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Dexmedetomidine for treatment of hyperactive delirium in non-intubated ICU patients: the 4D randomized clinical trial

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Keywords:

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Abstract

Purpose:

Whether dexmedetomidine improves the control of hyperactive delirium in non-intubated intensive care unit (ICU) patients as compared with placebo remains uncertain.

Methods:

In a multicenter, double-blind, placebo-controlled, two-arm, investigator-initiated, randomized trial conducted in 9 ICUs, we randomly assigned non-intubated critically ill adults with hyperactive delirium to receive continuous intravenous infusion of dexmedetomidine or placebo for at least 36 h. The primary outcome was a joint modelling of multiple outcomes of agitation duration (score of + 1 or higher on the Richmond agitation-sedation scale), delirium duration, or the need for intubation and deep sedation. Key secondary outcomes included the occurrence of complications (such as bradycardia or hypotension), length of stay in ICU, or death.

Results:

Enrollment occurred from December 2017 to February 2022. Final follow-up was in February 2023. The study was stopped for efficacy at the time of the preplanned interim analysis. Among the 151 patients who were included in the final analysis, the between-group difference in the primary outcome was statistically significant (median difference, -30 points; 95% CI, -49 to -12, $p = 0.001$). Agitation duration was shorter in the dexmedetomidine group (1.0 (1.0-2.0) vs 2.0 (1.0-7.0) hours, absolute difference 95% CI -1.0 (-2.0 to -0.1); ES, -0.60; 95% CI, -0.92 to -0.27, $p = 0.001$). Other key secondary outcomes were similar between groups.

Conclusion:

In non-intubated adult ICU patients with hyperactive delirium, the use of dexmedetomidine was associated with a greater clinical benefit than placebo for the joint modelling of multiple endpoints of agitation control, delirium resolution, and intubation with mechanical ventilation. Dexmedetomidine appears to be a valuable alternative that significantly reduced the median duration of agitation by approximately 1 h compared to placebo in hyperactive delirious non-intubated intensive care unit patients.

Trial registration:

ClinicalTrials.gov Identifier: NCT03317067. Registration on October 17th, 2017 prior to first patient inclusion. <https://clinicaltrials.gov/search?term=NCT03317067> .

Take-Home Message

Dexmedetomidine use to treat hyperactive delirium in non-intubated intensive care unit patients remains unknown. In this randomized clinical trial that included 151 adults, dexmedetomidine was significantly associated with a greater clinical benefit than placebo for the joint modelling of multiple composite endpoints of agitation control, delirium resolution, or intubation with mechanical ventilation. Dexmedetomidine appears to be a valuable alternative that significantly reduced the median duration of agitation by approximately 1 hour compared to placebo to treat hyperactive delirious non-intubated intensive care unit patients.

Introduction

Delirium is an acute syndromic brain dysfunction characterized by alterations in consciousness, attention, and cognition caused by a variety of medical conditions rather than a specific underlying neurocognitive disorder [1]. This condition affects 30–50% of intensive care unit (ICU) patients and is associated with increased mortality, ICU and hospital length of stay, healthcare-associated costs, and the development of long-term cognitive impairment [2]. Delirium presents in various motoric subtypes, primarily hyperactive, hypoactive, and mixed [3]. Hyperactive delirium, characterized by agitation, restlessness, and emotional lability, poses significant management challenges, often requiring pharmacological intervention due to patient safety concerns and interference with essential care [3]. In contrast, hypoactive delirium, marked by lethargy and reduced motor activity, is associated with a worse prognosis and has no specific pharmacological treatment [4]. Prevention of delirium is a main focus of the guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU [5], as a part of the so-called A2F bundle [6]. Apart from prevention, little is known about the pharmacological treatment of hyperactive delirium. Early sedation with dexmedetomidine increases the number of delirium-free or coma-free days compared with usual care (mainly propofol) [7]. However, in mechanically ventilated patients treated with light sedation, there was no difference in outcomes between dexmedetomidine and propofol infusions [8]. While antipsychotics like haloperidol are often considered for symptomatic management of agitation [9] and of delirium, whatever the phenotype (hypo- or hyperactive), their use is associated with limited effectiveness and requires careful consideration of side effects [10, 11]. Dexmedetomidine, with its unique pharmacological profile, providing conscious sedation and anxiolysis with minimal respiratory depression, has emerged as an alternative, particularly in hyperactive delirium [12, 13]. Non-intubated ICU patients bear the burden of intubation in the event of sedation escalation related to agitation control. Dexmedetomidine is a highly selective α_2 -agonist that provides sedation and anxiolysis that is not associated with significant respiratory depression. In a non-randomized trial published nearly a decade ago, Carrasco et al. compared dexmedetomidine versus haloperidol for the treatment of hyperactive delirium in non-intubated ICU patients [14]. In this trial, agitated delirious patients were first allocated to receive haloperidol and then, if inactive (as defined by persistent agitation), continuous dexmedetomidine infusion (or the maintenance of haloperidol). These authors found an improved control of agitation, time under satisfactory intensive care delirium screening

checklist (ICDSC score < 4 points) [15], and reduced need for additional medications and noninvasive ventilation due to over-sedation. ICU length of stay and healthcare-associated costs were improved in the dexmedetomidine group, with an encouraging safety profile. The lack of double-blinding, randomization, and inclusion in the event of haloperidol inefficacy makes the results encouraging but requires confirmation. Recent research, including ongoing trials [16], continues to explore the role of dexmedetomidine in managing delirium in non-intubated ICU patients, aiming to provide further clarity on its efficacy and safety profile in this specific population.

Given the limited evidence for a benefit of dexmedetomidine administration in hyperactive delirious non-intubated ICU patients, we conducted a randomized trial in which patients were allocated to receive dexmedetomidine or placebo. Our hypothesis was that dexmedetomidine would improve a joint modelling of multiple outcomes that included agitation control, delirium resolution, and mechanical ventilation compared to placebo.

