) there was a known contraindication to haloperidol or α_2-agonists.

Patients were randomized, stratified by site and age (<55 years and ≥55 years), in concealed permuted blocks of 2 to 6 by a computer-generated algorithm accessed via Internet connection to the Australian and New Zealand Research Centre at Monash University. Unblinded pharmacists or nurses neither caring for the patient nor involved in the trial prepared the study drug in identically labeled syringes. Patients in the dexmedetomidine group were started with a dose of 0.5 µg/kg/h. There was a clinician-directed option of a bolus of 1.0 µg/kg over 20 minutes.[10]

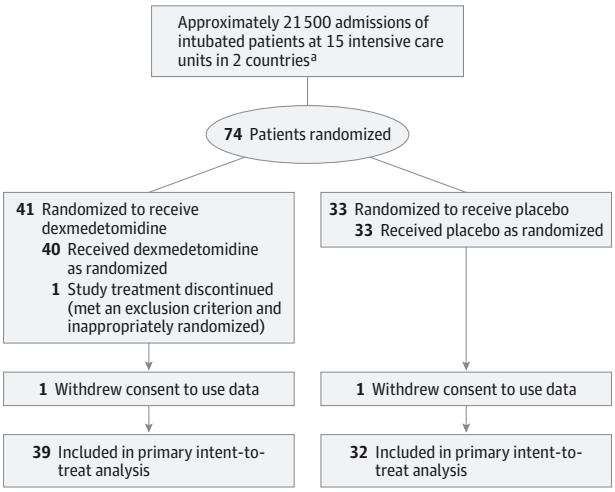
Patients randomized to placebo received an identically labeled infusion of saline at an equivalent rate. Study medication was titrated by the bedside nurse between 0 and 1.5 µg/kg/h to achieve a Richmond Agitation-Sedation Scale score[11] of 0 or to achieve physician-prescribed goals. After 48 hours of study drug infusion, the treating physician could prescribe open-label dexmedetomidine and the study drug infusion would be stopped. More than 7 days of infusion of study drug was considered treatment failure; at that point, the study drug was stopped and open-label dexmedetomidine could be commenced.

Extubation timing (or the decision to insert a tracheostomy) was determined by senior ICU physicians, taking into account the assessments of bedside nurses. This decision was not part of the protocol, but instead was tailored to individual patient circumstances, with a physician constantly present at each ICU. Physicians and nurses treating study patients, and the study staff at each site, remained blinded to group allocation.

The primary outcome was the number of ventilator-free hours (the number of hours alive and free from requiring invasive mechanical ventilation up until day 7 postrandomization) during the incident ICU admission. Patients who had tracheostomies inserted were considered to be free of sedation (and so likely to have been extubated had a tracheostomy not been inserted) after a 4-hour period in which they received no sedatives or opioid analgesics.

The 21 reported secondary outcomes that were defined a priori included time to extubation (in the case of tracheos-

Figure 1. Patient Flow Diagram of the DahLIA Trial



The number of patients not randomized due to not meeting the inclusion criteria or having met 1 of the exclusion criteria was not recorded. DahLIA indicates Dexmedetomidine to Lessen ICU Agitation.

[a] Estimated from total admission numbers to each intensive care unit along with data from the Australian and New Zealand Intensive Care Society Centre for Outcomes and Resource Evaluation[14] on the proportion of these admissions that were intubated.

tomy, with liberation from sedation and mechanical ventilation defined in the same manner as used for the primary outcome), time taken to achieve a satisfactory sedation score (Richmond Agitation-Sedation Scale score of −2 to 1), time taken to achieve a satisfactory agitation score (MAAS score of 2 to 4), proportion of study time with a satisfactory MAAS score, period until the nurse caring for the patient thought it was time to extubate, time to the first CAM-ICU results that indicated absence of delirium, time spent having CAM-ICU results that indicated presence of delirium, the requirement for sedative and antipsychotic medications, the proportion who underwent tracheostomy, requirement for reintubation, daily Sepsis-related Organ Failure Assessment score, and lengths of stay in the ICU and hospital. Adverse events were recorded both prospectively and by review of each clinical chart.

