ANESTHESIOLOGY

Prophylactic Haloperidol Effects on Long-term Quality of Life in Critically Ill Patients at High Risk for Delirium

Results of the REDUCE Study

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ABSTRACT

Background: Delirium incidence in intensive care unit patients is high and associated with impaired long-term outcomes. The use of prophylactic haloperidol did not improve short-term outcome among critically ill adults at high risk of delirium. This study evaluated the effects of prophylactic haloperidol use on long-term quality of life in this group of patients and explored which factors are associated with change in quality of life.

Methods: A preplanned secondary analysis of long-term outcomes of the pRophylactic haloperidol usE for DeliriUm in iCu patients at high risk for dElirium (REDUCE) study was conducted. In this multicenter randomized clinical trial, nondelirious intensive care unit patients were assigned to prophylactic haloperidol (1 or 2 mg) or placebo (0.9% sodium chloride). In all groups, patients finally received study medication for median duration of 3 days [interquartile range, 2 to 6] until onset of delirium or until intensive care unit discharge. Long-term outcomes were assessed using the Short Form-12 questionnaire at intensive care unit admission (baseline) and after 1 and 6 months. Quality of life was summarized in the physical component summary and mental component summary scores. Differences between the haloperidol and placebo group and factors associated with changes in quality of life were analyzed.

Results: Of 1,789 study patients, 1,245 intensive care unit patients were approached, of which 887 (71%) responded. Long-term quality of life did not differ between the haloperidol and placebo group (physical component summary mean score of 39 ± 11 and 39 ± 11, respectively, and $P = 0.350$; and mental component summary score of 50 ± 10 and 51 ± 10, respectively, and $P = 0.678$). Age, medical and trauma admission, quality of life score at baseline, risk for delirium (PRE-DELIRIC) score, and the number of sedation-induced coma days were significantly associated with a decline in long-term quality of life.

Conclusions: Prophylactic haloperidol use does not affect long-term quality of life in critically ill patients at high risk for delirium. Several factors, including the modifiable factor number of sedation-induced coma days, are associated with decline in long-term outcomes.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Delirium is a frequently occurring disorder in intensive care unit patients associated with impaired short-term and long-term outcomes
- Prophylactic haloperidol neither reduces delirium incidence nor its short-term clinical consequences
- Many intensive care unit survivors suffer from long-term impairment of physical, cognitive, or mental health status, but there is a gap in knowledge regarding which factors are associated with such a change in quality of life in the post–intensive care unit period

What This Article Tells Us That Is New

- Prophylactic haloperidol does not affect long-term outcome of critically ill patients at high risk for delirium
- Every additional day of sedation-induced coma is associated with further decline of long-term physical and mental function

With an incidence rate of approximately 30%[1] and prevalence rates up to 87%,[2] it is clear that delirium is a major burden for patients admitted to the intensive care unit (ICU). Delirium is characterized by acute confusion, inattention, and altered consciousness, and symptoms tend to fluctuate during the day.[3] Delirium is a complex syndrome that can be triggered by a plethora of factors (*e.g.*, use of sedatives and opioids, metabolic disturbances, pain, mechanical ventilation, and latency of sleep; so-called precipitating risk factors). These precipitating factors are of specific relevance in patients with predisposing risk factors such as advanced age, a history of cognitive dysfunction, and comorbidities.[4] Reducing delirium in ICU patients is

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paramount because it is associated with impaired short-term outcome (*e.g.*, prolonged mechanical ventilation, ICU, and hospital stay[5]) but also with worse long-term outcome.[6,7] Because increasing numbers of patients survive the ICU,[8] the long-term effects of ICU stay and interventions have become more relevant.

It is well known that many ICU survivors suffer from impaired physical, cognitive, or mental health status, a phenomenon known as "post–intensive care syndrome."[9] However, there is a paucity of knowledge on factors associated with these changes in quality of life.

In the present study, we primarily evaluated the effects of prophylactic haloperidol use on long-term quality of life.[10] The secondary aim was to explore which factors are associated with changes in long-term quality of life of ICU survivors.

Materials and Methods

The pRophylactic haloperidol usE for DeliriUm in iCu patients at high risk for dElirium (REDUCE) study was a randomized, double-blind, placebo-controlled study conducted in 21 Dutch hospitals, involving ICU patients at high risk of developing delirium. The short-term results of this study were recently published elsewhere.[11] The effect of haloperidol on long-term quality of life was a secondary outcome of the REDUCE study[10] and is the primary focus of this article. In addition, exploratory secondary analyses were carried out to determine which factors are associated with changes in long-term quality of life. This predefined substudy was conducted in 9 of the 21 ICUs participating in the REDUCE study.

