ORIGINAL ARTICLE

The Impact of Nursing Delirium Preventive Interventions in the ICU
A Multicenter Cluster-randomized Controlled Clinical Trial

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Abstract

Rationale: Delirium is common in critically ill patients and is associated with deleterious outcomes. Nonpharmacological interventions are recommended in current delirium guidelines, but their effects have not been unequivocally established.

Objectives: To determine the effects of a multicomponent nursing intervention program on delirium in the ICU.

Methods: A stepped-wedge cluster-randomized controlled trial was conducted in ICUs of 10 centers. Adult critically ill surgical, medical, or trauma patients at high risk of developing delirium were included. A multicomponent nursing intervention program focusing on modifiable risk factors was implemented as standard of care. The primary outcome was the number of delirium-free and coma-free days alive in 28 days after ICU admission.

Measurements and Main Results: A total of 1,749 patients were included. Time spent on interventions per 8-hour shift was median (interquartile range) 38 (14–116) minutes in the intervention period and median 32 (13–73) minutes in the control period ($P = 0.44$). Patients in the intervention period had a median of 23 (4–27) delirium-free and coma-free days alive compared with a median of 23 (5–27) days for patients in the control group (mean difference, −1.21 days; 95% confidence interval, −2.84 to 0.42 d; $P = 0.15$). In addition, the number of delirium days was similar: median 2 (1–4) days (ratio of medians, 0.90; 95% confidence interval, 0.75 to 1.09; $P = 0.27$).

Conclusions: In this large randomized controlled trial in adult ICU patients, a limited increase in the use of nursing interventions was achieved, and no change in the number of delirium-free and coma-free days alive in 28 days could be determined.

Clinical trial registered with www.clinicaltrials.gov (NCT03002701).

Keywords: critical care; delirium; nursing; nonpharmacological; intervention program

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A complete list of the UNDERPIN-ICU Study Investigators may be found before the beginning of the References.

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At a Glance Commentary

Scientific Knowledge on the Subject: In hospitalized patients outside the ICU, the use of nonpharmacological interventions has been shown to be effective to reduce delirium. In critically ill patients, the effectiveness of such interventions is currently unclear. A recent meta-analysis showed no beneficial effects of single-component nonpharmacological interventions. International guidelines suggest the application of multicomponent nonpharmacological interventions to prevent or minimize delirium burden in critically ill patients, but the recommendations are based on small studies. Therefore, an evaluation of the effectiveness of delirium bundles with adequately powered trials is warranted.

What This Study Adds to the Field: In this multicenter, stepped-wedge cluster-randomized controlled trial including 1,749 adult patients in 10 ICUs, the application of a multicomponent nursing intervention program focused on optimizing vision, hearing, orientation, sleep, cognition, and mobility to prevent delirium in the ICU was assessed. The number of delirium-free and coma-free days alive in 28 days was shown to be similar in patients who received the multicomponent nursing intervention program compared with patients in the control group; however, compared with other contexts, the level of application was already considerable, and delirium incidence and duration were relatively low in the control period.

Delirium is a frequently occurring clinical expression of impaired brain function and often fluctuates during the day (1, 2). On average, delirium burdens one in three ICU patients (3) and is associated with several adverse, short-term outcomes such as prolonged mechanical ventilation and ICU and hospital length of stay (4, 5). Furthermore, in the long term, adverse outcomes such as prolonged rehabilitation, more pronounced cognitive impairment, and increased institutionalization (5–7) are reported. This affects patients, proxies, healthcare providers, and the general society because of the more extensive use of healthcare resources (8, 9).

The current Society of Critical Care Medicine guideline for delirium (10) recommends restoring physiological homeostasis and does not recommend haloperidol prevention or treatment, because recent large randomized clinical trials showed no beneficial effects in either prevention or treatment of delirium in ICU patients (11–13). Although single-component nonpharmacological delirium prevention and treatment strategies have demonstrated a benefit in non-ICU patients (14), these beneficial effects have not been found in ICU patients (10). Current guidelines suggest the application of multicomponent nonpharmacological intervention programs aiming to optimize modifiable delirium risk factors such as visual and hearing impairment, orientation loss, sleep deprivation, cognitive impairment, and immobility (10, 15). However, the effects of such multicomponent interventions have not been unequivocally established in critically ill patients by adequately powered randomized controlled trials (10).

The aim of the present study was to determine the effect of a multicomponent program of nonpharmacological nursing interventions on the number of delirium-free and coma-free days alive and other relevant outcomes in critically ill patients.

