Journal of Critical Care 68 (2022) 114–120

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Effectiveness of combined non-pharmacological interventions in the prevention of delirium in critically ill patients: A randomized clinical trial

Tássia Nery Faustino [a,b,*], Nathália Almeida Suzart [c], Rebecca Neves dos Santos Rabelo [d], Juliete Lima Santos [b], Gyuliana Santana Batista [b], Yasmin Seixas de Freitas [e], Danilo Alves Saback [f], Nabila Monalisa Mendes Dantas Sales [g], Bruna Brandao Barreto [a,h], Dimitri Gusmao-Flores [a,h]

[a] Programa de Pós-Graduação em Medicina e Saúde, Faculdade de Medicina da Bahia, Universidade Federal da Bahia, Salvador, Bahia, Brazil
[b] Collegiate of Nursing, Department of Life Sciences, State University of Bahia, Salvador, Bahia, Brazil
[c] Assiste Vida Service, Salvador, Bahia, Brazil
[d] Santa Izabel Hospital, Salvador, Bahia, Brazil
[e] Bahia School of Medicine and Public Health, Salvador, Bahia, Brazil
[f] Cárdio Pulmonar Hospital, Salvador, Bahia, Brazil
[g] Municipal Secretariat of Health, Urgency/Emergency Care Service, Salvador, Bahia, Brazil
[h] Intensive Care Unit, Hospital da Mulher, Salvador, Bahia, Brazil

ARTICLE INFO

Keywords:
Critical Care
Delirium prevention
Intensive Care Unit
Non-pharmacological interventions
Randomized controlled trial

ABSTRACT

Purpose: Delirium is a common dysfunction in the intensive care unit (ICU) and it is associated with negative short- and long-term outcomes. This study evaluated the effectiveness of combined non-pharmacological interventions in preventing delirium in critically ill patients.

Materials and methods: This is a single-center randomized controlled trial conducted in three Brazilian ICUs from February to September 2019. Patients assigned to the control group received standard care ($n = 72$) and those assigned to the experimental group (n = 72) received a bundle of non-pharmacological interventions (periodic reorientation, cognitive stimulation, correction of sensory deficits [visual or hearing impairment], environmental management and sleep promotion) throughout the ICU stay. Delirium was monitored twice a day with the Confusion Assessment Method for the Intensive Care Unit Flowsheet. The primary outcome was the incidence density of delirium.

Results: The incidence density of delirium was lower in the intervention group (1.3×10^{-2} person-days) than in the control group (2.3×10^{-2} person-days), with a hazard ratio of 0.40 (95% confidence intervals, 0.17–0.95; $p = 0.04$) after adjustment for Simplified Acute Physiology Score III, surgical admission and alcoholism.

Conclusions: Combined non-pharmacological interventions reduced delirium in critically ill patients, compared to standard care.

Trial registration: Brazilian Registry of Clinical Trials (ReBEC), Identifier RBR-6xq95s, October 03, 2018.

1. Introduction

Critically ill patients are at high risk of developing delirium [1-3], a common organ dysfunction in the intensive care unit (ICU). The occurrence of delirium is associated with negative clinical outcomes in both the short- and long-term, such as increased ICU mortality and length of stay, and post-discharge neurocognitive impairment [4,5].

Given the absence of evidence to support the use of pharmacological measures to prevent this dysfunction [2], the use of non-pharmacological interventions is an important strategy that must be investigated. Studies involving exclusively non-pharmacological interventions demonstrate benefits in the prevention of delirium in ICU patients [6-12], however most studies evaluated different strategies. Since delirium

Abbreviations: aHR, adjusted hazard ratio; aOR, adjusted odds ratio; aRR, adjusted relative risk; CAM-ICU Flowsheet, Confusion Assessment Method for the Intensive Care Unit Flowsheet; CI, confidence interval; E-PRE-DELIRIC, *Early Prediction Model for Delirium in ICU Patients*; HR, *hazard ratio*; ICU, intensive care unit; IQR, interquartile range; RASS, Richmond Agitation Sedation Scale; RCT, randomized controlled trial; ReBEC, Registro Brasileiro de Ensaios Clínicos; SAPS3, Simplified Acute Physiology Score III; SD, *standard deviation*.

* Corresponding author at: State University of Bahia, Department of Life Sciences, College of Nursing, Silveira Martins Street, 2555, Cabula Neighborhood, ZIP Code 41.150-000 Salvador, Bahia, Brazil.
E-mail address: tassiafaustino@yahoo.com.br (T.N. Faustino).

https://doi.org/10.1016/j.jcrc.2021.12.015
0883-9441/

has a multifactorial basis, the clinical guidelines of the Society of Critical Care Medicine suggest the use of combined non-pharmacological interventions for the prevention and reduction of delirium duration [2].

To our knowledge, only two randomized controlled trials (RCT) have been published to evaluate the effect of a bundle of non-pharmacological interventions in the prevention of delirium in the ICU. Presenting discordant results, one was directed to a specific population of critical patients [12] and the second was used only in the first seven days of ICU admission [13].

This study aims to evaluate the effectiveness of the implementation of combined non-pharmacological interventions in the prevention of delirium in critically ill patients. Our hypothesis is that combined non-pharmacological interventions prevent the occurrence of delirium in critically ill patients when compared to the standard care offered in the critical unit.

2. Materials and methods

2.1. Study design and participants

This is a randomized, controlled, parallel, and open clinical trial, conducted in 3 ICUs of a large teaching hospital in Salvador, Brazil from February to September 2019. The study protocol was registered in the Brazilian Registry of Clinical Trials (ReBEC), identifier RBR-6xq95s. The study met the CONSORT Statement for Randomized Trials of Non-pharmacologic Treatments [14].