The medical ethics committee approved this study (study number 2012/424). The study is registered in the ClinicalTrials.gov database (NCT01785290). The published study protocol[10] provides detailed information regarding the inclusion and exclusion criteria of patients, randomization, and study medication procedures.

Briefly, patients aged 18 yr or older who were delirium-free at ICU admission and had an anticipated ICU stay of at least 2 days as estimated by the attending intensivist were eligible for study participation. The main exclusion criteria were delirium before study inclusion, an acute neurologic condition, use of antipsychotic agents, history of clinically relevant ventricular arrhythmia, and inability to provide written informed consent.[10,11] Patients or next of kin were asked for written informed consent, and if this was not possible, a deferred consent procedure was used. Patients were randomly assigned to the intervention group (intravenous administration 3 × 1 mg or 3 × 2 mg of haloperidol or the control group (0.9% sodium chloride). The first dose of study medication was administered within 24 h after ICU admission. The administration of study medication was terminated at day 28 or earlier in case of either ICU discharge or occurrence of delirium. In the latter case, patients were treated with open-label haloperidol according to the study protocol.[10] Because no dose–effect relation was established,[11] the data of the two haloperidol dosage groups were combined for the analyses described in this article.

Quality of life was measured using the Short Form-12[12] questionnaire. This is a validated instrument, consisting of eight domains: physical functioning, role–physical, bodily pain and general health, vitality, social functioning, role–emotional, and mental health, which are summarized into two components: physical component summary and mental component summary.[12] The Short Form-12 was completed at ICU admission (baseline) and at 1 and 6 months after ICU admission by patients or their next of kin in case patients were not able to fill in the questionnaire themselves.[13] The 1- and 6-month questionnaires were sent to patients' home addresses once, irrespective of whether the patient was still admitted to the hospital.

Demographic and in-hospital characteristics, including age, sex, Acute Physiology and Chronic Health Evaluation II score, (early) prediction of ICU delirium ([E-]PRE-DELIRIC) score,[14,15] admission type, mechanical ventilation, and length of stay (ICU and hospital), were collected from the electronic patient record. Patients were diagnosed with delirium when they had at least one positive delirium assessment using the confusion assessment method for ICU[2] during the first 28 days of their ICU-stay. A delirium day was defined by at least one positive delirium assessment on a given day. A coma day was defined by a Richmond agitation sedation score of less than −2 induced by the use of a sedative on a given day. The total dose of haloperidol was defined as the total amount (mg) of administered haloperidol (prophylaxis and/or open-label treatment together).

Statistical Analysis

Descriptive analyses were conducted before and at 1 and 6 months after ICU admission, including Spaghetti plots with the physical component summary and mental component summary scores of all individual patients. Differences in demographic characteristics and ICU-related variables between the prophylactic haloperidol group and placebo group were tested with the independent samples *t* test or the Mann–Whitney U test, depending on the distribution, and with the chi-square test for categorical variables.

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Differences in long-term quality of life (1 and 6 months after ICU admission) *versus* baseline were compared between the intervention group and control group. Changes over time in quality of life were determined using repeated measurement two-way ANOVA. The repeated measurement ANOVA analyses only included patients for whom data was available on each time point. Group, time, and group × time interaction effects were assessed.

To determine possible bias of nonresponders on the long-term outcomes, patient and ICU characteristics of the total group, responders, and nonresponders were compared. Linear regression analyses were carried out to identify factors associated with changes in physical component summary scores or mental component summary scores after 6 months for which mean difference scores of the physical component summary scores and mental component summary scores before ICU admission and at 6 months after ICU admission were calculated. The physical component summary and mental component summary score for deceased patients at 6 month was set at 0. The patient characteristics and ICU variables listed in table 1 were considered as covariates in the regression analyses.