Methods

Design

The UNDERPIN-ICU (Nursing Delirium Preventive Interventions in the Intensive Care Unit) study was a multicenter, stepped-wedge cluster-randomized controlled trial in ICU patients at high risk of developing delirium. Ten ICU centers (clusters) of one university hospital, four teaching hospitals, and five nonteaching hospitals participated, which were selected based on their membership in the Dutch ICU Delirium Consortium and their commitment to improve delirium care. Patients were included from December 31, 2016, to May 1, 2019, with a 90-day follow-up to August 1, 2019. The Medical Research Ethical Committee Arnhem-Nijmegen waived the need for informed consent, because the study evaluated a change in standard of care, for which, under Dutch law, no explicit patient consent was required (2013/173). The study protocol was previously published (16). No relevant changes to methods were made after trial commencement.

Participants

Medical, surgical, and trauma critically ill patients aged ⩾18 years who were at high risk of developing delirium (defined as an Early Prediction of Delirium in ICU Patients [E-PRE-DELIRIC] score of ⩾35%) (17) and delirium free at time of ICU admission were included. Patients were excluded if they had an expected ICU stay of less than 1 day or if the ICU team determined that reliable assessment for delirium was not possible (because of acute brain injury, audiovisual disorders, language problems, mental disability, aphasia, or sustained coma during complete ICU stay, defined as a Richmond Agitation Sedation Score [RASS] of −3 or lower) (18).

Interventions and Implementation

The UNDERPIN-ICU program focused on optimizing modifiable delirium risk factors: visual and hearing impairment, orientation loss, sleep deprivation, cognitive impairment, and immobility, which have been proven effective in non-ICU patients (19, 20). These domains were customized specifically for ICU patients (16), of which feasibility was determined by expert consensus (21) and pilot testing (22). The interventions in our bundle were hypothesized to be most efficient in prevention, but nurses were also stimulated and encouraged to use them in the case in which the patient developed delirium, aiming at shortening the delirium duration. Nurses were allowed to—based on their professional expertise—individually tailor the program to patient needs while covering all UNDERPIN-ICU domains as much as possible, starting within 24 hours after ICU admission until ICU discharge (Figure 1 and Supplement E1 in the online supplement).

At the start of the study, all centers started in the control period. The extent to which nonpharmacological delirium interventions were already being applied varied among centers, but their use was generally unstructured, incomplete, and not well defined in the existing local delirium