Modified intention-to-treat analyses were performed. Modification was permitted to account for postrandomization circumstances that prevented use of data from certain patients. Because there were no missing data for the primary outcome and less than 5% missing for all secondary outcomes, no data imputation was performed. Due to nonnormality, all continuous outcomes were compared using Mann-Whitney tests with location shifts between treatment groups calculated using the Hodges-Lehmann estimate and reported using distribution-free 95% confidence limits.

The sensitivity analysis accounting for multiple sites was performed using the van Elteren statistic. Categorical outcomes were compared using χ^2 or Fisher exact tests and reported as differences in proportion (95% confidence interval). Time-to-event data were compared using log-rank tests and presented as Kaplan-Meier curves. To account for any effect of site and for baseline imbalances, a Cox proportional hazards regression model was used with patients nested within site, and site treated as a random effect with the following covariates included in the model: Acute Physiology and Chronic Health Evaluation II diagnosis, duration of intubation, and elective status. Proportionality assumptions were determined using log survival plots.

All statistical analyses were performed using Stata version 11.2 (StataCorp) or SAS version 9.4 (SAS Institute Inc) with a 2-sided *P* value of less than .05 considered significant. No adjustment was made for multiple comparisons, and so the secondary outcomes presented (although all prespecified) should be considered exploratory, yielding hypothesis-generating findings.

Based on a pilot study with a mean control estimate of 108 ventilator-free hours (SD, 46 ventilator-free hours),[12] a sample size of 96 patients was estimated to provide 80% power to detect a 20-hour difference (ie, half the effect size observed in a pilot study) using a 2-tailed hypothesis at an α level of .05. These calculations include an inflation rate of 15% to account for the possibility that ventilation-free days would not be normally distributed.[13]

However, the sponsoring pharmaceutical company (Hospira Australia) decided against extending funding and provision of study drug beyond a date that had been earlier agreed. Consequently, the trial was terminated prematurely in December 2013 after 74 patients had been randomized. At no stage did the pharmaceutical company have access to the study data, and no data analysis by the study investigators had occurred prior to this decision.

To account for the possibility that early termination may exaggerate the effect size, additional analyses were performed post hoc to assess the likelihood of a null finding had the study been completed as originally planned. These analyses were performed using 10 000 simulations based first on the assumption that nonenrolled patients came from the original projected population and then second based on the assumption that the nonenrolled patients came from the observed population.

Results

From May 2011 until December 2013, we randomized 74 patients (**Figure 1**). However, 1 patient allocated to dexmedetomidine had been randomized in error, and 1 patient in each

Table 1. Baseline Patient Characteristics[a]

	Dexmedetomidine (n = 39)	Placebo (n = 32)
Tertiary ICU with >18 beds	17 (43.6)	15 (46.9)
Age, median (IQR), y	58 (47-65)	56.5 (46-69.5)
Male sex	28 (71.8)	25 (78.1)
Weight, median (IQR), kg	83 (72-100)	85 (78-105)
Living at home	39 (100)	31 (96.9)
APACHE II score immediately prior to randomization, median (IQR)		
Acute physiology	11 (8-16)	11.5 (8.5-16.5)
Total	14 (10-22)	14 (11-20)
APACHE II comorbidity score ≥2	10 (25.6)	6 (18.8)
APACHE II diagnostic category		
Nonoperative	17 (43.6)	12 (37.5)
Respiratory	5 (29.4)	5 (41.7)
Cardiovascular	4 (23.5)	0
Neurological	4 (23.5)	2 (16.7)
Other	4 (23.5)	5 (41.7)
Operative	22 (56.4)	20 (62.5)
Multiple trauma	4 (18.2)	2 (10.0)
Cardiovascular	10 (45.5)	15 (75.0)
Respiratory	1 (4.5)	0
Neurosurgery including neurotrauma	0	1 (5.0)
Gastrointestinal	5 (22.7)	1 (5.0)
Other	2 (9.1)	1 (5.0)
Emergency ICU admission	29 (74.4)	18 (56.3)
During the 24 h prior to randomization		
Mechanical restraint	13 (33.3)	11 (34.4)
Use of pharmacotherapy	(n = 38)	(n = 32)
Midazolam	4 (10.5)	5 (15.6)
Propofol	38 (100.0)	29 (90.6)
Morphine	9 (23.7)	9 (28.1)
Fentanyl	14 (36.8)	11 (34.4)
Antipsychotic (haloperidol, olanzapine, risperidone, or quetiapine)	9 (23.7)	6 (18.8)
Duration of intubation prior to enrollment, median (IQR), h	63 (26-96)	43.5 (23-72)

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; IQR, interquartile range.