Patients over 18 years were included if their expected length of ICU stay was greater than 48 h, with the Early Prediction Model for Delirium in ICU Patients (E-PRE-DELIRIC) score [15] ≥ 10%. This tool stratifies the risk of developing delirium into four categories: very low (0–10%), low (10–20%), moderate (20–35%), and high risk (> 35%) [15]. Those admitted in a state of delirium, with receptive aphasia, severe hearing and/or visual disturbances preventing adequate communication, advanced cognitive impairment, and/or a score on the Richmond Agitation-Sedation Scale (RASS) ≤ −4 for over 24 h after initial screening evaluation, were excluded, despite posterior neurological improvement. Patients were randomized within 24 h of admission to the ICU. The screening process and the non-pharmacological intervention were performed by a team of researchers, who were not part of the ICU staff.

2.2. Randomization and allocation

Randomization was performed in random blocks of 4, 6, and 8 participants with the RStudio randomization system (Boston, MA, USA). Allocation concealment was ensured by opaque envelopes, sequentially numbered, and sealed. This process was carried out by a professional, who was external to the research team. The envelopes were opened only after they had been irreversibly assigned to the participants. Therefore, the confidentiality of the participants' allocation was guaranteed until they were recruited and allocated to the study groups.

2.3. Procedures

Patients were randomly allocated in two groups. The control group received standard care, with the intervention group receiving standard care and a bundle of five combined non-pharmacological interventions: periodic reorientation, cognitive stimulation, correction of sensory deficits, environmental management, and sleep promotion. The application started within 24 h of ICU admission, after randomization, and applied daily until ICU discharge. Each non-pharmacological intervention was chosen to minimize potentially modifiable risk factors for delirium [1-3], thus meeting the recommendations found in the current guideline of the Society of Critical Care Medicine: cognitive stimulation, sleep promotion and correction of visual and auditory deficits [2]. In addition, we included the periodic reorientation and environmental management components, since they have been investigated in previous studies with favorable results [11,16]. Researchers that were not members of the ICU staff, visited the ICU twice a day to apply the intervention.

2.3.1. Periodic reorientation

Twice a day, the research team helped patients orient themselves to the ICU environment, the multidisciplinary team, and the evolution of their clinical condition. In addition, patients were asked about their lives, work, family, leisure activities, and recent issues to stimulate thinking, awareness of their identities, and short- and long-term memories. Photos, personal items, and a radio were requested from the family and kept in the ICU to help with reorientation.

2.3.2. Cognitive stimulation

The research team performed seven different cognitive training activities throughout the ICU stay: digit span, digit game, memory task, block test, executive functioning, bells test, and difference searching (Supplementary Appendix 1). They were organized in sets of three (Supplementary Appendix 1), with six cognitive activities per day (three in the morning and three in the afternoon). Cognitive training activities in this trial are considered feasible for nursing staff use with critically ill patients, including those in delirium. They aimed to stimulate different cognitive domains affected by this dysfunction: attention, memory, and executive function [17].

A folder that was comprised of magazines, word search activities, crossword and Sudoku puzzles, calculus, and painting, was distributed. In cases of motor deficit, the family helped the patient to fill in the magazines, encouraging engagement in all the activities. The researchers also asked the families to bring more books and magazines with topics of interest to the patients.

2.3.3. Correction of sensory deficits

The research team asked families for glasses and/or hearing aids for those patients who previously used them.

2.3.4. Environmental management

This intervention consisted of installing a calendar and a clock in a place that was easy for patients to see.

2.3.5. Sleep promotion

In order to promote sleep, the research team distributed eye masks and earplugs. They also requested the ICU staff to avoid the period from 10:00 pm to 6:00 am for scheduling elective procedures and administration of oral, subcutaneous, and intramuscular medications; however, the assistance team was responsible for patient compliance.

Several factors could interfere with full adherence to the bundle:

1. Except for environmental management, the bundle was only implemented if patients were given RASS ≥ −2 at each clinical evaluation by the research team, as monitoring the intervention was not possible for patients with lower levels of consciousness.
2. If the patient was on mechanical ventilation, only periodic reorientation, environmental management, and avoidance of late-night hours for scheduling medication and elective procedures were applied, resuming other interventions (correction of sensory deficits and cognitive stimulation) after withdrawal of this therapeutic support.
3. The intervention could not be performed when the patient was outside of the ICU (e.g., surgical theater or radiology floor) or undergoing medical examination. For these occasions, the team tried to execute the bundle of measures at another time.
4. The patient could refuse to participate in the intervention at any time during the ICU stay. The research team was oriented to respect the patient's autonomy and register the lack of adherence during that shift.

If patients in the intervention group did not adhere to all proposed interventions, the issue was investigated and corrected. If the research

team could not resolve the problem, the family was contacted to encourage patient compliance. Early mobilization and extended visits were registered and counted for both trial groups.

Due to characteristics of the intervention bundle, it was not possible to blind participants, research staff, and ICU care providers. Therefore, aiming to limit biases, bundle interventions performed in the control group by people outside the research team were counted.