Because of the exploratory nature of the analyses pertaining to associated factors, no correction for multiple testing was performed. Multicollinearity was assessed for all included variables. The maximum variance inflation factor statistic was 4.58 for the physical component score and 4.56 for the mental component score in the variable PRE-DELIRIC (risk for developing delirium) score; all other variables had variance inflation factor statistics of less than 3.0, indicating no multicollinearity. For this substudy, no *a priori* statistical power calculation was performed. The main study was powered on the primary outcome measure of 28-day survival.[10,11]

To explore in more detail which factors were associated with a decline in long-term quality of life, logistic regression analyses were carried out. For this analysis, the mean difference scores were divided into tertiles. Patients in the lowest tertile were classified in the "declined" group; all other patients were classified as "not declined" (Supplemental Digital Content 1, http://links.lww.com/ALN/B967, and Supplemental Digital Content 2, http://links.lww.com/ALN/B968). Deceased patients were included in the declined group.[16] Patients characteristics and ICU variables listed in table 1 served as covariates and were included in the logistic regression analyses with declined (1) or not declined (0) for physical component summary score or mental component summary score as the dependent variable.

Table 1. Demographic Characteristics and ICU and Outcomes Variables

	In-hospital Group			6-month Follow-up Group		
	Haloperidol Group n = 558	Placebo Group n = 329	*P* Value	Haloperidol Group n = 248	Placebo Group n = 165	*P* Value
Patient variables						
Age in yr, mean ± SD	65 ± 13	66 ± 12	0.448	64 ± 13	66 ± 11	0.101
Male/female, n (%)	349/209 (62/38)	217/112 (66/34)	0.307	156/92 (63/37)	117/48 (71/29)	0.092
ICU variables						
Admission type, n (%)						
Surgical	309 (55)	169 (51)	0.099	154 (62)	90 (55)	0.098
Medical	220 (39)	149 (45)		81 (33)	70 (42)	
Trauma	32 (6)	11 (3)		13 (5)	5 (3)	
Urgent admission, n (%)	439 (79)	266 (81)	0.438	195 (79)	132 (80)	0.737
Mechanically ventilated, n (%)	429 (77)	232 (71)	0.036	186 (75)	114 (69)	0.187
Number of mechanical free days in 28-days, median [IQR]	26 [21–27]	26 [22–27]	0.265	26 [21–27]	26 [22–28]	0.230
APACHE II score, mean ± SD	19 ± 7	19 ± 7	0.968	19 ± 7	19 ± 6	0.529
Sepsis, n (%)	157 (28)	100 (30)	0.474	62 (25)	46 (28)	0.514
PRE-DELIRIC score, mean ± SD	26 ± 12)	26 ± 12	0.891	25 ± 11	24 ± 11	0.934
Treatment dose of haloperidol day/mg, median [IQR]*	3 [2–4] (n = 191)	3 [2–5] (n = 125)	0.895	3 [2–4] (n = 83)	4 [2–5] (n = 64)	0.774
Number of sedation induced coma days in 28 days, median [IQR]	1 [0–4]	1 [0–3]	0.054	0 [0–3]	1.0 [0–3]	0.008
Length of stay in ICU, median [IQR]	5 [2–10]	4 [2–10]	0.297	5 [3–10]	4 [2–8]	0.095
Length of stay in hospital, median [IQR]	18 [11–33]	16 [10–29]	0.039	18 [10–33]	17 [10–31]	0.203
Outcome variables						
Incidence of delirium at 28 days, n (%)	219 (39)	131 (40)	0.867	94 (38)	67 (41)	0.581
Number of delirium days in 28-days, median [IQR]	0 [0–2]	0 [0–2]	0.983	0 [0–2]	0 [0–3]	0.763
Alive at 28 days, n (%)	473 (85)	282 (86)	0.702	n.a.	n.a.	
Alive at 90 days, n (%)	449 (81)	269 (82)	0.635	n.a.	n.a.	

*Haloperidol prophylaxis and/or open-label treatment.

APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; IQR, interquartile range, 25th-75th percentiles; n.a., not applicable; PRE-DELIRIC, prediction of ICU delirium.