[a] Data are expressed as No. (%) unless otherwise indicated.

group withdrew consent, leaving data from 39 patients in the dexmedetomidine group and 32 in the placebo group for analysis. The baseline characteristics of study participants appear in **Table 1**.

Almost all patients were sedated with propofol. Approximately one-third of the patients required mechanical restraint immediately prior to randomization and 20% received an antipsychotic drug. The median Acute Physiology and Chronic Health Evaluation II score immediately prior to randomization was low, reflecting the inclusion criterion that these patients should be ready for extubation except for having agitated delirium.

One male patient randomized to receive dexmedetomidine did not receive any study drug because his physician decided the delirium had resolved almost immediately after randomization. While blinded to study drug allocation, the treating physician of 1 patient randomized to placebo decided, after 48 hours of administering the placebo study drug, optimal treatment would be dexmedetomidine. Therefore, open-label dexmedetomidine was commenced, and the placebo study drug was stopped. Five patients (1 allocated to dexmedetomidine and 4 to placebo) received open-label dexmedetomidine after administration of the study drug for 7 days.

Compared with the dexmedetomidine group, patients allocated to the placebo group received a significantly greater rate and volume of study drug on days 1 and 2 (**Table 2**). More patients in the placebo group received antipsychotic medications (haloperidol, risperidone, olanzapine, or quetiapine) on any day than was true for the dexmedetomidine group (65.6% vs 36.8%, respectively; mean difference between groups, −28.8% [95% CI, −51.3% to −6.3%; P = .02). There were no significant differences in the use of individual antipsychotic drugs (eTable 1 in Supplement 2). On several days, significantly lower quantities of intercurrent sedatives (propofol and midazolam) and opioids (morphine and fentanyl) were used in the dexmedetomidine group compared with the placebo group (eTable 2).

Table 2. Quantification of Study Drug Use and Administration of Intercurrent and Subsequent Medications