Methods

Trial oversight

The study was an investigator-initiated, prospective, two-arm, multicenter, double-blind, placebo-controlled, randomized trial conducted at 9 French centers aimed at evaluating the efficacy of dexmedetomidine versus placebo in non-intubated ICU patients with hyperactive delirium. The trial protocol used at all centers was approved by a central ethics committee and has been previously published [17].

Participants

Patients who had been admitted to a participating ICU were eligible for enrollment if they were 18 years of age or older, were not receiving invasive mechanical ventilation, had a Richmond agitation sedation scale (RASS) score [18] of + 1 or higher, and had received a positive result on the screening test for delirium according to the Confusion Assessment Method for the ICU (CAM-ICU) [19]. We excluded patients who were extubated or required pressure support ventilation via tracheostomy in the previous 24 h, or had received dexmedetomidine and/ or haloperidol in the previous 72 h. Written informed consent for enrollment or for the continuation and use of data was obtained from each patient or from a legal representative. A complete list of inclusion and exclusion criteria is provided in Supplementary Appendix.

Randomization and blinding

Participants were randomly assigned 1:1 to receive dexmedetomidine or placebo via a web-based system. To ensure the blinding of study drug administration, opaque reinforced envelopes were available, identified by a unique number, each containing a study drug vial (Figure S1). Study drug preparation was performed in a dedicated, secured preparation area within the participating ICUs by a nurse and/or a physician independent of the study protocol and not responsible for the enrolled patient to ensure double-blinding. Further details are provided in the Supplementary Appendix.

Trial procedures

Enrolled patients were assigned to receive either intravenous dexmedetomidine infusion starting at a dose of 0.2 to 0.5 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ or placebo (0.9% sodium saline). Study medication was adjusted by the bedside nurses or clinicians between 0.2 and 1.4 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ depending on agitation control, targeting a RASS score of 0 or -1 . Continuous infusion was maintained for at least 36 h after the resolution of delirium (that means after 4 consecutive negative CAM-ICU), or until the patient was discharged from the ICU. After enrollment and randomization, patients presenting with a RASS $\geq +2$ immediately received an intravenous bolus of haloperidol (2.5 mg) to promptly protect the patient from self-harm [20], while the introduction of the study drug infusion occurred. If the study medications were insufficient to control agitation beyond the maximum doses, new boluses of haloperidol were repeated (with a maximum daily dose of 30 mg). If maximum doses were reached, the use of open-label rescue medications was left to the discretion of the treating physician (promoting clorazepate) and was documented. Illustration of study interventions is presented in Figure S2.

Trial outcomes

The primary outcome was a joint modelling of multiple outcomes of duration of agitation (in hours, defined by a RASS $\geq +1$) or duration of delirium (in days, defined by the time to reach a negative score on the CAM-ICU), or the use of intubation with deep sedation and mechanical ventilation. Joint modelling of multiple outcomes was proposed to illustrate the stepwise care involved in the management of hyperactive delirious non-intubated ICU patients. Control of agitation and delirium might necessitate the use of several sedatives (other than dexmedetomidine), whose accumulation might precipitate respiratory depression and eventually require mechanical ventilation. Secondary outcomes were the individual components of the joint modelling of multiple primary outcomes; number of ventilator-free and/or delirium-free days at day 30; length of ICU stay; all-cause mortality at day 7 and day 30; occurrence of septicemia and pneumonia; delirium recurrence and related use of dexmedetomidine; use of open-label rescue medications during the first 30 days; adverse respiratory, neurological, or cardiovascular events. Additional secondary outcomes are detailed in Supplementary Appendix.

Statistical analysis

The sample size estimation was based on O'Brien's work concerning composite endpoints [21]. Treatment groups were compared with respect to the average z-score of the primary efficacy outcome. Based on available data from the literature in non-intubated ICU patients regarding the duration of agitation [14, 22], the duration of delirium [2, 22, 23] and the proportion of delirious patients requiring deep sedation with mechanical ventilation [24], 110 patients per group were required for a type I error of 0.018 (correction due to multiple components of the composite outcome) and 90% power. Finally, it was decided to include 150 patients per group to account for potential protocol deviations and losses to follow up. As the sample size estimation was based on a composite criterion for which each of the expected effect sizes associated with each component could be re-evaluated, and considering that the correlation between the components is unknown, it seemed reasonable and relevant to perform an interim analysis after the inclusion of 150 patients. An independent data safety

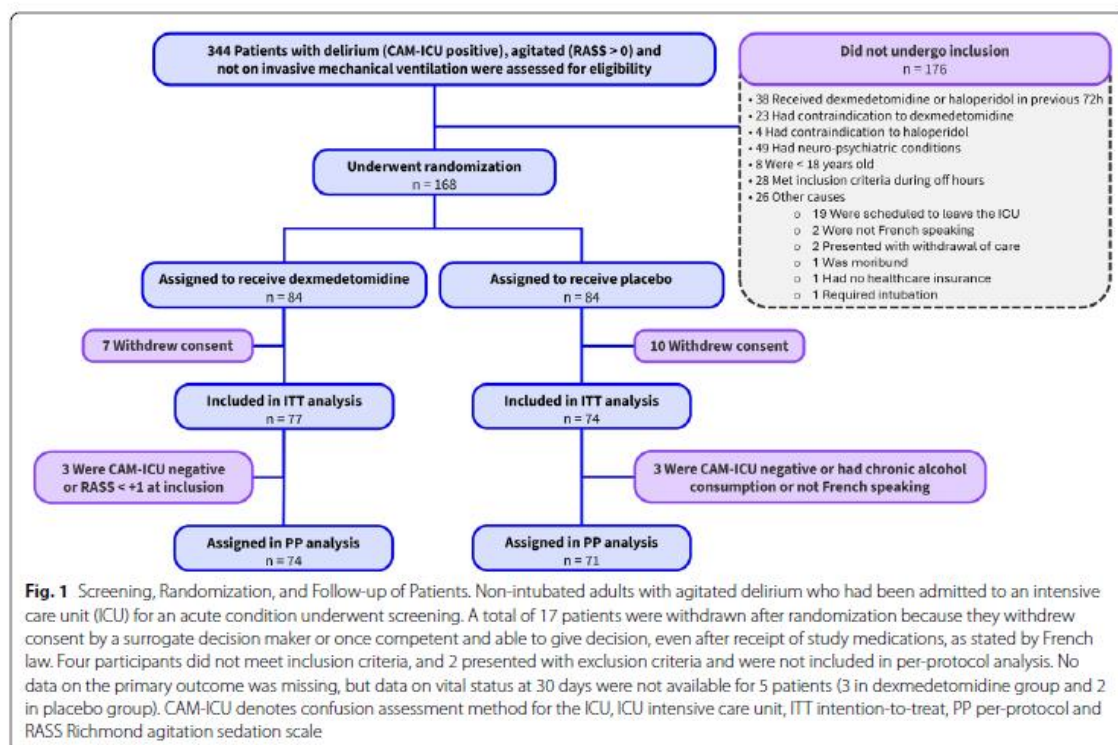
monitoring board was scheduled in case of safety issues between trial groups. The stopping rule for trial discontinuation was a difference between the randomization groups considered statistically significant with a type I error of 0.01 (Kim-DeMets correction). Accordingly, the study promoter and steering committee reviewed the results of the interim analysis and recommended trial discontinuation. Details are provided in Supplementary Appendix.