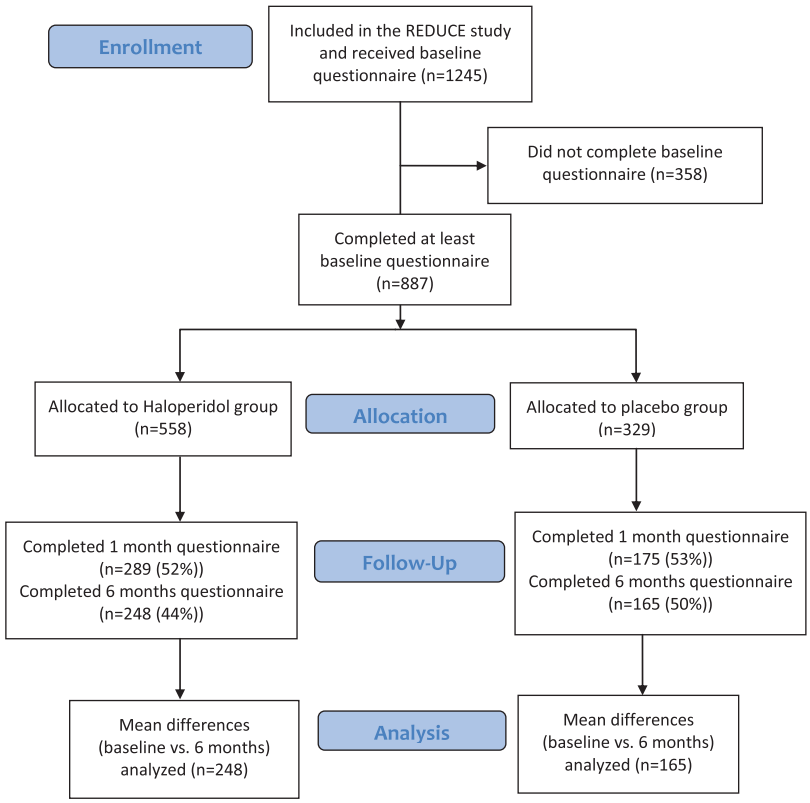

Fig. 1. Flow diagram of study. REDUCE, pRophylactic haloperidol usE for DeliriUm in iCu patients at high risk for dElirium.

Two-sided tests were used with $P < 0.05$ indicating statistical significance. The analyses were performed using SPSS Statistics version 25.0.

Results

Of the 1,789 patients in the REDUCE study, 1,245 patients (70%) were approached at baseline, of whom 887 (71%) patients completed the questionnaire at ICU admission. The response rates at 1 and 6 months were 52% (n = 464) and 47% (n = 413), respectively. At baseline, the mean ± SD age was 66 ± 13 yr, and 556 (64%) patients were male. In total, 558 patients were included in the haloperidol group, and 329 patients were in the placebo group.[11] There were no clinically relevant differences between the total REDUCE group (N = 1,789), the long-term follow-up group (N = 1,245), the responders (N = 887), and the nonresponders (N = 358; Supplementary Digital Content 3, http://links.lww.com/ALN/B969). There was no missing information regarding patient and ICU characteristics. Of all tested variables, only the proportions of patients who were mechanically ventilated (77% *vs.* 71%, $P = 0.036$) and length of hospital stay (18 *vs.* 16 days, $P = 0.039$) differed significantly between the

Table 2. Quality of Life Summarized Score of Patients That Completed the Questionnaire on All Time Points

	Baseline		1-month Follow-up		6-month Follow-up				
	Haloperidol Group n = 181	Placebo Group n = 127	Haloperidol Group n = 181	Placebo Group n = 127	Haloperidol Group n = 181	Placebo Group n = 127	Group Difference *P* Value	Time Difference *P* Value	Group × Time Interaction *P* Value
Physical component summary score, mean ± SD	39 ± 12	37 ± 12	32 ± 9	32 ± 8	39 ± 11	39 ± 11	0.350	< 0.0001	0.246
Mental component summary score, mean ± SD	49 ± 11	49 ± 11	47 ± 11	48 ± 11	50 ± 10	51 ± 10	0.678	< 0.0001	0.753

intervention and placebo groups. Outliers were evaluated, but no action was necessary. Survival rate and duration of delirium did not differ between the haloperidol and placebo groups (table 1; fig. 1).

Effects of Prophylactic Haloperidol Use on Quality of Life

The mean physical component summary scores and mental component summary scores at baseline and at 1 and 6 months after ICU admission of patients assigned to the prophylactic haloperidol group or to the placebo group are described in Supplemental Digital Content 4 (http://links.lww.com/ALN/B970). Mean physical component summary scores and mental component summary scores of patients who completed the questionnaire on all three time points (and were thus included in the repeated measurement ANOVA analyses) are described in table 2. Over time, the physical component summary scores and mental component summary scores varied significantly (time effects: both $P < 0.0001$), but there were no significant differences between the haloperidol and placebo group (group effects: $P = 0.350$ and $P = 0.678$; table 2; fig. 2). Furthermore, no interaction effects were observed ($P = 0.246$ and $P = 0.753$, respectively; table 2).

Factors Associated with Changes in the Physical Component Summary Score

Linear regression analyses showed that age, medical admission, trauma admission, physical component summary score at baseline, PRE-DELIRIC score (risk for developing delirium), and days of sedation-induced coma were inversely associated with changes in the physical component summary score (table 3).