	Dexmedetomidine (n = 39)	Placebo (n = 32)	Difference Between Groups (95% CI)	*P* Value
Bolus at start of study drug infusion, No./total No. of observations (%)	2/37 (5.4)	2/32 (6.3)	−0.8 (−12.0 to 10.3)	>.99
Time until peak infusion rate of study drug reached, median (IQR), h	8.3 (5.0 to 17.0)	8.3 (4.0 to 15.3)	0 (−3.0 to 2.0)	.68
Total duration of study drug infusion, median (IQR), h	23.5 (19.5 to 35.0)	35.0 (24.8 to 71.5)	−10.0 (−262.8 to −2.8)	.004
Study drug continued after extubation, No. (%)	4 (10.3)	4 (12.5)	−2.2 (−17.1 to 12.7)	>.99
Day 1				
Study drug rate, median (IQR), mL/h[a]	12.8 (8.3 to 22.2)	25.4 (21.3 to 30.4)	−12.2 (−16.2 to −7.7)	<.001
Total volume of study drug administered, median (IQR), mL/h[b]	9.8 (5.5 to 18.4)	25.2 (20.5 to 29.5)	−13.7 (−17.6 to −8.7)	<.001
Day 2	(n = 13)	(n = 18)		
Study drug rate, median (IQR), mL/h[a]	11.0 (4.6 to 20.3)	25.9 (20.4 to 32.0)	−14.1 (−22.1 to −5.1)	.004
Total volume of study drug administered, median (IQR), mL/h[b]	13 (5.7 to 21.6)	25.9 (19.4 to 32.8)	−12.0 (−21.2 to −2.9)	.01
Day 3	(n = 8)	(n = 13)		
Study drug rate, median (IQR), mL/h[a]	17.9 (7.0 to 27.2)	26.0 (20.0 to 30.2)	−7.6 (−19.8 to 6.2)	.26
Total volume of study drug administered, median (IQR), mL/h[b]	17.9 (6.9 to 27.3)	27.4 (18.7 to 30.6)	−8.6 (−19.6 to 5.2)	.19
Day 4	(n = 3)	(n = 6)		
Study drug rate, median (IQR), mL/h[a]	22.2 (18.7 to 32.3)	21.9 (9.6 to 35.6)	3.6 (−22.5 to 23.3)	.90
Total volume of study drug administered, median (IQR), mL/h[b]	22.2 (17.5 to 32.3)	20.3 (9.0 to 35.6)	4.6 (−23.7 to 31.5)	.90
Day 5	(n = 3)	(n = 4)		
Study drug rate, median (IQR), mL/h[a]	17.8 (14.4 to 19.2)	30.2 (15.1 to 38.4)	−13.4 (−26.8 to 13.7)	.38
Total volume of study drug administered, median (IQR), mL/h[b]	17.8 (14.4 to 19.2)	30.2 (15.1 to 38.4)	−13.3 (−26.8 to 13.7)	.38
Day 6	(n = 2)	(n = 2)		
Study drug rate, median (IQR), mL/h[a]	18.4 (13.6 to 23.3)	38.4 (35.6 to 41.2)	−20.0 (−27.6 to 12.4)	.25
Total volume of study drug administered, median (IQR), mL/h[b]	18.4 (13.6 to 23.3)	22.6 (4.0 to 41.2)	−4.2 (−27.6 to 19.3)	>.99
Day 7	(n = 1)	(n = 2)		
Study drug rate, median (IQR), mL/h[a]	9.8 (9.8 to 9.8)	38.4 (35.6 to 41.2)	−28.6 (−31.4 to 25.8)	.54
Total volume of study drug administered, median (IQR), mL/h[b]	9.8 (9.8 to 9.8)	38.4 (35.6 to 41.2)	−28.6 (−31.4 to 25.8)	.54
Received open-label dexmedetomidine, No./total No. of observations (%)				
Between 48 h and 7 d of receiving the study drug	0/39	1/32 (3.1)	−3.1 (−9.2 to 2.9)[c]	.45
After 7 d of receiving the study drug	2/39 (5.1)	3/32 (9.4)	−4.2 (−16.5 to 8.0)[c]	.65
Received any antipsychotic on any day, No./total No. of observations (%)	14/38 (36.8)	21/32 (65.6)	−28.8 (−51.3 to −6.3)[c]	.02
Study days in which any antipsychotic medication was administered, median (95% CI), %[d]	26.3 (21.3 to 39.0)	40.0 (20.6 to 49.0)	−11.4 (−20.6 to 3.3)	.08
Study days requiring vasopressor for blood pressure support, median (95% CI), %[d]	0 (0 to 35.5)	16.7 (3.0 to 20.7)	−9.5 (−16.7 to 10.1)	.27

Abbreviation: IQR, interquartile range.

[a] In patients receiving the study drug.

[b] In patients remaining in the study.

[c] Data are expressed as percentages.

[d] Indicates the days following randomization until discharge from the intensive care unit or day 7, whichever was sooner. Each daily percentage was calculated using the number of patients who received medication that day divided by the number of patients remaining in the study on that day.

During the 7 days after randomization, propofol use was common in both groups (71.8% of the dexmedetomidine group and 87.5% of the placebo group). The median dosage was significantly higher in the placebo group (5390 mg [interquartile range {IQR}, 1880 to 10 803 mg]) compared with the dexmedetomidine group (980 mg [IQR, 280 to 3050 mg]) (median difference between groups, −3094.5 mg [95% CI, −5852 to −940 mg]; $P < .001$). Patients in the placebo group were more likely to receive morphine (34.4% vs 12.8% of the dexmedetomidine group; mean difference between groups, −21.6% [95% CI, −41.1% to −2.0%]; $P = .03$), and received a significantly higher median dosage of fentanyl (1543 µg [IQR, 335 to 6629 µg] vs 310 µg [IQR, 200 to 680 µg], respectively; median difference between groups, 609 µg [95% CI, 50 to 2225 µg]; $P = .03$) (eTable 3 in Supplement 2).