All the analyses were performed by the study statistician according to a predefined statistical analysis plan. Statistical analyses were performed using Stata software and R software. A two-tailed p-value of less than 0.05 was considered to indicate statistical significance (except for the primary outcome in the interim analysis). An intention-to-treat analysis was considered for the primary analysis. Secondarily, a per-protocol analysis was also considered, including all randomized patients except those having one or more major protocol violations defined as trial inclusion and exclusion criteria (Supplementary Appendix). For the primary outcome, the comparison between groups was analyzed using the Mann–Whitney test. The difference between randomization groups is considered statistically significant for a type I error at 0.01 (Kim-DeMets correction), taking into account pre-planned interim analysis and the primary outcome based on a composite criterion. The primary endpoint was defined as a composite score of the duration of agitation (in hours), defined by a RASS $\geq + 1$; duration of delirium (in days), defined by a positive CAM-ICU; and requirement of intubation and mechanical ventilation related to deep sedation to control delirium. As aforementioned, the primary endpoint was calculated as suggested by O'Brien: weighted summation of single endpoints with standard procedures leads to asymptotically normal statistics. Continuous (RASS delay and CAM-ICU delay) and dichotomous (intubation) variables were converted to z-scores by subtracting an individual's value from the overall mean and dividing by the standard deviation of the pooled group. The z-scores were then aligned to the same direction so that worse outcomes have smaller scores. The z-scores were then averaged across endpoints for each patient and rescaled by a factor of 100. Treatment groups were compared with respect to this average z-score. The higher the value of the primary endpoint, the more unfavorable it was. Special attention was given to the magnitude of differences (i.e., effect sizes) and clinical relevance. When appropriate, the results were expressed using Hedge's effect sizes (ESs) and 95% CIs and were interpreted according to the recommendations of Cohen, who defined the ES bounds as small (ES = 0.2), medium (ES = 0.5), and large (ES = 0.8). The analysis of the primary outcome was then completed by multivariable analysis using a linear mixed model taking into account covariates determined according to univariate results and clinical relevance in addition to center as a random effect. Results were expressed as regression coefficients with 95% confidence intervals. Prespecified subgroup analyses were performed to examine the influence of each component, examining the interaction of randomization group x subgroup in regression models. Categorical parameters were analyzed using Chi² or Fisher's exact test in univariable analysis. Secondary outcomes were pre-specified but intended for exploratory analysis. No formal adjustments for multiple comparisons were applied, as these analyses were considered hypothesis-generating rather than confirmatory. Finally, a sensitivity analysis was performed, and the nature of missing data was studied (missing at random or not) to propose the most appropriate approach to the imputation. Additional details on the statistical methods are provided in the Supplementary Appendix.

Results

Study discontinuation

Recruitment was stopped prematurely after the preplanned interim analysis, when 168 participants had been recruited. A statistician performed safety and composite primary outcome analyses, while trial data were masked to the trial investigators. The decision to stop recruitment was supported by the promoter and trial steering committee. The trial was stopped for efficacy.



Participants

Patients were enrolled at 9 centers between December 2017 and February 2022. A total of 344 patients were screened, of whom 168 were enrolled in the study (Fig. 1). Primary endpoint data were available for all patients. At the time of the preplanned interim analysis, a total of 17 patients (7 in the dexmedetomidine group and 10 in the placebo group) were excluded after randomization and 151 patients were included in the intention-to-treat analysis (77 in the dexmedetomidine group and 74 in the placebo group), and 145 in the perprotocol analysis (74 in the dexmedetomidine group and 71 in the placebo group) (Fig. 1). The baseline characteristics of the patients were well balanced between the two groups (Table 1 and Tables S1 to S4, Figure S3). Intervention and additional treatments During the intervention period, patients in the dexmedetomidine group received a median daily dose of 0.32 (interquartile range, 0.20 to 0.53) $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ of dexmedetomidine for a median duration of 4 (2 to 5) days, and patients in the placebo group received a median daily dose equivalent of 0.46 (interquartile range, 0.30 to 0.60) $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ for a median duration of 4 (3 to 5) days (Table 2). Fewer patients allocated to dexmedetomidine received haloperidol (30 (40.5%) vs 18 (23.4%), absolute difference 95% CI - 17 (- 32 to - 3), relative risk 95% CI 0.58 (0.35 to

0.94), $p = 0.03$, Table 2), with equivalent doses administered on inclusion day (5 (3 to 5) vs 5 (3 to 5) mg). Fewer patients allocated to dexmedetomidine required additional open-label rescue medication on inclusion day [13 (16.9%) vs 24 (32.4%)], absolute difference 95% CI -15.5 (-29.1 to -2.0), effect size 95% CI -0.36 (-0.68 to -0.04), $p = 0.03$, Table 2). Open-label rescue medications were administered in 45 (58.4%) patients in the dexmedetomidine group and 60 (81.1%) patients in the placebo group (absolute difference 95% CI -23 (-37 to -8), relative risk 95% CI 0.72 (0.58 to 0.90), $p = 0.003$, Table 3) during the first 30 days.