2.4. Outcomes and follow-up

The primary outcome was the incidence density of delirium, which is the ratio of patients in delirium to the number of person-days of exposure. The number of person-days was obtained by adding individual times elapsed from admission to the ICU, to the first episode of delirium (for those patients presenting the outcome) or discharge from the ICU (for patients not presenting the outcome). We also calculated the cumulative incidence of delirium in the allocation groups. Delirium was defined as a positive episode detected by the Confusion Assessment Method for the Intensive Care Unit Flowsheet (CAM-ICU Flowsheet), a tool with a sensitivity of 72.5% and specificity of 96.2%, already validated in the Portuguese language [18]. The research team investigated the presence of delirium once in the morning and afternoon shifts for every patient with RASS ≥ −3 after randomization, throughout the ICU stay. The research team consisted of eight trained researchers who were assigned shifts (morning or afternoon) during seven consecutive days. In each shift, a single researcher applied the scale to patients in the control group. In patients from the experimental group, the application of the scale preceded the application of the intervention.

The predetermined secondary outcomes were incidence density of delirium according to delirium subtype; overall duration of delirium (in days and proportion of days with delirium); duration of delirium by subtype; length of ICU and hospital stay; ICU mortality at 30 and 90 days; number of days on mechanical ventilation; days free of delirium and coma; number of delirium episodes; delirium-free survival; delirium-free days; reintubation; occurrence of falls; and accidental removal of the devices. Patients with RASS of −4 or − 5 were classified as being in a coma, regardless of the cause (sedation or illness).

Delirium subtypes were defined by the RASS scale in patients with positive CAM-ICU, in accordance with the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition [19]. Hyperactive delirium was diagnosed in patients with RASS from +1 to +4; hypoactive delirium in those with RASS from −1 to −3; and mixed-type delirium in patients with RASS at 0 or fluctuation between values of hyperactive and hypoactive delirium in 24 h. Duration of delirium was assessed by the total number of days with one episode of positive CAM-ICU, from the patient's admission to the ICU until discharge. For patients discharged from the hospital before 30 days after admission, data on mortality at 30 and 90 days were found through telephone contact.

Three variables were not prespecified in the protocol when the trial was designed: persistent (>24 h) delirium, delirium severity and stratified duration of intervention. The severity of delirium was assessed using the Confusion Assessment Method for the ICU-7 Delirium Severity Scale [20]. Due to variable adherence to the bundle during ICU stay (see item 2.3. Procedures), the duration of each intervention was stratified into three categories: equal to or greater than 50% of the ICU stay, less than 50% of the ICU stay, or that an intervention was not performed.

The investigated outcomes were obtained from the medical record, with the delirium monitoring form completed by the research team.

2.5. Statistical analysis

A pilot study was conducted to determine incidence of delirium to calculate sample size. The result was a general cumulative incidence of delirium at 43.15%. We estimated that with a sample of 140 patients (70 in each group), the current study would have a power of 80% to detect a 50% reduction of delirium incidence in the intervention group [10], at a two-sided alpha level of 5%. To consider a potential loss to follow-up of 10%, the sample was increased to 160 patients (80 in each group).

Enrolled patients were included in the intention-to-treat analysis. Descriptive statistics (frequency and percentage, person-days, median and interquartile range [IQR], mean and standard deviation [SD]) were applied based on the characteristics of each variable. Normally distributed data were reported as mean ± SD, while non-normally distributed data were reported as median (IQR). Chi-square, Fisher Exact, and Mann-Whitney *U* tests were used to determine whether baseline covariates differed between allocation groups. The Chi-square and Fisher Exact tests were also used to identify differences in the application of interventions between allocation groups.

To compare the primary outcomes between the trial groups, univariate and multivariate Cox Regression models were used, as well as to assess the secondary outcome density of incidence of delirium by delirium subtype. The robust Poisson regression model was used to compare the cumulative incidence of delirium between the study groups.

To compare remaining secondary outcomes, univariate and multivariate linear regression and logistic regression were used. Adjustment for covariates was made by identifying those with $p < 0.20$ in the univariate analysis, and included them in the complete multivariate model to check for potential confounders. Hazard ratio (HR), adjusted hazard ratio (aHR), adjusted relative risk (aRR) and adjusted odds ratio (aOR) were estimated with 95% confidence intervals (CIs). Time-to-event was compared with the log-rank test and shown in Kaplan-Meier curves. A post-hoc analysis of the association between duration of interventions and density of incidence of delirium was performed with the Cox univariate regression, as well as a sensitivity analysis according to severity (patients under mechanical ventilation versus spontaneously breathing patients). Variables were not included in the analysis if there were no episodes of delirium, regardless of the intervention's duration in the ICU or if adherence was uniform (no categories of intervention duration could be created). A two-tailed significance level of 5% was adopted for all analyses. Stata version 12 (Stata Corp, College Station, TX, USA) was used for statistical analysis.

3. Results

3.1. Participants and adherence to the protocol

From February 15 to September 3, 2019, 1266 patients were admitted to ICUs. Of these, 1106 were excluded (Fig. 1) and 160 patients were enrolled. Sixteen patients were lost to follow-up (eight in each group), while 144 patients were analyzed.

Patients' baseline characteristics were similar across groups, except for the percentage of clinical admission that was higher in the control group (97.2% versus 83.3%) and the percentage of arterial hypertension (59.7% versus 76.4%) that was higher in the intervention group (Table 1). The application of the five non-pharmacological interventions in the bundle was significantly higher in the intervention group (Table 2).

3.2. Primary outcome

The density of incidence of delirium was significantly lower in the intervention group (1.34×10^{-2} versus 2.29×10^{-2} person-days), with a 60% lower risk of developing this dysfunction compared to the control group (aHR, 0.40; 95% CI, 0.17–0.95; $p = 0.04$) after adjusting for Simplified Acute Physiology Score III, surgical admission and alcoholism. The cumulative incidence of delirium in the control group was 22.2% ($n = 16$) and 12.5% ($n = 9$) in the intervention group, with statistically significant difference between groups (aRR, 0.44; 95% CI, 0.21–0.91; $p = 0.03$), after adjustment for the same confounders (Table 3).