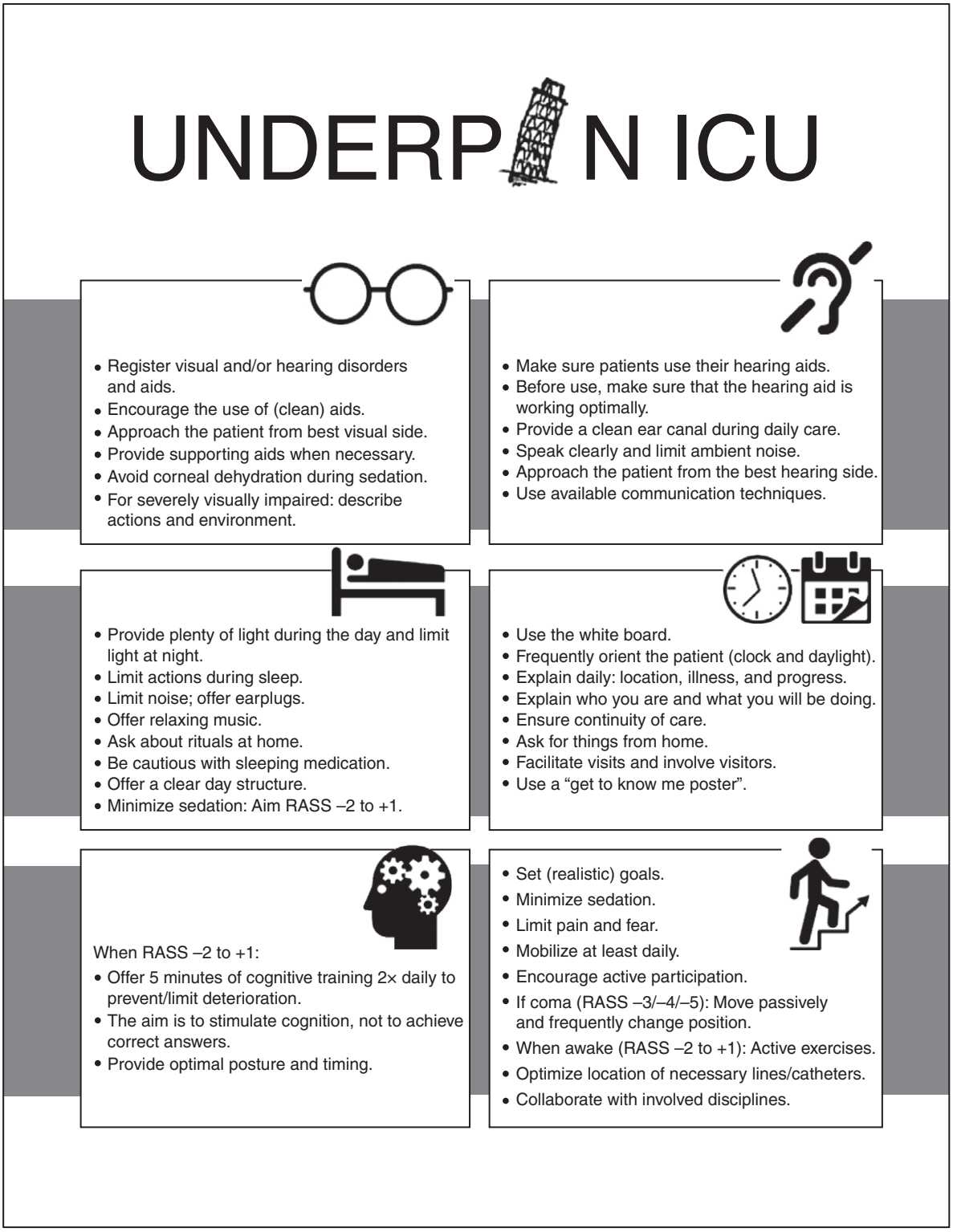

Figure 1. Program visual summary. UNDERPIN-ICU was sponsored by ZonMw. RASS = Richmond Agitation Sedation Score.

protocols. All ICU nurses received a physical/digital refresher course concerning the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) on top of their in-house CAM-ICU training. This remained available during the study for refreshing their memory in the tablet computers used for data gathering. Every second month, the UNDERPIN-ICU program was implemented as standard of care in a randomly assigned center. After this 2-month training period, the program was considered standard care, and the intervention period started, which lasted until the end of the study.

The training period included implementation of the UNDERPIN-ICU program in the local delirium protocol, formation of a local delirium working group, tailoring of template program materials to local standards and wishes, and training of the nursing and medical staff. Nurses were instructed to start working according to the program after they had received their training, supported by the local working group. In all centers, the local working group was involved in the implementation strategy, which was aimed at the level of the intervention, the patient, the provider, and the organization and included education, motivational strategies, and outreach visits (23). All centers were supported through training, presentations, and the provision of standardized and plasticized posters and practical materials to enhance awareness. Based on local needs and wishes, additional specific presentations (e.g., delirium background, screening, or specific program content) were provided. Real-time feedback on noise levels was given by a sound level monitor stoplight (Yacker Tracker; Attention Getters Inc.) for a period of 2 months after implementation of the program, and coffee mugs containing the UNDERPIN-ICU program pictograms were distributed as a daily reminder. Study information was communicated through posters and information letters accompanied by general information about delirium. The interventions started as soon as possible after ICU admission, based on the nurses' assessment. Every 3 months, newsletters were sent summarizing the progress of the study, and specific feedback was given to the local working group on the team performance of the application of cognitive training exercises, light levels, and sound levels for adequate enforcement of the execution of the program.

Outcomes

The primary outcome was the number of delirium-free and coma-free days alive in 28 days after ICU admission. Secondary outcomes were as follows: delirium incidence (defined as the new onset of delirium [positive CAM-ICU or treatment with haloperidol] after ICU admission), delirium duration (defined as time from the first positive CAM-ICU or treatment with haloperidol until the beginning of 2 consecutive days of negative delirium screenings while awake and/or termination of haloperidol treatment), mortality at 28 and 90 days, duration of mechanical ventilation (calendar days), incidence of reintubation, incidence of ICU readmission, incidence of unplanned removal of tubes/catheters, use of physical restraints, and ICU and hospital length of stay (calendar days). In addition, exploratory analyses were performed on prespecified subgroups: admission type (surgical, trauma, and medical), predicted delirium risk (E-PRE-DELIRIC score) (17), Acute Physiology and Chronic Health Evaluation (APACHE) IV score (24), ICU length of stay, and mortality. Furthermore, a mixed methods process evaluation of cost effectiveness and the effects on long-term quality of life and cognitive function was conducted, which will be published separately. The exact definitions of endpoints were published in the study protocol (16). No changes in the outcome measures were made after the study was started.