Patients randomized to dexmedetomidine had significantly more ventilator-free hours at 7 days (median, 144.8 hours vs 127.5 hours in the placebo group; median difference between groups, 17.0 hours [95% CI, 4.0-33.2 hours]; $P = .01$; van Elteren site-adjusted $P = .04$) (**Table 3**). There were no

Table 3. Primary and Secondary Study Outcomes

	Dexmedetomidine (n = 39)	Placebo (n = 32)	Difference Between Groups (95% CI)	*P* Value
Primary Outcome				
Time ventilator-free during the first 7 d after randomization, median (IQR), h	144.8 (114.0 to 156.0)	127.5 (92.0 to 142.8)	17.0 (4.0 to 33.2)	.01
Secondary Outcomes				
Time taken to achieve a satisfactory sedation score, median (IQR), d[a]	1 (1 to 1)	1 (1 to 1)	0 (0 to 0)	.90
Time until bedside nurse thought patient was ready for extubation (not tracheostomy), median (IQR), h	19.1 (16.7 to 25.8)[b]	40.5 (21.1 to 90.7)[c]	−21.1 (−34.5 to −6.0)	<.001
Time to extubation (not tracheostomy), median (IQR), h	21.9 (18.3 to 27.7)	44.3 (25.3 to 94.2)	−19.5 (−31.1 to −5.3)	<.001
Underwent tracheostomy, No. (%)	7 (17.9)	2 (6.3)	11.7 (−3.0 to 26.4)	.14
Time to tracheostomy, median (IQR), h	41.9 (20.2 to 101.8)[d]	71.1 (70.3 to 71.9)[e]	−29.2 (−71.9 to 95.2)	.88
Required intubation for a second time, No. (%)	0	1 (3.2)	−3.1 (−9.2 to 2.9)	.45
Extubated, No. (%)				
<24 h after randomization	8 (20.5)	2 (6.3)	14.3 (−0.9 to 29.5)	.09
<48 h after randomization	30 (76.9)	19 (59.4)	17.5 (−4.0 to 39.1)	.13
On the same calendar day as randomization	6 (15.4)	2 (6.3)	9.1 (−5.0 to 23.2)	.23
On the first or second calendar day after randomization	22 (56.4)	14 (43.8)	12.6 (−10.6 to 35.8)	.28
Confusion Assessment Method for the ICU				
Time to first results indicating absence of delirium, median (IQR), h	23.3 (13.0 to 54.0)	40.0 (25.3 to 76.0)	−16.0 (−28.0 to −3.0)	.01
Time spent with results indicating presence of delirium, median (IQR), h	36 (24 to 66)	62 (42.5 to 106.75)	−24 (−41 to −6)	.009
Proportion of days postrandomization spent with results indicating presence of delirium, median (IQR), %	47 (30 to 76)	62 (46 to 86)	−10 (−30 to 0)	.05
Time spent with at least 1 assessment indicating presence of delirium postrandomization, median (IQR), d	1 (1 to 3)	3 (1 to 4)	−1 (−2 to 0)	.02
Required mechanical restraint on any day, No. (%)	10 (26.3)[f]	15 (46.9)[b]	−20.6 (−42.8 to 1.7)	.07
Proportion of study days in which mechanical restraint was required, median, %	20.0	25.0	−6.8 (−15.6 to 6.1)	.34
Proportion of study days spent lightly sedated, median, %	82.4	74.1	7.8 (−6.6 to 20.2)	.37
ICU length of stay, median (IQR), d				
Postrandomization	2.9 (2.1 to 4.9)	4.1 (3.0 to 7.9)	−1.0 (−2.1 to 0.1)	.09
Overall	5.9 (3.7 to 10.2)	7.5 (4.7 to 11.7)	−1 (−3 to 1)	.29
Hospital length of stay, median (IQR), d				
Postrandomization	8.5 (6.2 to 13.6)	9.5 (6.5 to 13.5)	0 (−3 to 3)	.96
Overall	14.0 (10.0 to 20.0)	12.5 (9.0 to 21.0)	1 (−3 to 5)	.61
Location of death, No. (%)				
ICU	1 (2.6)	0	2.6 (−2.4 to 7.5)	>.99
Hospital	2 (5.1)	0	5.1 (−1.8 to 12.1)	.50
Discharged to rehabilitation rather than home or other acute hospital, No. (%)	5 (13.2)[f]	3 (9.7)[c]	3.5 (−11.5 to 18.4)	.65
Adverse event, No. (%)				
Related to bradycardia	2 (5.3)[f]	0[g]	5.3 (−1.8 to 12.4)	.50
Related to agitation	1 (2.6)[f]	2 (6.7)[g]	−4.0 (−14.3 to 6.2)	.58