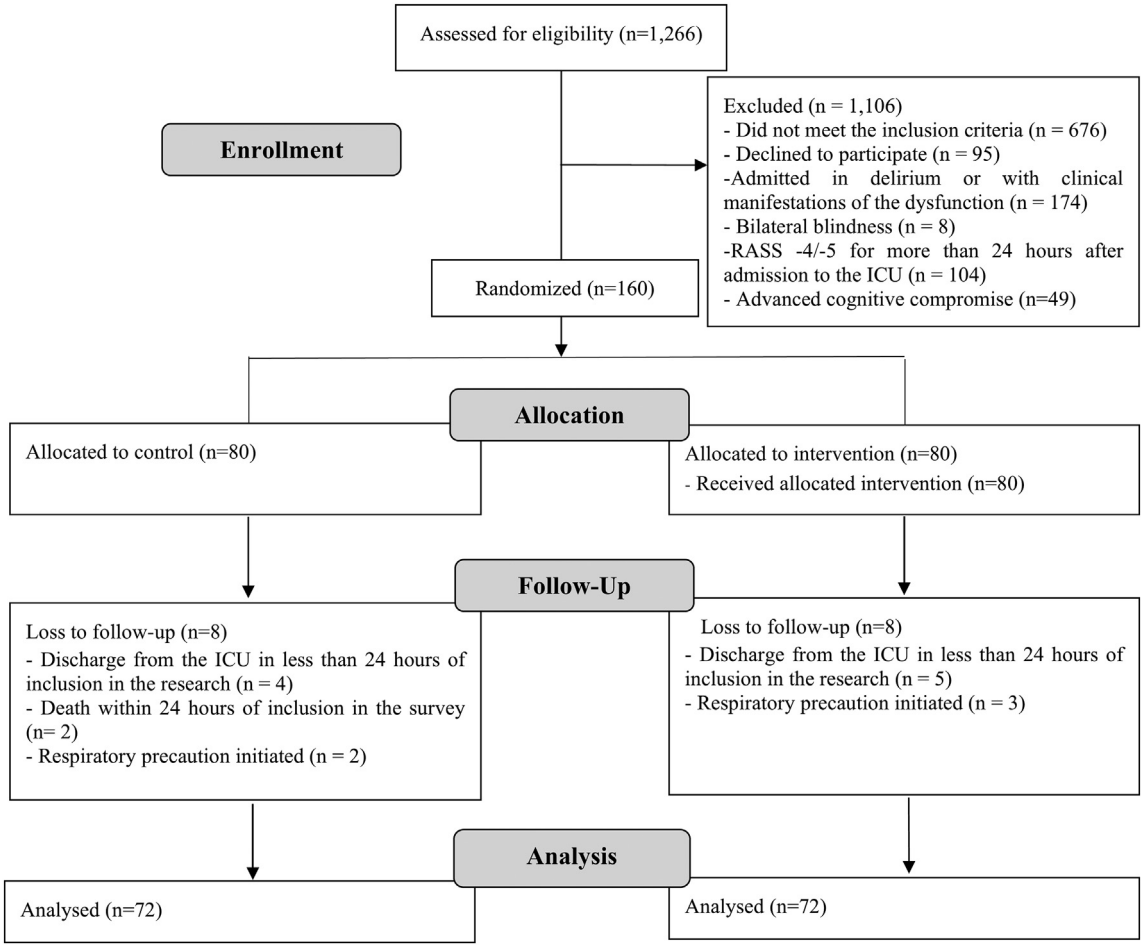

Fig. 1. Study Flow Chart.

3.3. Secondary outcomes

There were seven cases of hypoactive delirium and nine cases of mixed delirium in the control group, while in the intervention group there were seven cases of hypoactive delirium, one case of mixed delirium, and one case of hyperactive delirium. There was no difference in the incidence density and the duration of delirium subtypes across groups, as well as other secondary outcomes shown in Table 3, including duration of delirium in days, days of hospitalization, mortality, and delirium-free survival (Fig. 2). There was no fall in the sample and only two cases of reintubation in the control group, and two cases of device removal (one in each group). Details on the duration of delirium (proportion of days with delirium; delirium-free days; persistent delirium [> 24 h]) are presented in Supplementary Appendix 2 (Table S1).

Some interventions could not be performed during the ICU period of admission (Materials and methods – 2.3. Procedures). Adherences to interventions during the ICU stay are in Table S2 to S6 in the Supplementary Appendix 2. A post hoc analysis was made to identify an association between duration of some interventions and the incidence density of delirium (Table 4) – with a lower density of incidence of delirium in patients undergoing orientation, cognitive training, filing magazines and using glasses for a period equal to or greater than 50% of the ICU stay, when compared to those who adhered for a period of less than 50% of time spent in the ICU. Regardless of the duration, there were no cases of delirium in patients who used sleep promotion measures, hearing aids, photographs, and bedside radios, as well as reading books and magazines of general interest.

The median SAPS3 score was significantly higher in the group of patients who performed cognitive training activities for less than 50% of the length of stay in the ICU when compared to patients who performed this intervention for a time equal to or greater than 50% (21.5 points [IQR, 16–50] versus 10 points [IQR, 4–19] respectively; $p = 0.016$). No statistically significant differences were observed between SAPS3 medians regarding duration of interventions in the orientation component (24 points [IQR, 16–50] versus 10.5 points [IQR, 5.5–26.5] respectively; $p = 0.066$).

When performing a sensitivity analysis of the effect of the intervention in patients under mechanical ventilation and spontaneously breathing patients, a greater benefit from the bundle of interventions was observed in spontaneously breathing patients (HR 0.13; 95% CI, 0.06–0.29; $p = 0.000$).