Data Collection

Pseudonymized process data (screening, daily scores, application of cognitive training) were gathered by the attending nurses using tablet computers (iPad Air 2; Apple), for which an application was developed to support the execution of this study (PIECA, BeagleBoxx; Brightfish) that contained links to online questionnaires (SurveyMonkey). This allowed for remote real-time monitoring by the study team to process the data during the study. The application was also used for e-learnings, screening, and treatment tools; the dissemination of UNDERPIN-ICU program information and newsletters; and the provision of additional recreational features (television, newspapers, magazines, and puzzles).

Delirium was assessed using the CAM-ICU (25) including the RASS (18) or using the Delirium Observation Screening Scale (26) when patients were discharged to the ward. Detailed definitions were described in the study protocol (16). CAM-ICU quality checks were performed comparing bedside assessments of ICU nurses with expert CAM-ICU assessments executed by the first author (an experienced ICU nurse with several years of delirium interest and research experience, who received training by several reference standards before the interrater assessments) at all centers. Daily sleep quality was inquired about using the Numeric Rating Scale for Sleep (27), and nursing workload was determined using the Nursing Activities Score (28).

Participating unobtrusive observations were performed by nursing students, who coworked in all centers in five half-yearly rounds assessing a total of 110 day shifts in which the time spent on UNDERPIN-ICU interventions before and after implementation was observed and registered per activity in minutes. Furthermore, they collected perceived workload and work stress measurements using a numeric rating score (range 0–10). Light (lux) and sound (decibels) were measured within 1 m of the patient's head by two smartphones (LG Nexus 5X; LG Electronics) in each center, which were equipped with an application that sampled at 1 Hz (every second) (VitalMinds; Philips), for which an additional waiver was obtained (Supplement E2). Outcome data were gathered through a secured cloud-based and certified electronic data capture platform (CastorEDC). All systems used complied with local security and privacy standards, and centers could only access their own data.

Sample Size, Randomization, and Blinding

A difference between the interventional group and the control group of 2 days or more in delirium-free and coma-free days alive was considered clinically relevant (29). Our stepped-wedge design of 10 clusters with 14 measurement periods having 12–13 patients/period/cluster contained a standard stepped-wedge design of 8 clusters with 9 measurement periods with 8 patients/period/cluster. Therefore, our design was estimated to provide more than 80% power to detect the targeted difference with $\alpha = 0.05$ and intraclass correlation coefficient = 0.01 for clustering at ward levels, even accounting for the possible loss of patients and/or one ICU, resulting in a requirement of approximately 1,750 patients (16, 30). Because of the nature of the interventions, blinding was not possible. Using the stepped-wedge method, all centers started as controls, and every

second month, the program was implemented in a randomly assigned center. No interim analyses were performed.

Statistical Analyses

Depending on their distribution, descriptive statistics are presented as mean (SD) or median (25th–75th interquartile range [IQR]). Based on missing value analysis (0.2%), no imputation was performed. When patients died before day 28, their delirium-free and coma-free days while alive were used. Thus, if a patient died after 10 days but had 2 days delirium free and coma free alive during those 10 days, the outcome is 2. For the outcome measures, all continuous variables were compared using linear multilevel models (including fixed effects for intervention and the different periods and a random cluster effect for patients nested within centers). Skewed distributed variables were log transformed. (If the range included 0, the value +1 was log transformed). Effects were reported as the ratio of medians (MR) in the intervention versus the control condition. Binary variables were compared using logistic multilevel models for which odds ratios were reported. Model fit was assessed using residual plots and by comparing the observed and predicted profiles of the centers over time. Time-to-event data were analyzed using multilevel Cox proportional hazards models (SAS PROC PHREG with random statement). (Because these models did not converge, we reverted to Cox regression models with a fixed effect for center as preplanned in the study protocol) (16). For the exploratory analyses of outcomes, admission type, predicted delirium risk, mortality risk, length of stay, and observed mortality and their interaction with the intervention were included in the multilevel analyses.

Process measures were assessed for normality, and statistical significance was assessed using independent samples *t* test or Mann-Whitney *U* test. All patients were analyzed according to their assigned treatment ("intention to treat" principle). In addition, subgroup analyses and a "per-protocol" analysis were performed, which excluded patients who were persistently comatose throughout their ICU admission and those who were admitted to the ICU during the implementation period (Supplements E3–E4).

All outcome data were analyzed by an independent statistician (S.T.). Data were analyzed using SPSS Statistics version 25 (IBM), SAS version 9.2 (SAS Institute Inc.), MATLAB R2019b (MathWorks), and GraphPad Prism version 8.3 (GraphPad Software Inc.). Statistical significance was defined as $P < 0.05$.