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

[a] Assessed as Richmond Agitation-Sedation Scale score of −2 to 1.

[b] There were 32 patients with recorded data.

[c] There were 31 patients with recorded data.

[d] There were 7 patients with recorded data.

[e] There were 2 patients with recorded data.

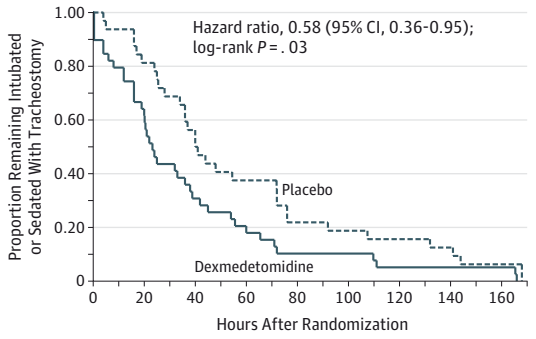
[f] There were 38 patients with recorded data.

[g] There were 30 patients with recorded data.

differences between groups in the proportion of patients who required tracheostomy (Table 3). A sensitivity analysis examining only patients who did not receive a tracheostomy showed the same qualitative difference in ventilator-free hours (median, 147.3 hours [IQR, 131-158 hours] in the dexmedetomidine group vs 128 hours [IQR, 92-143 hours] in the placebo group; median difference between groups, 19.5 hours [95% CI, 6.5-36.0 hours]; *P* = .002).

In the time to event analysis, dexmedetomidine was associated with earlier extubation (hazard ratio [HR], 0.58 [95% CI, 0.36-0.95]; *P* = .03) (**Figure 2**). In the hierarchical Cox proportional hazards regression model adjusting for baseline characteristics (eTable 4 in Supplement 2), allocation to dexmedetomidine remained associated with earlier extubation (HR, 0.47 [95% CI, 0.27-0.82]; *P* = .007). In a sensitivity analysis that used right censoring for patients with tracheostomy at the time

Figure 2. Kaplan-Meier Analysis of the Proportion of Patients Remaining Intubated During the First 7 Days of the Study



No. at risk

Dexmedetomidine	39	10	4	2
Placebo	32	13	6	2

of the procedure, there was no difference in qualitative outcome (HR, 0.39 [95% CI, 0.21-0.71]; P = .002).

The median time to extubation was 21.9 hours for the dexmedetomidine group vs 44.3 hours for the placebo group (median difference between groups, 19.5 hours [95% CI, 5.3 to 31.1 hours]; P < .001; van Elteren site-adjusted P = .004). Bedside nurses thought their patients were ready to extubate significantly earlier (P < .001) if they were receiving dexmedetomidine (median, 19.1 hours [IQR, 16.7 to 25.8 hours]) than if they were receiving placebo (median, 40.5 hours [IQR, 21.1 to 90.7 hours]) (median difference between groups, −21.1 hours [95% CI, −6.0 to −34.5 hours]). The median ICU length of stay was 2.9 days (IQR, 2.1 to 4.9 days) with dexmedetomidine vs 4.1 days (IQR, 3.0 to 7.9 days) with placebo (P = .09).