4. Discussion

In this randomized clinical trial conducted in three ICUs at a single center, the implementation of a bundle of non-pharmacological measures significantly reduced the incidence of delirium in critically ill patients, compared to standard care.

Each of the non-pharmacological measures used in this RCT were evaluated in other studies, also promoting a significant reduction in the incidence and risk of developing delirium [11,12,16]. In one study [13], the use of non-pharmacological intervention did not decrease delirium incidence, however cognitive stimulation activities were not included in the intervention.

Table 1
Baseline characteristics of participants.

Characteristics	Intervention Group (*N* = 72)	Control Group (N = 72)
Age in years, median (IQR)	68.5 (62.0–78.0)	64.5 (57.0–75.5)
Age ≥ 65 years, n (%)	46 (63.9)	36 (50.0)
Female sex, n (%)	36 (50.0)	41 (56.9)
Type of admission, n (%)		
Clinic	60 (83.3)	70 (97.2)
Surgical	12 (16.7)	2 (2.8)
Elective	9 (75.0)	
Emergency	3 (25.0)	2 (100.0)
E-PRE-DELIRIC, median (IQR)	17 (14.0–23.5)	17 (13.0–23.5)
SAPS III, median (IQR)	11 (5.0–19.5)	9 (4.0–17.0)
Previous cognitive impairment, n (%)	9 (12.5)	9 (12.5)
Alcoholism, n (%)	8 (11.1)	5 (6.9)
Smoking, n (%)	7 (9.7)	9 (12.5)
Systemic Arterial Hypertension, n (%)	55 (76.4)	43 (59.7)
Mechanical ventilation, n (%)	11(15.3)	12 (16.7)
Coma, n (%)	10 (13.9)	12 (16.7)
Physical constraint, n (%)	14 (19.4)	17 (23.6)
Previous use of medications with anticholinergic action, n (%)	37 (51.4)	37 (51.4)
Use of medications, n (%)		
Vasopressors	19 (26.4)	12 (16.7)
Opioids	23 (31.9)	15 (20.8)
Parenteral sedation	12 (16.7)	15 (20.8)
Dexmedetomidine	2 (2.8)	4 (5.6)
Antipsychotics	6 (8.3)	7 (9.7)
Benzodiazepines	10 (13.9)	17 (23.6)
Drugs with anticholinergic action	66 (91.7)	67 (93.1)
Use of blood components, n (%)	14 (19.4)	11 (15.3)
Early mobilization, n (%)	47 (65.3)	51 (70.8)
Extended visit, n (%)	16 (22.2)	22 (30.6)

Abbreviations: E-PRE-DELIRIC - Early Prediction Model for Delirium in ICU Patients; IQR-interquartile range; SAPS III - Simplified Acute Physiology Score III.

We did not find any difference between groups regarding the secondary outcomes. Low patient severity (defined by the low value SAPS III and low proportion of patients mechanically ventilated), small number of delirium cases and small sample size may have contributed to these results. We also did not recruit the patients who remained in a coma (RASS − 4 or − 5) for more than 24 h after admission to the ICU, given the need to start interventions as early as possible, thus excluding a proportion of the most severe patients and with a higher risk of developing this dysfunction [2]. However, it is worth mentioning that one of the inclusion criteria in our study was an E-PRE-DELIRIC score ≥ 10%, a imed at eliminating patients at very low risk of developing delirium.

Table 2
Description of implementing interventions.

Interventions	Intervention Group (N = 72)	Control Group (N = 72)	*p* Value
Periodic reorientation, n (%)			
Patient orientation	72 (100)	0	
Photos at the bedside	5 (6.9)	0	
Radio at the bedside	4 (5.6)	0	
Personal objects at the bedside	14 (19.4)	10 (13.9)	0.37
Cognitive stimulation n (%)			
Filling in magazines with cognitive activities	28 (38.9)	0	
Cognitive training activities	72 (100)	0	
Reading books and magazines brought by the family	5 (6.9)	7 (9.7)	0.55
Correction of sensory deficits, n (%)[1]			
Use of glasses	35 (100)	24 (72.7)	0.001
Use of hearing aid	6 (100)	5 (55.6)	0.1
Sleep Promotion, n (%)			
Use of eyes mask	20 (27.8)	1 (1.4)	<0.001
Use of earplugs	15 (20.8)	0	
Environmental management, n (%)			
Bed clock	72 (100)	30 (41.7)	<0.001
Bed calendar	72 (100)	0	

[1]In the intervention group, 35 patients had visual and 6 patients had hearing deficits. In the control group, 33 patients had visual and 9 patients had hearing deficits.

The delirium duration in our study was short (2 days in each group), another fact that could explain the absence of impact of our intervention in mortality and days free of delirium and coma. This is also seen in rapidly reversible delirium (in which the condition resolves itself within two hours of cessation of sedation) and in subsyndromic delirium [21,22]. Patients with rapidly reversible delirium have shorter durations of mechanical ventilation, ICU duration and overall hospital stay when compared to patients with persistent delirium (in which the dysfunction remains after two hours of sedation interruption) [21], while subsyndromic delirium is not associated with increased mortality [22].

We found an association between the duration of the intervention throughout the ICU stay and a decrease of incidence, suggesting that patients should receive these interventions for the longest time possible while receiving intensive care. However, we compared the severity of the groups who receive the cognitive training activities for less than 50% of the time to those who received it for a longer period of time, and the former were more severely ill than the latter. This finding could indicate that the effect on the incidence of delirium may have been influenced by the clinical severity of the patients. Since the application of most of our interventions depended on the participants' collaboration, patients who were more severely ill, and therefore with a higher risk of developing delirium, likely received the intervention for a shorter time due to lack of collaboration.