Results

Between 2016 and 2019, 24,657 patients were admitted to the participating centers. Of them, 22,908 were excluded, mainly postoperative patients with an anticipated ICU stay of less than 24 hours (Figure 2). Ultimately, 1,749 ICU patients were included (mean [SD] age 71 [10] yr, 1,047 [60%] men, mean [SD] APACHE-IV score 82 [30], and median [IQR] E-PRE-DELIRIC score 42% [37–49%]), 924 in the intervention period and 825 in the control period (Table 1).

In all centers, after implementation of the UNDERPIN-ICU program, a formalized local protocol was used (Supplement E1). All centers appointed a local working group that consisted of a mean of 5 (range 2–6) professionals. In 9 of 10 hospitals, over 70% of the nursing/medical staff received a training presentation. In all hospitals, the plasticized standardized materials were actively hung in each patient room and family rooms by the local working group.

The time spent per shift on the UNDERPIN-ICU interventions was median (IQR) 38 (14–116) in the intervention period and median 32 (13–73) minutes in the control period ($P = 0.44$). The time spent on improving cognitive function increased, and light levels during nighttime and noise levels during daytime decreased significantly after implementation of the program. Sedation levels, quality of sleep, and objective workload did not significantly change after implementation. The subjective work stress score (0–10) as perceived by the nursing staff increased significantly from a median score of 4 (IQR, 2–5) to a median score of 5 (IQR, 4–6) ($P = 0.01$) (Table 2).

Primary Outcome

The median (IQR) number of delirium-free and coma-free days alive in 28 days was 23 (4–27) days in the intervention period and 23 (5–27) days in the control period (mean difference, −1.21 d; 95% confidence interval [95% CI], 2.84–0.42 d; $P = 0.15$) (Table 3). During the study, no adverse effects of the multicomponent intervention program were reported.

Secondary Outcomes

The delirium incidence was 39% in the intervention period and 40% in the control period (odds ratio, 1.10; 95% CI, 0.79–1.53; $P = 0.59$). In incident delirium cases, the median (IQR) number of delirium days was 2 (1–4) days in the control period and 2 (1–4) days in the intervention period (MR, 0.90; 95% CI, 0.75–1.09; $P = 0.27$). The number of coma days was 2 (0–4) days in the intervention period and 1 (0–4) day in the control period (MR, 1.09; 95% CI, 0.94–1.27; $P = 0.27$) (Table 3). The CAM-ICU interrater reliability measurement showed a Cohen's kappa of 0.88.

The exploratory analyses revealed no relevant intervention effects in subgroups. ICU length of stay significantly interacted with delirium incidence ($P < 0.05$) and delirium duration ($P = 0.02$) (Supplement E3).

For the per-protocol analysis, 300 patients who not actually meet the inclusion criteria and 81 who were enrolled during the implementation period were excluded. For all endpoints, similar outcomes were found (Supplement E4).

Discussion

In this multicenter, stepped-wedge cluster-randomized controlled trial, we evaluated the effects of a nonpharmacological nursing intervention program aimed at preventing delirium in critically ill patients with a high risk of delirium. Despite extensive preparation, including baseline assessment, the unstructured application of interventions in the control period was higher and the delirium duration lower than anticipated. Our large implementation efforts—which included education, motivational strategies, and outreach visits—did not further increase the already substantial time spent on program interventions, although the application of several interventions improved. We were unable to demonstrate any difference in the number of delirium-free and coma-free days alive in 28 days or in any of the secondary outcomes between the control-group and the intervention-group patients.

Delirium is a complex syndrome with multiple predisposing (e.g., frailty, age, dementia, hypertension, and pre-ICU emergency surgery or trauma) and precipitating (e.g., respiratory insufficiency, acute kidney injury, and coma) risk factors