Outcomes

Joint modelling of multiple primary outcomes was significantly improved in the dexmedetomidine group (median difference, -30.9 points; 95% CI, -49.4 to -12.4 ; ES, -0.46 ; 95% CI, -0.78 to -0.12 , $p = 0.001$) (Table 3 and Fig. 2). Agitation duration was shorter in the dexmedetomidine group (1.0 (1.0–2.0) vs 2.0 (1.0–7.0) hours, absolute difference 95% CI -1.0 (-2.0 to -0.1); ES, -0.60 ; 95% CI, -0.92 to -0.27 , $p = 0.001$). There was no between-group difference in the median time to reach a negative CAM-ICU score (0.83 [interquartile range, 0.50 to 1.29] days in the dexmedetomidine group and 0.98 [interquartile range, 0.50 to 1.71] days in the placebo group; absolute difference, -0.17 [95% CI, -0.36 to 0.13]; ES, -0.09 [95% CI, -0.41 to 0.23], $p = 0.38$) and in the number of patients requiring intubation (2 [2.6%] patients in the dexmedetomidine group and 3 [4.1%] patients in the placebo group; absolute difference, -1.5 [95% CI, -7.2 to 4.3]; ES, -0.08 ; 95% CI, -0.40 to 0.24 , relative risk, 0.64 [95% CI, 0.11 to 3.75], $p = 0.62$). Pre-planned sensitivity analysis of the primary outcome adjusted for patient age was significant for patients aged 65 years or older (treatment effect, -35 [95% CI, -60 to 10], $p = 0.01$) but for patients younger than 65 years (treatment effect, -13 [95% CI, -51 to -25], $p = 0.12$) (Table S6). Multivariable analysis yielded similar results (mean difference, -26 [95% CI, -44 to -9], $p = 0.003$) (Table S9). Effect sizes for primary endpoints are presented in Figure S4. Characteristics of the per-protocol cohort are presented in Table S7 and are similar to the intention-to-treat cohort. The primary outcome was significant in the per-protocol analysis (median difference, -27 points; 95% CI, -46 to -8 , $p = 0.001$) (Table S8).

At 30 days, 10 of 74 patients (13.5%) in the dexmedetomidine group and 13 of 72 patients (18.1%) in the placebo group had died (absolute difference, -5 [95% CI, -16 to 7]; relative risk 0.75 [95% CI, 0.35 to 1.60], $p = 0.46$) (Table 3 and Figure S5).

Adverse events

The number of patients with adverse events was similar in the two groups (Table 3, and Tables S12a and S12b). Clinically significant events requiring treatment were similar between groups (Table 3, Table S16, and Figures S6 to S8).

Table 1 Demographic and clinical characteristics of the patients at baseline

Characteristic	Placebo (N = 74)	Dexmedetomidine (N = 77)
Median age (IQR) – years	72 (64–77)	69 (63–77)
Female sex	18 (24)	14 (18)
Median body-mass index (IQR) – kg.m ⁻²	26.0 (23.4–29.8)	27.5 (24.2–32.3)
Coexisting conditions		
Cardiovascular		
Hypertension	38 (51)	29 (38)
Dyslipidemia	10 (14)	12 (16)
Arteriopathy	10 (14)	10 (13)
Chronic cardiac failure	1 (1)	7 (9)
Arrhythmia	12 (16)	15 (19)
Ischemic cardiopathy	12 (16)	18 (23)
Pulmonary		
COPD	15 (20)	21 (27)
Chronic respiratory insufficiency	3 (4)	3 (4)
Metabolic		
Diabetes	20 (27)	20 (26)
Chronic kidney injury	13 (18)	14 (18)
Intoxication		
Alcohol abuse	11 (15)	11 (14)
Tobacco	19 (26)	22 (29)
Drugs abuse	3 (4)	0
Neurology		
Cognitive impairment ^{&}	3 (4)	2 (3)
Mild	2 (3)	1 (1)
Moderate	1 (1)	1 (1)
Neurovascular disease	6 (8)	7 (9)
Epilepsy	3 (4)	2 (3)
Chronic liver disease (cirrhosis)	6 (8)	6 (8)
Malignancy		
Metastatic neoplasia	4 (5)	3 (4)
Hematology	7 (10)	10 (13)
Median time from hospital admission to randomization (IQR)—days	6 (3 to 14)	7 (3 to 15)
Median time from ICU admission to randomization (IQR) – days	5 (2 to 9)	4 (2 to 10)
Admission type		
Medical	46 (62)	42 (55)
Elective surgery	15 (20)	17 (22)
Urgent surgery	13 (18)	18 (23)
Median SAPS 2 (IQR) §	40 (32 to 48)	38 (29 to 48)
Median predicted in-hospital mortality (IQR) – percentage §	24.7 (12.8 to 41.5)	21.3 (9.7 to 41.5)
Delirium phenotype at randomization [†]		
Hypoxic	31 (42)	27 (35)
Septic	40 (54)	47 (61)
Sedation	24 (32)	19 (25)
Metabolic	13 (18)	17 (22)
Unclassified	11 (15)	11 (14)
Median RASS score (IQR) [*]	1 (1 to 2)	1 (1 to 2)

^a Data are presented as median and 25th – 75th percentiles (interquartile range) or number (percentage). Characteristics listed are available baseline data for patients in the two groups who did not withdraw consent. There were no significant differences in baseline characteristics between the trial groups. Additional baseline characteristics are listed in Table S1 to S4 in the Supplementary Appendix. No data was missing for patients at baseline

[&] Cognitive impairment was measured using Mini Mental State Examination tool [40]. Scores above 27 were considered to characterize a normal cognitive function, between 27 and 20 a mildly impaired cognitive function and between 11 and 20 a moderately impaired function