In association with this finding, Fig. 2 suggests that non-pharmacological interventions were more important in patients with longer ICU stays. However, it is possible that this result occurred by chance, due to the limited number of patients who remained after the first seven days of admission in the ICU.

The greatest benefit of interventions in spontaneously breathing patients can be attributed to the smaller number of interventions that the patients were submitted to while on mechanical ventilation (only periodic reorientation, environmental management and avoidance of late-night hours for scheduling medication and elective procedures), resulting in impact on the occurrence of delirium.

We also found low adherence to some of the components of the bundle, such as filling magazines with cognitive activities, use of eye masks and ear plugs, absence of photos, significant personal objects, radio and books/magazines in beds. However, the adherence to those interventions depended exclusively on patient/family cooperation. When questioned, patients informed that they were not interested in these interventions and/or family members justified that the patient's stay in the ICU would be short, not providing these materials even after numerous requests and explanation on the importance of these measures by the research team.

There is also an important difference between the cumulative incidence observed in the pilot study and the one found in the control group in this RCT. This can be explained by the fact that in the pilot study, which was carried out exclusively to determine the incidence of delirium in the study setting, there were a greater number of critically ill, sedated and mechanically ventilated patients, while in our RCT we excluded those patients who remained with RASS ≤ −4 for more than 24 h after admission to the ICUs.

We recognize some limitations in this study. First, the monitoring of delirium was carried out exclusively by the research team; and due to the fluctuating course of the dysfunction, underdiagnosis may have occurred. Second, there was low adherence to some protocol measures, which may have reduced the effectiveness of the intervention. Third, eligibility criteria for this study excluded patients in a coma, who are at a high risk of developing delirium [2] and could have benefited from the prevention protocol. Fourth, this was a single center study.

Table 3
Primary and Secondary Study Outcomes.

Outcomes	Intervention Group (N = 72)	Control Group (N = 72)	Adjusted Difference (95% CI)[1]	Relative Effect of Intervention (95% CI)[1,2]	p Value
Primary					
Density of incidence of delirium, person-days	1.34×10^{-2}	2.29×10^{-2}	NA	0.40 (0.17 to 0.95)	0.04
Cumulative incidence of delirium, n (%)	9 (12.5)	16 (22.2)	NA	0.44 (0.21 to 0.91)	0.03
Secondary					
Duration of delirium, days, median (IQR)	2 (1–3)	2 (1–7.5)	−0.01 (−0.39 to 0.41)	NA	0.95
Density of incidence of delirium by subtype, person-days[3]					
Hypoactive	1.06×10^{-2}	1.06×10^{-2}			0.66
Hyperactive	0.16×10^{-2}	0			
Mixed	0.16×10^{-2}	1.34×10^{-2}			0.55
Number of patients developing delirium by subtype, n (%)					
Hypoactive	7 (77.8)	7 (43.75)			
Hyperactive	1 (11.1)	0			
Mixed	1 (11.1)	9 (56.25)			
Duration of delirium by subtype, days, mean (SD)[3]					
Hypoactive	3 (2.08)	2.57 (2.64)			0.49
Hyperactive	1	0			
Mixed	1	5 (4.12)			0.30
Days in the ICU, median (IQR)	4 (3–7.5)	5 (3–7)	−0.06 (−0.15 to 0.03)	NA	0.20
Days in hospital, median (IQR)	12 (7.5–21.5)	13.5 (7.5–22)	−0.01 (−0.13 to 0.11)	NA	0.84
Days on mechanical ventilation, median (IQR)	2 (1–7)	8 (2–11.5)	−0.15 (−0.68 to 0.37)	NA	0.54
Days free from delirium/coma, median (IQR)	3 (3–5)	4 (3–5.5)	−0.61 (−1.74 to 0.51)	NA	0.28
Number of delirium episodes, median (IQR)	2 (1–4)	2 (1–11)	−1.20 (−6.13 to 3.73)	NA	0.61
Severity of delirium, median (IQR)	5.5 (4–6)	6 (4.35–7)	−0.23 (−1.84 to 1.39)	NA	0.77
ICU mortality, n (%)	6 (8.3)	9 (12.5)	NA	0.47 (0.14 to 1.55)	0.22
Mortality in 30 days, n (%)	13 (18.0)	13 (18.0)	NA	0.93 (0.37 to 2.34)	0.88
Mortality in 90 days, n (%)	15 (20.8)	16 (22.2)	NA	0.90 (0.38 to 2.13)	0.81

Abbreviations: CI - confidence interval; ICU - intensive care unit; IQR - interquartile range; NA - not applicable; *SD - standard deviation.*
[1]Delirium adjusted by Simplified Acute Physiology Score III, surgical admission and alcoholism.
[2]Hazard Ratio for density of incidence of delirium; Relative Risk for cumulative incidence of delirium; Odds Ratio for ICU mortality at 30 and 90 days.
[3]It was not possible to adjust potential confounders in analyzing the incidence and duration between delirium subtypes by allocation group: this was due to an insufficient sample.

Single-center clinical trials tend to overestimate the effects of an intervention due to the generally small sample size to identify a true clinical effect and the inclusion of a homogeneous population, among other factors [23]. Therefore, the generalization of results may be limited and the performance of multicentric trials to confirm our findings is necessary. Fifth, due to low incidence of delirium in our sample, it was not possible to perform an appropriate analysis of its subtypes. Future studies with larger sample sizes are needed to evaluate this specific research question. Sixth, this study was not pragmatic and the investigated interventions were applied exclusively by researchers (professionals external to the health care providers in the ICUs), which limits the external validity of the research and applicability in other scenarios. However, those interventions were chosen in view of the simple and quick execution by any health professional category in the ICU setting [16].