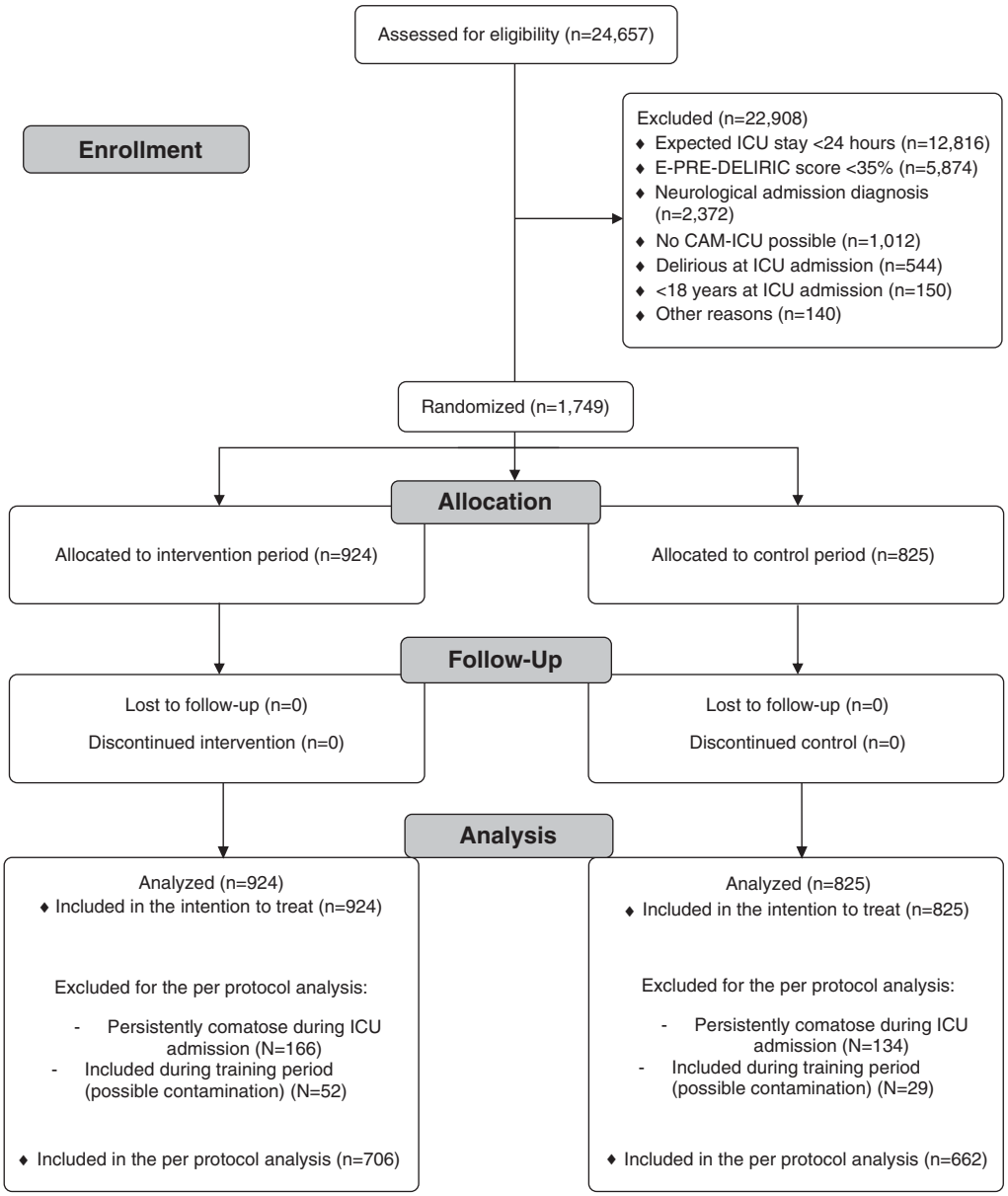

Figure 2. Patient flow diagram. CAM-ICU = Confusion Assessment Method for the Intensive Care Unit; E-PRE-DELIRIC = Early Prediction of Delirium in ICU Patients.

(31–33), and its manifestation is the consequence of the derangement of multiple complex pathways (34). This may implicate that its susceptibility to therapeutic influence may be limited, or at least individually tailored therapies aimed to restore homeostasis may be needed (10). The lack of efficacy of, e.g., haloperidol, for occurrence and duration of delirium in the ICU may illustrate this latter notion (11, 12, 35).

Because in noncritically ill patients the application of a multicomponent nonpharmacological program has been shown to be effective in reducing delirium burden (19, 20), its use is recommended in the current version of the Society of Critical Care Medicine guideline for delirium management in the ICU (10). In ICU trials, the early mobilization of ICU patients was associated with a shorter duration of delirium (29), and a multicomponent bundle was shown to be successful in a single center before-after ICU study ($n = 287$) (36); however, a recent meta-analysis showed no effects in single-component or multicomponent interventions when ICU studies were combined (37). Because the present larger multicenter study also showed no beneficial effect, this also may imply that the efficacy of nonpharmacological programs to prevent or reduce delirium in the ICU may be limited or absent. However, alternative explanations for the lack of a beneficial clinical effect are still relevant to discuss. Possibly, this relatively high quantity of interventions already applied for delirium prevention/treatment in the control period may have masked the therapeutic effects of these interventions. As typically higher delirium occurrences are observed (36, 38), and a low application of nonpharmacological interventions to prevent delirium is still