[§] The Simplified Acute Physiology Score (SAPS) II is a prediction tool for death and measures severity of disease in the ICU; scores range from 0 to 163, with higher scores indicating a greater severity of illness [41]

[§] The predicted in-hospital mortality was calculated with the use of the SAPS II, on which scores range from 0 to 163 (corresponding with a range of predicted in-hospital mortality of 0 to 100%) [41]

[†] Delirium phenotypes have been described by Girard et al.[2] Several phenotypes might be identified in the same patient

^{*} The Richmond Agitation and Sedation Scale (RASS) is a tool to assess depth of sedation on a scale of – 5 to + 4, with negative values denoting increased sedation and positive values denoting increased agitation [18]

COPD denotes chronic obstructive pulmonary disease, ICU intensive care unit, IQR interquartile range, RASS Richmond agitation sedation scale and SAPS simplified acute physiology score

Discussion

In this multicenter, randomized trial involving non-intubated adult ICU patients with hyperactive delirium, in accordance with our hypothesis, we found that dexmedetomidine reduced a joint modelling of multiple outcomes of duration of agitation or delirium or intubation with deep sedation and mechanical ventilation over a placebo. Moreover, the incidence of adverse event rates requiring treatments was similar, even in pre-specified subgroups according to age above or below 65 years old [7].

Our results suggest that dexmedetomidine allows for improved control of agitation in non-intubated hyperactive delirious ICU patients, and reduces the need for additional psychotropic agents to control psychomotor agitation. These findings add to those published by Carrasco et al. [14] which found that dexmedetomidine allowed for better control of agitation and reduced the use of mechanical ventilation when compared to haloperidol. As a selective alpha-2 agonist, dexmedetomidine provides sedation and anxiolysis (thus addressing agitation) without necessarily resolving the underlying brain dysfunction that is delirium [3]. Agitation might be a symptom of delirium [3, 9], and its control does not always equate to delirium resolution. The impact of haloperidol administration at the start of dexmedetomidine infusion raises questions. Post-hoc analyses suggest that agitation control was much longer in the placebo group that received haloperidol, despite a slightly higher RASS score at inclusion (see Tables S17 to S19 in the Supplementary Appendix). These results support the superiority of dexmedetomidine over placebo and haloperidol. They are also consistent with the previously reported inefficacy of haloperidol treatment in approximately 30% of cases, as documented by Carrasco [14] and Dumont [25].

Table 2 Use of dexmedetomidine or placebo, and open-label rescue medication on inclusion day in the ICU after randomization

	Placebo (N = 74)	Dexmedetomidine (N = 77)	Absolute Difference or Median Difference (95% CI)	P
Median duration of trial intervention (IQR)—days	4 (3–5)	4 (2–5)	0 (-1 to 1)	0.31
Median daily dose (IQR)— $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ *	0.46 (0.30–0.60)	0.32 (0.20–0.53)	- 0.13 (- 0.24 to - 0.03)	0.03
Median cumulative dose (IQR)—milligrams *	1.7 (1.2 to 2.4)	1.2 (0.6–2.4)	- 0.5 (- 0.9 to - 0.1)	0.02
Use of open-label rescue medication on inclusion day §				
Number of patients requiring haloperidol	30 (40.5)	18 (23.4)	- 17 (- 32 to - 3)	0.03
Median haloperidol dose (IQR)—milligrams (30/18) †	5 (3–5)	5 (3 to 5)	0 (0 to 0)	0.38
Number of patients requiring other open-label rescue medication	24 (32.4)	13 (16.9)	- 16 (- 29 to - 2)	0.03

* Data are presented as median and 25th–75th percentiles (interquartile range) or number (percentage). Results are expressed for the dexmedetomidine group as compared with the placebo group using relative risks (95% CI) for binary and categorical outcomes and with median differences (95% CI) for continuous outcomes

† The median daily infusion rate (in micrograms per kilogram per hour) and the median cumulative dose (in milligrams during trial drug administration) were calculated as the cumulative infusion rate received divided by the total number of days that the patient received dexmedetomidine or placebo; and the cumulative dose received during the total number of days that the patient received dexmedetomidine or placebo, respectively. Doses for placebo are presented as dexmedetomidine-equivalents

§ Patients could receive more than one rescue medication on the same day. Rescue medication was defined as the use of any psychotropic agent to treat uncontrollable agitation, insomnia or delirium (e.g. haloperidol or other psychotropic drugs such as propofol, benzodiazepines or any antipsychotic drug)

† Figures depict the number of patients that received haloperidol on inclusion day according to randomization group

CI denotes confidence interval, ICU intensive care unit and IQR interquartile range

P-values < 0.05 are provided in bold

Recruitment was stopped before the planned sample size was reached, due to the absence of safety issues and statistical significance of joint modelling of multiple primary outcomes. Using type I error correction and a statistical significance of 0.01, the trial was considered adequately powered to detect a 0.5 effect-size difference between groups for the primary outcome. The decision to stop enrollment was made by the investigators and the sponsor, who

were unaware of the study groups. The absence of a difference in safety outcomes obviated the need to convene a data safety monitoring board.