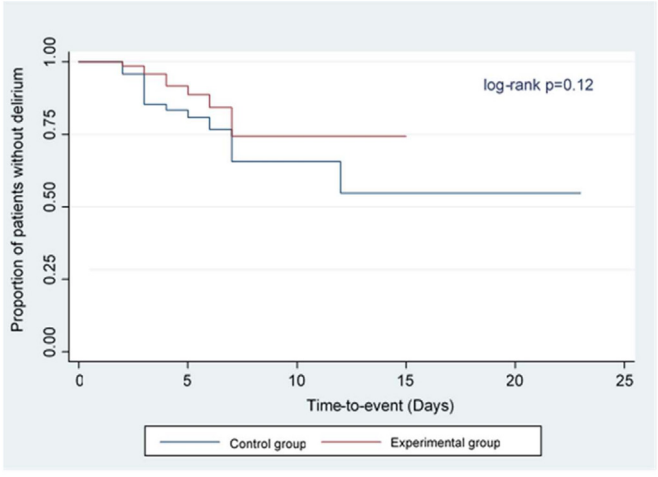

Fig. 2. Delirium-free survival during ICU stay.

The strengths of our study include design of RCT, implementation of multicomponent interventions throughout the participant's ICU hospitalization, analysis of the interventions in reducing the occurrence of delirium, and monitoring important outcomes such as delirium severity by allocation group. Our bundle of combined non-pharmacological measures may have minimized cognitive decline in patients in the intervention group, thereby reducing the occurrence of delirium.

Table 4
Analysis of association between duration of interventions and density of incidence of delirium in the intervention group.

Duration of interventions	Density of incidence of delirium	Hazard ratio (95% CI)	p Value
Patient orientation[1]			
<50% of the ICU stay	17.39 person-days	Reference	
≥ 50% of the ICU stay	1.47 person-days	0.09 (0.02 to 0.34)	<0.001
Personal objects at the bedside[2]			
Intervention not performed	2.59 person-days	Reference	
<50% of the ICU stay	0		
≥ 50% of the ICU stay	4.65 person-days	1.98 (0.40 to 9.72)	0.40
Cognitive training activities[1]			
<50% of the ICU stay	17.85 person-days	Reference	
≥ 50% of the ICU stay	1.19 person-days	0.07 (0.02 to 0.26)	<0.001
Filling in magazines with cognitive activities[2]			
Intervention not performed	4.30 person-days	Reference	
<50% of the ICU stay	1.23 person-days	0.26 (0.03 to 2.14)	0.21
≥ 50% of the ICU stay	0		
Use of glasses			
<50% of the ICU stay	2.51 person-days		
≥ 50% of the ICU stay	0		

Abbreviations: CI - confidence interval; ICU - intensive care unit.
[1]All patients in the intervention group underwent periodic reorientation and cognitive training activities.

The investigated interventions are accessible, low cost, and quick to apply (ranging from 10 to 15 min), and can be easily incorporated into the ICU's clinical practice, without increasing the workload of the multi-professional team. In addition, none of these interventions have the potential to cause harm or complications to the patients.

5. Conclusion

Combined non-pharmacological interventions were effective in significantly reducing the incidence of delirium in critically ill patients, compared to standard care. The longer the intervention was performed during the ICU stay, the greater the decrease in incidence density of delirium. However, this finding should be interpreted with caution since patients with a shorter duration of intervention were also more severely ill. Non-pharmacological interventions seem to have a greater benefit in patients that had longer stays in the ICU, however this may be a chance finding due to the small sample size with prolonged length of stay in the ICU.

Funding

This study was funded by the Institutional Scientific Initiation Program (PICIN) of the University of the State of Bahia (Edital n° 026/2018), which provided grants for nursing students who participated in data collection. There was no involvement of the funding source in the study design, collection, analysis, and interpretation of results, or in writing this paper and the decision to submit it for publication.

Ethics approval

The study was approved by the Research Ethics Committees of the University of the State of Bahia and Hospital Santa Izabel, approval n° CAAE 76595317.5.0000.0057 and approval n° CAAE 76595317.5.3000.5520, respectively. Written consent to participate in the study was obtained from all patients or their guardians, after receiving verbal and written information about the research.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Acknowledgements

We thank Laio Magno Santos de Sousa for supporting the data analysis; Patricia Bispo de Oliveira Ouais, Márcia Maria Carneiro Oliveira, the nursing staff and physicians, the leadership of the ICU, and the Teaching and Research Directorate at Hospital Santa Izabel for all the support and efforts to develop this research. We also thank patients and guardians for agreeing to participate in the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2021.12.015.