An additional post hoc simulation analysis calculating the probability of finding no difference in the median duration of ventilator-free hours during the first 7 days after randomization if the trial included the planned number of patients (using both the original design effects and the observed effects) found a chance of less than 7% of producing a null result (P > .05) (calculated using either approach). This lack of likely qualitative difference occurred because the observed treatment effect in this study was very similar to that projected.

Allocation to dexmedetomidine was associated with several improved indices of delirium (Table 3). With dexmedetomidine, delirium resolved more rapidly (median, 23.3 hours vs 40.0 hours in the placebo group; median difference between groups, 16.0 hours [95% CI, 3.0-28.0 hours]; P = .01; van Elteren site-adjusted P = .04). Compared with the patients who received placebo, the patients who received dexmedetomidine had delirium for a lower proportion of their ICU stay, and had a median of 2 additional delirium-free days during their ICU stay. There was no between-group difference in the time taken to achieve a satisfactory sedation score.

The time taken to achieve a satisfactory MAAS score (or proportion of time spent with a satisfactory MAAS score) cannot be reported because almost no patients had a MAAS score recorded after that which was assessed by the study research coordinator at the time of study entry. The protocol required bedside nurses to collect MAAS scores; however, less attention was provided to educate the nurses regarding collection of the MAAS score than the CAM-ICU. This absence of data was missed during interim monitoring, preventing remediation of the problem during the conduct of the trial.

Adverse events (bradycardia requiring interruption of study drug, hypotension requiring vasopressor support, and agitation requiring temporarily increased sedation) were rare and not different between study groups. Two of 39 patients in the dexmedetomidine group and 2 of 32 patients in the placebo group received a bolus of dexmedetomidine. None of these patients were among those who experienced a bradycardia-related adverse event. A patient with known cardiomyopathy developed ventricular tachycardia 8 hours after cessation of the study drug; however, the data and safety monitoring committee ruled that this was not related to the study, and the protocol continued without modification.

There were no statistically significant differences between the groups in Sepsis-related Organ Failure Assessment score on any study day. As expected in this comparatively recovered cohort of critically ill patients, ICU and hospital mortality were low and not different between groups. Only 1 patient required reintubation, which occurred 2 hours following elective extubation. No patient self-extubated.

Discussion

In this double-blind placebo-controlled randomized trial involving patients with agitated delirium receiving mechanical ventilation, who were primarily receiving propofol-based sedation and antipsychotic medications determined by their treating physicians, dexmedetomidine increased the number of ventilator-free hours during the 7 days following randomization. Compared with placebo, dexmedetomidine hastened the resolution of delirium and extubation in patients by approximately 1 day. Adverse events were rare and not different between the groups.

The results of this study are consistent with earlier large randomized clinical trials comparing dexmedetomidine with benzodiazepines or propofol as a sedative, which found dexmedetomidine was associated with less delirium in the ICU[15,16] and reduced time to extubation.[17] However, these were trials of dexmedetomidine as a sedative rather than as a treatment for delirium. Suggestion of a therapeutic effect of dexmedetomidine in established delirium was present in the Safety and Efficacy of Dexmedetomidine Compared With Midazolam trial.[16] In the post hoc analysis of the 60% of patients who had CAM-ICU results indicating the presence of delirium at the time of randomization, there was a reduction in the prevalence of delirium from 95.5% to 68.7%.

Dexmedetomidine had a propofol- and fentanyl-sparing effect on day 1. It is possible that deliriogenic sedatives were replaced with alternatives less prone to cause delirium. However, propofol and opioids are probably less deliriogenic than benzodiazepines,[18] and nonbenzodiazepine alternatives were the overwhelming choice for intercurrent care. Therefore, a direct antidelirium effect of dexmedetomidine remains possible. How an α_2-agonist might exert this

effect remains speculative.[19] It is possible that the analgesic effects of dexmedetomidine might have lessened both agitation and delirium.