Table 3 Clinical outcomes and adverse events

Outcome	Placebo (N = 74)	Dexmedetomidine (N = 77)	Absolute Difference or Median Difference (95% CI)	P
Primary outcome †	3.0 (– 23.4 to 51.3)	– 26.8 (– 45.4 to 10.2)	Z-score: – 30.9 (– 49.4 to – 12.4) Effect-size: – 0.46 [– 0.78 to – 0.13]	0.001
<i>Separate items</i>				
Median delay to RASS < 1 (IQR)—hours	2.0 (1.0 to 7.0)	1.0 (1.0 to 2.0)	– 1.0 (– 2.0 to – 0.1) Z-score: – 54.3 (– 98.2 to – 10.3) Effect-size: – 0.60 [– 0.92 to – 0.27]	0.001
Median delay to negative CAM-ICU (IQR)—days	1.0 (0.5 to 1.7)	0.8 (0.5 to 1.3)	– 0.1 (– 0.3 to 0.1) Z-score: – 25.1 (– 69.5 to 19.4) Effect-size: – 0.09 [– 0.41 to 0.23]	0.38
Intubation—no. (%)	3 (4.1)	2 (2.6)	– 1.5 (– 7.2 to 4.3) Z-score: – 8.1 (– 40.5 to 24.3) Effect-size: – 0.08 [– 0.40 to 0.24]	0.62
<i>Secondary outcomes £</i>				
Median days alive without delirium or mechanical ventilation (IQR)	4 (2–6)	4 (2–6)	0 (– 1 to 1)	0.61
Median days alive without delirium (IQR)	6 (4–9)	6 (3–9)	0 (– 1 to 1)	0.75
Median days alive without mechanical ventilation (IQR)	6 (3–7)	7 (2–13)	1 (– 1 to 6)	0.38
Median length of ICU stay (IQR)—days	12 (8–19)	13 (7–21)	1 (– 3 to 5)	0.77
Median length of ICU stay post-randomization (IQR)—days	6 (4 to 10)	6 (3–12)	0 (– 2 to 2)	0.90
All-cause mortality at day 7—no. / total no. (%)	5 (6.8)	6 (7.8)	1 (– 7 to 9)	0.81
All-cause mortality at day 30—no. / total no. (%) §	13/72 (18.1)	10/74 (13.5)	– 5 (– 16 to 7)	0.46
Septicemia—no. (%)	4 (5.4)	6 (7.8)	2 (– 5 to 10)	0.56
Pneumonia—no. (%)	14 (18.9)	10 (13.0)	– 6 (– 18 to 6)	0.33
Delirium recurrence—no. (%) ¶	7 (9.5)	13 (16.9)	7 (– 3 to 18)	0.19
Median number of delirium recurrence (IQR)	1 (1 to 2) (/7)	1 (1 to 2) (/13)	0 (– 2 to 2)	0.73
Open-label dexmedetomidine use during recurrence—no. (%)	4/7 (57.1)	7/13 (53.9)	– 3 (– 49 to 42)	0.89
Median duration of open label dexmedetomidine use in case of delirium recurrence (IQR)—days	9 (3–15) (/4)	3 (2 to 5) (/7)	– 5 (– 15 to 3)	0.34
<i>Safety &</i>				
Median number of days with use of open-label rescue medication (60/45) (IQR)	2 (1–5)	2 (1 to 6)	0 (– 1 to 1)	0.79
Use of open-label rescue medication during first 30 days—no. (%)	60 (81.1)	45 (58.4)	– 23 (– 37 to – 8)	0.003
Benzodiazepines—no. (%)	23 (53.0)	23 (67.7)	18 (– 4 to 39)	0.11
Hydroxyzine—no. (%)	25 (54.4)	15 (44.1)	– 10 (– 32 to 12)	0.38
Haloperidol—no. (%)	41 (55.4)	33 (42.9)	– 13 (– 28 to 3)	0.13
Neuroleptics—no. (%)	46 (62.2)	34 (44.2)	– 18 (– 34 to – 2)	0.03
<i>Adverse Events §</i>				
Serious adverse event in ICU related to treatment—no. (%)	0 (0.0)	0 (0.0)	NE	NE
Serious adverse event in ICU non-related to treatment—no. (%)	27 (36.5)	26 (33.8)	– 3 (– 18 to 13)	0.73
<i>Hypotension</i>				
Number of patients with at least 1 episode—no. (%)	41 (55.4)	52 (67.5)	12 (– 3 to 28)	0.13
Number of patients requiring treatment—no./total no. (%)	25/74 (33.8)	34/77 (44.2)	10 (– 5 to 26)	0.20
Days with at least one event requiring treatment during study drug administration—no./total no. (%)	39/71 (54.9)	69/103 (67.0)	12 (– 3 to 27)	0.30
<i>Bradycardia</i>				
Number of patients with at least 1 episode—no. (%)	36 (48.7)	37 (48.1)	0 (– 17 to 15)	0.94
Number of patients requiring treatment—no./total no. (%)	2/74 (2.7)	3/77 (3.9)	1 (– 4 to 7)	0.69
Days with at least one event requiring treatment during study drug administration—no./total no. (%)	2/58 (3.5)	1/59 (1.7)	– 2 (– 7 to 4)	0.56
<i>Any other cardiovascular event</i>				
Number of patients with at least 1 episode—no. (%)	4 (5.4)	8 (10.4)	5 (– 4 to 14)	0.27
Number of days with at least one event—no./total no. (%)	5/58 (8.6)	23/103 (22.3)	14 (3 to 25)	0.05
Days with at least one event during study drug administration—no./total no. (%)	1/5 (20.0)	4/23 (17.4)	– 3 (– 41 to 36)	0.89

† Data are presented as median and 25th – 75th percentiles (interquartile range) or number (percentage). Results are expressed for the dexmedetomidine group as compared with the placebo group using median differences (95% CI) for continuous outcomes. The absolute difference is given in percentage points for categorical outcomes. Confidence intervals for differences between groups for secondary outcomes are not adjusted for multiple comparisons of secondary outcomes and cannot be used to infer treatment effects

[†] Difference between randomization groups is considered statistically significant for a type I error at 0.01 (Kim-DeMets correction), taking into account pre-planned interim analysis and primary outcome based on a composite criterion. The primary endpoint was defined as a composite score of duration of agitation (in hours), defined by a RASS $\geq +1$; duration of delirium (in days), defined by a positive CAM-ICU; and requirement of intubation and mechanical ventilation related to deep sedation to control delirium. As aforementioned, the primary endpoint was calculated as suggested by O'Brien: weighted summation of single endpoints with standard procedures leads to asymptotically normal statistics. Continuous (RASS delay and CAM-ICU delay) and dichotomous (intubation) variables were converted to z-scores by subtracting an individual's value from the overall mean and dividing by the standard-deviation of the pooled group. The z-scores were then aligned to the same direction so that worse outcomes have smaller scores. The z-scores were then averaged across endpoints for each patient. Composite Z-scores were multiplied by a factor of 100 to improve readability. Treatment groups were compared with respect to this average z-score. The higher the value of the primary endpoint, the more unfavorable it was. Groups were also compared using Hedge's effect-sizes (ESs) and 95% CIs and were interpreted according to the recommendations of Cohen, who defined the ES bounds as small (ES=0.2), medium (ES=0.5), and large (ES=0.8). Further details are provided in Figure S4 (Supplementary Appendix)