References

[1] Van Rompaey B, Elseviers MM, Schuurmans MJ, Shortridge-Baggett LM, Truijen S, Bossaert L. Risk factors for delirium in intensive care patients: a prospective cohort study. Crit Care. 2009;13:R77. https://doi.org/10.1186/cc7892.
[2] Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med. 2018;46:e825–73. https://doi.org/10.1097/CCM.0000000000003299.
[3] Zaal IJ, Devlin JW, Peelen LM, Slooter AJC. A systematic review of risk factors for delirium in the ICU. Crit Care Med. 2015;43:40–7. https://doi.org/10.1097/CCM.0000000000000625.
[4] Salluh JIF, Wang H, Schneider EB, Nagaraja N, Yenokyan G, Damluji A, et al. Outcome of delirium in critically ill patients: Systematic review and meta-analysis. BMJ. 2015;350:1–10. https://doi.org/10.1136/bmj.h2538.
[5] Wolters AE, van Dijk D, Pasma W, Cremer OL, Looije MF, de Lange DW, et al. Long-term outcome of delirium during intensive care unit stay in survivors of critical illness: A prospective cohort study. Crit Care. 2014;18:1–7. https://doi.org/10.1186/cc13929.
[6] Kamdar BB, King LM, Collop NA, Sakamuri S, Colantuoni E, Neufeld KJ, et al. The effect of a quality improvement intervention on perceived sleep quality and cognition in a medical ICU. Crit Care Med. 2013;41:800–9. https://doi.org/10.1097/CCM.0b013e3182746442.
[7] Rosa RG, Tonietto TF, Da Silva DB, Gutierres FA, Ascoli AM, Madeira LC, et al. Effectiveness and safety of an extended icu visitation model for delirium prevention: A before and after study. Crit Care Med. 2017;45:1660–7. https://doi.org/10.1097/CCM.0000000000002588.
[8] Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009;373:1874–82. https://doi.org/10.1016/S0140-6736(09)60658-9.
[9] Van Rompaey B, Elseviers MM, Van Drom W, Fromont V, Jorens PG. The effect of earplugs during the night on the onset of delirium and sleep perception: A randomized controlled trial in intensive care patients. Crit Care. 2012;16. https://doi.org/10.1186/cc11330.
[10] Álvarez EA, Garrido MA, Tobar EA, Prieto SA, Vergara SO, Briceño CD, et al. Occupational therapy for delirium management in elderly patients without mechanical ventilation in an intensive care unit: A pilot randomized clinical trial. J Crit Care. 2017;37:85–90. https://doi.org/10.1016/j.jcrc.2016.09.002.
[11] Colombo R, Corona A, Praga F, Minari C, Giannotti C, Castelli A, et al. A reorientation strategy for reducing delirium in the critically ill. Results of an interventional study. Minerva Anestesiol. 2012;78:1026–33.
[12] Guo Y, Sun L, Li L, Jia P, Zhang J, Jiang H, et al. Impact of multicomponent, nonpharmacologic interventions on perioperative cortisol and melatonin levels and postoperative delirium in elderly oral cancer patients. Arch Gerontol Geriatr. 2016;62:112–7. HR.
[13] Moon KJ, Lee SM. The effects of a tailored intensive care unit delirium prevention protocol: A randomized controlled trial. Int J Nurs Stud. 2014;52:1423–32. https://doi.org/10.1016/j.ijnurstu.2015.04.021.
[14] Boutron I, Altman DG, Moher D, Schulz KF, RPCNG. CONSORT Statement for randomized Trials of nonpharmacologic treatments: A 2017 update and a CONSORT extension for nonpharmacologic trial abstracts. Ann Intern Med. 2017;167:40–7. https://doi.org/10.7326/M17-0046.
[15] Wassenaar A, van den Boogaard M, van Achterberg T, Slooter AJC, Kuiper MA, Hoogendoorn ME, et al. Multinational development and validation of an early prediction model for delirium in ICU patients. Intensive Care Med. 2015;41:1048–56. https://doi.org/10.1007/s00134-015-3777-2.
[16] Rivosecchi RM, Kane-Gill SL, Svec S, Campbell S, Smithburger PL. The implementation of a nonpharmacologic protocol to prevent intensive care delirium. J Crit Care. 2016;31:206–11. https://doi.org/10.1016/j.jcrc.2015.09.031.
[17] Wassenaar A, Rood P, Boelen D, Schoonhoven L, Pickkers P, van den Boogaard M. Feasibility of cognitive training in critically ill patients: a pilot study. Am J Crit Care an Off Publ Am Assoc Crit Nurses. 2018;27:124–35. https://doi.org/10.4037/ajcc2018467.
[18] Gusmao-Flores D, Salluh JIF, Dal-Pizzol F, Ritter C, Tomasi CD, de Lima MASD, et al. The validity and reliability of the Portuguese versions of three tools used to diagnose delirium in critically ill patients. Clinics. 2011;66:1917–22. https://doi.org/10.1590/S1807-59322011001100011.
[19] American Psychiatric Association. Manual diagnóstico e estatístico de transtornos mentais [recurso eletrônico]: DSM-5, vol. 11; 2014. https://doi.org/10.5007/interthesis.v11i2.34753.
[20] Khan B, Perkins AJ, Gao S, Hui SL, Campbell NL, Farber MO, et al. The confusion assessment method for the ICU-7 delirium severity scale: a novel delirium severity instrument for use in the ICU. Crit Care Med. 2017;45:851–7. https://doi.org/10.1097/CCM.0000000000002368.
[21] Patel SB, Poston JT, Pohlman A, Hall JB, Kress JP. Rapidly reversible, sedation-related delirium versus persistent delirium in the intensive care unit. Am J Respir Crit Care Med. 2014;189:658–65. https://doi.org/10.1164/RCCM.201310-1815OC.
[22] Serafim RB, Soares M, Bozza FA, Lapa e Silva JR, Dal-Pizzol F, Paulino MC, et al. Outcomes of subsyndromal delirium in ICU: a systematic review and meta-analysis. Crit Care. 2017;21. https://doi.org/10.1186/S13054-017-1765-3.
[23] Unverzagt S, Prondzinsky R, Peinemann F. Single-center trials tend to provide larger treatment effects than multicenter trials: a systematic review. J Clin Epidemiol. 2013;66:1271–80. https://doi.org/10.1016/J.JCLINEPI.2013.05.016.