Our study is the same size as the largest previous trial[20] of therapy for patients with agitated delirium determined by the CAM-ICU; that study compared (nonblinded) dexmedetomidine with midazolam in 72 patients who had been intubated after undergoing elective cardiac surgery. Patients in the dexmedetomidine group were extubated earlier (46.6 hours vs 58.3 hours in the midazolam group, $P < .001$), but the between-group comparisons of agitated delirium were not reported. This study showed the superiority of dexmedetomidine over midazolam as a sedative for patients with agitated delirium who had undergone intubation. However, given consensus recommendations against benzodiazepines in these circumstances,[18] this is less relevant than the question addressed by our study.

To our knowledge, the only other published trial targeting patients with agitated delirium was a single-center pilot study of 20 patients, which compared nonblinded infusions of dexmedetomidine or haloperidol. Dexmedetomidine shortened time to extubation (from 42.5 hours to 19.2 hours, $P = .02$) and ICU length of stay (from 6.5 days to 1.5 days, $P = .004$). In our larger trial, only 30.4% of patients received haloperidol and a higher percentage received atypical antipsychotics.

The only previous delirium pharmacotherapy placebo-controlled trial (in which only 30.6% had a Riker Sedation-Agitation Scale[21] score of ≥5 at the time of enrollment, suggesting agitated delirium)[22] had a similar design to that of our study. Patients (not all intubated at the time of enrollment) were randomized to quetiapine or placebo, with all other elements of care as directed by the physician. Both groups received as-needed haloperidol. Delirium resolved faster with quetiapine but duration of mechanical ventilation and ICU length of stay were similar to placebo.

This study has several strengths. First, it used a double-blind, multicenter, randomized, permuted block, placebo-controlled design. Second, the study had objective enrollment criteria. Third, the primary end point was patient centered and with likely financial cost-benefit implications. Fourth, the protocol replicated current practice by having bedside nurses independently titrating the study drug to either a physician-prescribed sedation goal or a default goal of light sedation. Fifth, all other therapies were consistent with current consensus recommendations.[18] Sixth, the development of lack of physician equipoise was accommodated by permitting open-label dexmedetomidine after patients had received the study drug for 48 hours, but this had no effect on the results.

The study also has some limitations. The planned 96 patients were not recruited. Unplanned early termination of clinical trials can exaggerate effect size. However, the probability of finding a qualitatively different result in the primary outcome had the trial recruited to the target sample size was less than 7%. The relatively small sample size led to several chance imbalances in baseline characteristics, notably the duration of ventilation before randomization. However, when adjusted for this imbalance, dexmedetomidine remained associated with earlier extubation. Although there was a difference in the primary outcome and several congruent secondary outcomes, the study was underpowered to detect differences in important end points including ICU length of stay.

Many patients (n = 21 500) were screened in the effort to recruit only 74 patients; therefore, the results may not be generalizable to patients earlier in the course of their critical illness, with other forms of delirium, or not intubated. Only patients who could be extubated (were it not for agitated delirium) were recruited. Although we cannot say if the results apply to patients with agitated delirium in the ICU earlier in their illnesses, the dexmedetomidine sedative trials provide reassuring evidence of safety and a suggestion of efficacy in this patient group.

We cannot comment on whether dexmedetomidine might be effective in patients with traumatic brain injury or dementia. However, there is no evidence that dexmedetomidine would harm such patients. Resolution of delirium was one of the most important end points, but identification of delirium in critically ill patients is problematic, as previously argued.[23] Delirium was defined using the CAM-ICU, which has been the subject of criticism for its false-positive results in the context of recently discontinued sedation.[24,25] Nonetheless, the CAM-ICU is recommended by consensus guidelines[18] and our study was blinded.

Even though clinicians were blinded to study drug allocation, dexmedetomidine often causes bradycardia,[10] which might have suggested study drug allocation. However, in agitated patients receiving strong doses of sedating drugs to avoid self-injury, changes in heart rate are common.

Conclusions

Among patients with agitated delirium receiving mechanical ventilation in the ICU, the addition of dexmedetomidine to standard care compared with standard care alone (placebo) resulted in more ventilator-free hours at 7 days. The findings support the use of dexmedetomidine in patients such as these.

ARTICLE INFORMATION

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