£ Secondary outcomes are censored at day 30

[§] Safety description of the use of open-label rescue medication during first 30 days include data on inclusion day (D0). Further details are provided in Table S5 (Supplementary Appendix)

[§] Three patients in dexmedetomidine group and 2 patients in placebo group were lost of sight at 30 days

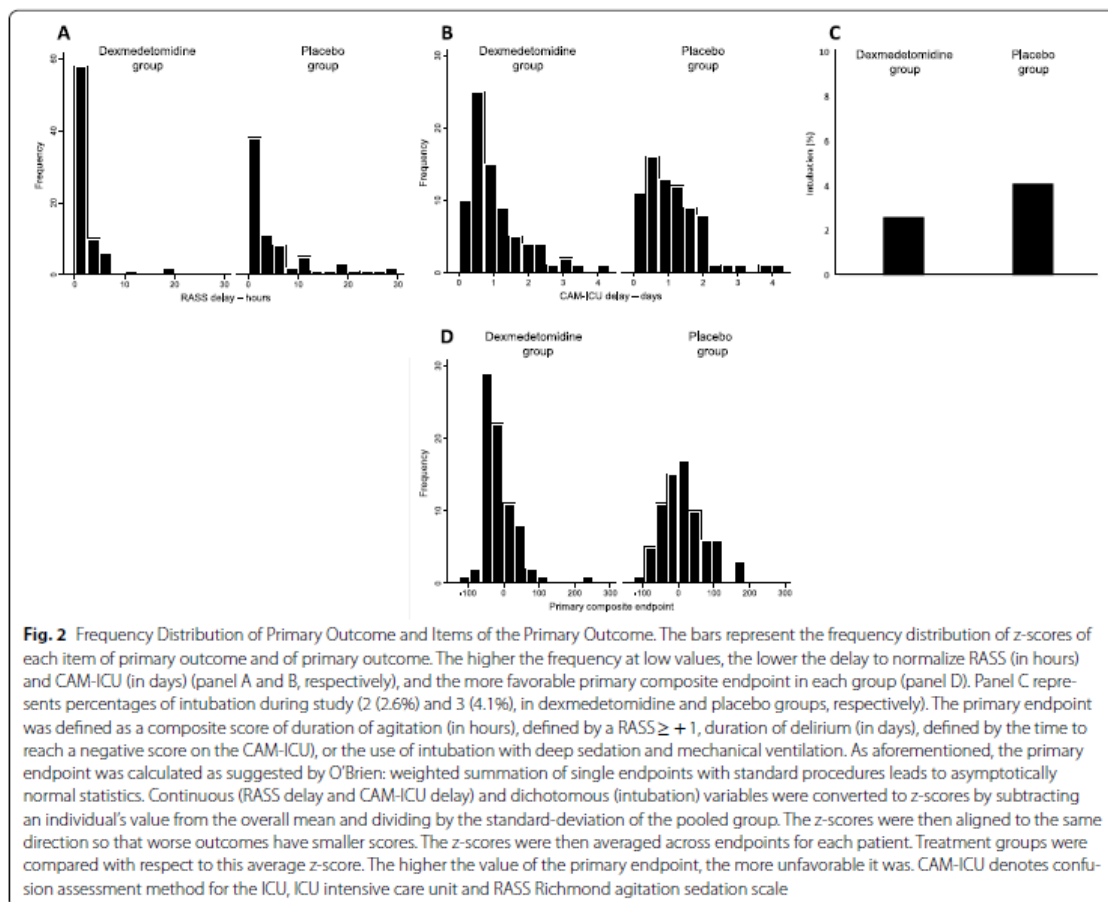
€ Delirium recurrence was defined as a CAM-ICU positive result after initial delirium resolution (i.e. 4 consecutive CAM-ICU) during ICU stay

[§] Further details on adverse events are proposed in Supplementary Appendix

[§] Cardiovascular events include the occurrence of any rhythm disorder and/or myocardial ischemia and/or tachycardia and/or hypertension and/or prolonged corrected QTc interval on the electrocardiogram

CAM-ICU denotes confusion assessment method for the ICU, CI confidence interval, ICU intensive care unit, IQR interquartile range and RASS Richmond agitation sedation scale

P-values < 0.05 are provided in bold



This study has many strengths. First, to our knowledge and to date, this is the only randomized trial evaluating the effect of dexmedetomidine in non-intubated ICU patients with hyperactive delirium. Second, the study design includes a double-blind, placebo-controlled fashion, a relatively large sample size, and a high level of data completeness. The protocol and statistical analysis plan were published before the last patient underwent randomization [17]. Third, the primary outcome was clinically relevant and patient-centered. Fourth, we used a single validated tool (CAM-ICU) to homogenize delirium diagnosis. Fifth, the population included in the present study represents critical ICU patients for whom control of delirium-related agitation remains difficult to manage because the addition of sedatives may compromise respiratory status. Sixth, the generalizability of results relies on the relatively

frequent encounter of this typology of patients for whom control of agitation might overcome delirium. The study design allowed for the initial administration of haloperidol to control delirium-associated agitation (without reducing delirium-free days) [10, 20] and the additional use of rescue medications so that clinical staff could safely manage patients with hyperactive delirium and maintain routine practices. Therefore, the rapid addition of dexmedetomidine might limit in-hospital and post-discharge antipsychotic prescribing [26].