Table 1. Patient Characteristics

	Intervention (*n* = 924)	Control (*n* = 825)	*P* Value
Sex, M/F, *n* (%)	539/385 (58/42)	508/317 (62/38)	0.167
Age, yr, mean (SD)	71 (10)	71 (11)	0.466
Urgent admission, *n* (%)	842 (91)	786 (95)	0.770
Admission specialty, *n* (%)			<0.001
Surgical	63 (7)	105 (13)	—
Trauma	72 (8)	57 (7)	—
Medical	789 (85)	663 (80)	—
APACHE IV score, mean (SD)	81 (31)	83 (29)	0.189
Documented history of cognitive impairment*, *n* (%)	86 (10)	109 (14)	0.023
History of alcohol abuse, *n* (%)	103 (12)	81 (10)	0.224
Mean arterial pressure at admission, mm Hg, mean (SD)	79 (19)	77 (21)	0.092
Corticosteroids at admission, *n* (%)	286 (34)	272 (34)	0.769
Mechanically ventilated, *n* (%)	770 (90)	685 (86)	0.010
Serum urea level at admission, mmol/L, median (IQR)	7 (5 to 13)	8 (5 to 12)	0.797
E-PRE-DELIRIC score, %, mean (SD)†	40 (15)	42 (14)	0.032
RASS at admission, median (IQR)	−3 (−5 to 0)	−3 (−4 to 0)	0.115
Preadmission use of visual or hearing aids, *n* (%)	472 (51)	402 (49)	0.418

Definition of abbreviations: APACHE IV = Acute Physiology and Chronic Health Evaluation IV; E-PRE-DELIRIC = Early Prediction of Delirium in ICU Patients; IQR = interquartile range; RASS = Richmond Agitation Sedation Score.
*History of dementia, mild cognitive impairment, or delirium.
†Estimated chance for development of delirium; >35% equals high risk.

Table 2. Process and Compliance Data

	Intervention	Control	*P* Value
Minutes spent on UNDERPIN-ICU themes per 8-h shift*, median (IQR)	38 (14 to 116)	32 (13 to 73)	0.44
Visual and hearing impairment	4 (0 to 7)	4 (0 to 7)	0.51
Sleep deprivation	5 (1 to 9)	3 (1 to 6)	0.35
Cognitive impairment	10 (3 to 29)	7 (2 to 14)	<0.05
Immobility	15 (3 to 46)	12 (4 to 55)	0.70
RASS†, median (IQR)			
Night	−1 (−3 to 0)	−1 (−3 to 0)	0.55
Day	−1 (−3 to 0)	−1 (−3 to 0)	0.55
Evening	−1 (−3 to 0)	−1 (−3 to 0)	0.57
NRS sleep†, mean (SD)	6 (2)	6 (2)	0.53
Light intensity, lx‡, median (IQR)			
Day	144 (65 to 263)	130 (49 to 296)	0.85
Night	12 (9 to 15)	17 (14 to 26)	<0.01
Noise levels, dB‡, median (IQR)			
Day	41 (38 to 42)	41 (38 to 44)	<0.05
Night	38 (37 to 39)	38 (36 to 42)	0.33
Number of cognitive trainings performed§	1,738	—	—
Duration of cognitive training, min§, median (IQR)	2 (1–3)	—	—
Nursing Activity Score: workload†, median (IQR)	55 (46 to 71)	56 (45 to 73)	0.73
Subjective work load (0–10)*, median (IQR)	6 (5 to 7)	6 (4 to 7)	0.61
Subjective work stress (0–10)*, median (IQR)	5 (4 to 6)	4 (2 to 5)	0.01

Definition of abbreviations: IQR = interquartile range; NRS = numeric rating score; RASS = Richmond Agitation Sedation Score; UNDERPIN-ICU = Nursing Delirium Preventive Interventions in the Intensive Care Unit.
Process measures were assessed for normality, and statistical significance was assessed using independent samples *t* test or Mann-Whitney *U* test.
**n* = 110 8-h shift observations/interviews.
†*n* = 10,258 daily nursing scores.
‡*n* = 22,130 measurement days (1 Hz).
§Digitally applied and monitored by a tablet computer.

frequently reported, it is possible that the implementation of these domains may be of benefit in other situations. Because they are cheap and relatively easy to apply (although successful implementation requires a change in culture and attitude) and no adverse effects have been reported, further evaluation of the effect of nonpharmacological programs in other contexts may be warranted.