Finally, all data were fully monitored at participating sites by dedicated researchers unaware of group allocation. This study has several limitations. First, the trial was stopped early as advised by the steering committee and the promotor after the pre-planned interim analysis [27, 28]. This can lead to an overestimation of the treatment effect because early signs of benefit often appear larger than the actual effect that would be observed in a fully completed trial [27, 29]. It can also restrict the ability to fully assess less frequent or long-term adverse events, with a complete safety profile of dexmedetomidine remaining unclear. Furthermore, it can raise concerns about the interpretation of the clinical significance of the findings (e.g. the limited reduction in agitation duration (approximately 1 h), while being statistically significant, has debatable clinical meaningfulness. Second, the primary endpoint was a joint modelling of multiple outcomes of duration of agitation or delirium, or intubation with deep sedation and mechanical ventilation, which could challenge the interpretation of the results [30], but all items showed similar trends. Third, the difference in joint modelling of multiple primary outcomes was driven by a significant reduction in median delay to control agitation of about 1 h, but there was no effect on delirium duration and intubation in the study population. This small reduction in agitation duration may be beneficial in some scenarios, such as enabling essential procedures or limiting the removal of crucial devices, while recognizing that it may not fundamentally alter patient trajectory in some other cases. The main benefit of improved control of agitation may be the impact on nursing workload [31–34] and therefore patients' outcomes [35]. Moreover, additional post-hoc analyses showed that a substantial subset of patients experienced prolonged agitation in the placebo group whereas it resolved more quickly and more consistently in the dexmedetomidine group. Complementary threshold-based analyses (dichotomizing the delay to RASS < 1 at multiple time points) revealed that the risk of persistent agitation beyond 3, 5, 8, or even 15 h was significantly higher in the placebo group, with relative risks ranging from 2 to over 9 (Figure S9). These findings support the idea that the benefit of dexmedetomidine is not limited to a median effect but is particularly relevant for preventing prolonged and potentially harmful agitation in a subgroup of patients. Fourth, the uneven number of patients enrolled at inclusion sites may limit the generalizability of the findings despite the absence of a center effect as demonstrated by multivariable analysis (Table S9). Fifth, the low enrollment rate may be related, in part, to the low incidence of hyperactive delirium in non-intubated ICU patients in including centers with expected high adherence to the A2F bundle, which remains unreported [5, 6]. Sixth, inflection of enrollment rate may be due to dexmedetomidine overuse during and after the COVID-19 pandemic [36] and non-inclusion criteria of the present study (absence of dexmedetomidine or haloperidol in the previous 72 h). The study has focused on a very specific patient population: non-intubated, agitated, and delirious ICU patients. This narrow focus is a strength for internal validity but questions generalizability. Application of results to populations under invasive mechanical ventilation or presenting with hypoactive or mixed delirium motor subtype remains unknown. Eighth, the administration of haloperidol and of open-label rescue medications are potential confounders, despite being intended to represent the real-life management of agitated ICU patients. However, the dexmedetomidine group required fewer rescue medications, suggesting improvements in the management of non-intubated, agitated, and delirious ICU patients (Tables 2 and 3). Further post-hoc analyses

indicated that dexmedetomidine was superior to placebo and haloperidol (Figure S9 and Tables S17 to S19). However, definitive exclusion of confounding effects would require a new randomized clinical trial with a different design. Ninth, while being numerically more frequent in the dexmedetomidine group, adverse events exploratory outcomes did not reach statistical significance, and thus must be interpreted with caution. Tenth, despite rigorous physical blinding procedures, clinical side effects such as bradycardia and/or hypotension might have compromised blinding. Eleventh, no long-term outcomes have been explored in the present study. Twelfth, the use of an alternative delirium screening tool, such as the ICDSC [15] or the subjective bedside assessment by clinicians [37] (not recommended) might have led to different results. Finally, given the multiple secondary outcomes analyzed, we acknowledge the potential for false positive findings.

These results should therefore be interpreted with caution and validated in independent studies before drawing firm conclusions. Our secondary outcomes were prespecified but intended for exploratory analysis, rather than definitive hypothesis testing. As such, we did not apply formal adjustments for multiple comparisons, in line with established recommendations for secondary and hypothesis-generating analyses [38, 39]. While these findings provide valuable insights, they should be interpreted with caution and considered hypothesis-generating, requiring confirmation in future studies, including diverse populations with a wider range of patients, and comparing dexmedetomidine to other standard medications for agitation and delirium.

Conclusions

Among non-intubated patients with hyperactive delirium in the ICU, the administration of dexmedetomidine was associated with a greater clinical benefit than placebo for the joint modelling of multiple endpoints of duration of agitation or delirium, or intubation with deep sedation and mechanical ventilation. Dexmedetomidine appears to be a valuable alternative that significantly reduced the median duration of agitation by approximately 1 h compared to placebo in hyperactive delirious non-intubated ICU patients. Present findings are hypothesis-generating and require validation by additional trials.

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Author contributions

TG, CL, and JMC designed the study. TG, CL, GP, PC, BR, NB, LB, MJ, EF, and JMC collected data. TG, ADJ, and BP conducted statistical analyses. TG, MJ, EF, SJ, GC, and JMC participated in manuscript writing and reviewing. All authors read and approved the final manuscript.

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Data availability

Deidentified data will be shared with other authenticated researchers for further research and research publications on this topic, but only if they guarantee to preserve the confidentiality of the information requested. Requests for data sharing will be considered by the data sharing committee of the Clermont-Ferrand University Hospital in accordance with its data sharing policy.

Declarations

Conflicts of interest

SJ is the Editor in Chief of Intensive Care Medicine. He has not taken part in the review or selection process of this article. Dr. De Jong reports receiving speaker fees from Medtronic, Sanofi, Fisher and Paykel Healthcare, Sedana Medical, Viatrix, and Mindray. Dr. Couhault reports receiving lecture fees from AOP Health. Dr. Jabaudon reports receiving lecture and consulting fees from Abbvie and Sedana Medical. Dr. Rieu reports receiving travel fees and honoraria from LFB Biomédicaments. Dr. Godet reports receiving lecture and consulting fees from General Electrics Healthcare, Dräger, Fisher and Paykel Healthcare, Edwards

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