Such studies should include extensive preparation, including formulating

Table 3. Primary and Secondary Outcomes (Intention-to-Treat Analyses)

	Intervention (*n* = 924)	Control (*n* = 825)	Intervention Effect	95% CI	*P* Value
Delirium-coma-free days alive	23 (4–27)	23 (5–27)	−1.21	−2.84 to 0.42	0.15
Delirium days	0 (0–1)	0 (0–1)	0.99*	0.88 to 1.12	0.89
Only in patients with delirium	2 (1–4)	2 (1–4)	0.90*	0.75 to 1.09	0.27
Coma days	2 (0–4)	1 (0–4)	1.09*	0.94 to 1.27	0.27
Sedation days	2 (0–5)	2 (0–4)	1.12*	0.96 to 1.30	0.14
Delirium medication days	0 (0–2)	0 (0–3)	1.14*	0.81 to 1.61	0.43
Delirium incidence	361 (39)	327 (40)	1.10†	0.79 to 1.53	0.59
Duration of mechanical ventilation	4 (2–8)	3 (1–7)	1.11*	0.94 to 1.30	0.21
Incidence of reintubation	103 (11)	80 (10)	1.12†	0.64 to 1.99	0.69
Incidence of readmission	62 (7)	59 (7)	1.00†	0.53 to 1.89	0.99
Incidence of unplanned removal of tubes/catheters	49 (5)	40 (5)	0.79†	0.38 to 1.66	0.53
Incidence of physical restraints‡	343 (37)	332 (40)	0.85†	0.57 to 1.27	0.43
Duration of physical restraints‡	0 (0–2)	0 (0–3)	0.99*	0.86 to 1.16	0.94
ICU length of stay	6 (3–12)	6 (3–11)	1.09*	0.94 to 1.26	0.27
Hospital length of stay	16 (9–27)	15 (8–26)	1.07*	0.92 to 1.23	0.38
28-d mortality	297 (32)	273 (33)	1.16†	0.85 to 1.59	0.34
90-d mortality	350 (38)	312 (38)	1.24†	0.92 to 1.67	0.17

Definition of abbreviations: CI = confidence interval; IQR = interquartile range.
Data are presented as median (IQR) or *n* (%), unless noted otherwise.
*The ratio of the median of calendar days in the intervention condition to the median in the control condition as estimated from the linear mixed model after log transformation (*see* METHODS).
†Odds ratio as estimated from the generalized linear mixed model with logit link (*see* METHODS).
‡Wrist, ankle, or abdominal bands or boxing gloves.

generalizable definitions (10) and extensive pilot testing (39), as the Delphi round undertaken before this study (21) overestimated feasibility in daily practice. Furthermore, extensive interprofessional collaboration (40), as well as combining promising pharmacological (e.g., low-dose dexmedetomidine) (41) and nonpharmacological strategies (e.g., occupational therapy) (42), may lead to optimized delirium prevention and treatment, especially when incorporated in existing frameworks such as the A–F bundle (43).

This study has several strengths, including its sample size, cluster-randomized stepped-wedge design, and extensive implementation efforts (16). However, several limitations also need to be addressed. First, only patients at high risk of delirium were included. We hypothesized that the effect size would, plausibly, be greatest in this high-risk subgroup of patients. Possibly, these interventions may be effective in patients who are already delirious before ICU admission or those who are at lower baseline risk; however, the subgroup analyses performed show no trend toward benefit in the lower-delirium-risk subgroup. Second, intervention fidelity was monitored using several proxy measurements (unobtrusive participating observations and process measures) instead of direct nursing registration, which may have limited adequate estimation of the effects achieved. This approach was chosen to minimize the additional workload as well as prevent bias due to additional registrations.

Third, the overall duration of delirium was lower compared with other recent trials (12, 29, 36, 38), which may have limited our ability to show a beneficial effect of an intervention. Fourth, the already relatively high adherence at baseline and the large number of interventions of the UNDERPIN-ICU program may have limited the effect determined. Fifth, more detailed information about risk factors and their outcomes (such as cumulative doses of sedatives) would have provided additional insight into the effects determined. Sixth, we did not assess delirium in patients with a RASS of −3 at that moment, which means that delirium occurrence may have been underestimated; however, in the context of this study, the extent to which patients with a RASS of −3 would be receptive to—and would benefit from—our interventions would probably be minimal.

Conclusions

In this large randomized controlled trial in adult ICU patients focused on optimizing vision, hearing, orientation, sleep, cognition, and mobility to reduce delirium, a limited increase in the use of nursing interventions was achieved, and no change in the number of delirium-free and coma-free days alive in 28 days or in any of the secondary outcomes could be determined. ■

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