Factors associated with physical decline (n = 306, 53%) compared to no physical decline (n = 275, 47%) after 6 months were age (odds ratio, 1.02; 95% CI, 1.01 to 1.04), medical admission (odds ratio, 2.08; 95% CI, 1.39 to 3.10), trauma admission (odds ratio, 5.34; 95% CI, 1.65 to 17.27), baseline physical component summary score (odds ratio, 1.06; 95% CI, 1.04 to 1.08), and number of sedation-induced coma days (odds ratio, 1.15; 95% CI, 1.05 to 1.25; Supplemental Digital Content 5, http://links.lww.com/ALN/B971).

Factors Associated with Changes in the Mental Component Summary Score

Age, medical admission, baseline mental component summary score, and days of sedation-induced coma were inversely associated with changes in the mental component summary score (table 3). Factors associated with patients that showed mental decline (n = 305, 53%) compared with those who exhibited no mental decline (n = 274, 47%) after 6 months were age (odds ratio, 1.03; 95% CI, 1.01 to 1.04), medical admission (odds ratio, 2.09; 95% CI, 1.43 to 3.03), baseline mental component summary score (odds ratio, 1.03; 95% CI, 1.01 to 1.05), and the number of sedation-induced coma days (odds ratio, 1.09; 95% CI, 1.01 to

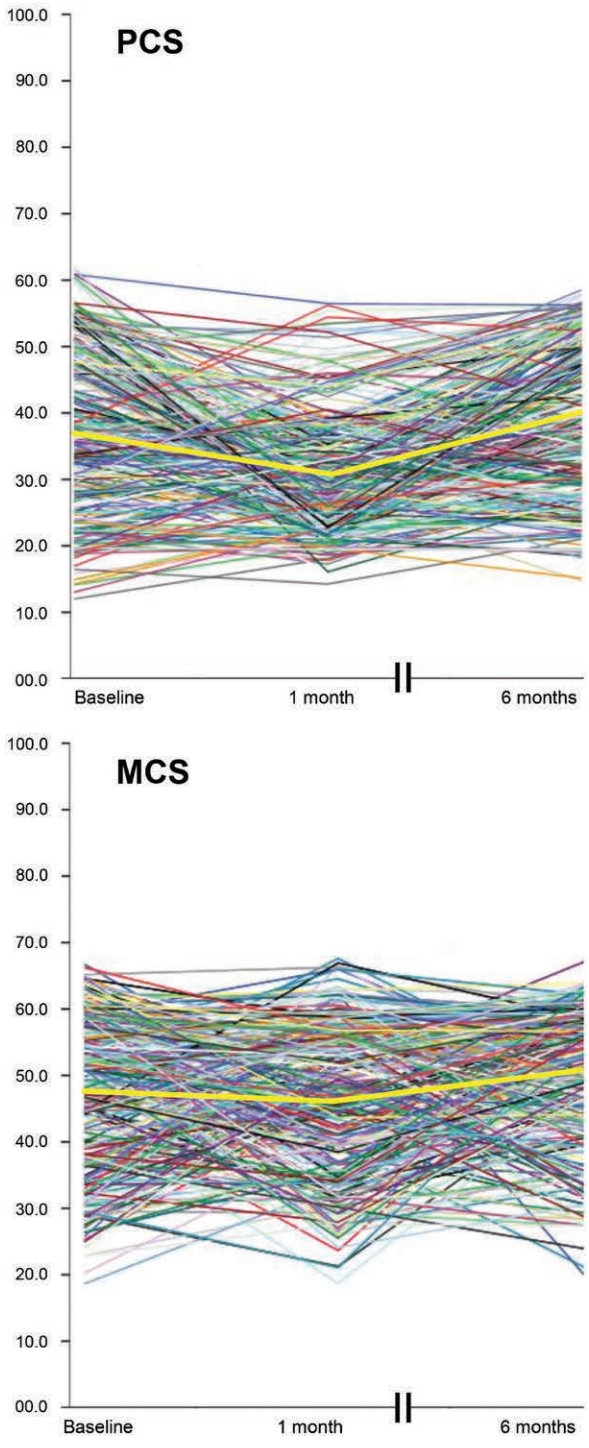

Fig. 2. Spaghetti plot of individual physical component summary (PCS; *top*) and mental component summary (MCS; *bottom*) scores of patients who completed all questionnaires (n = 308). MCS, mental component summary; PCS, physical component summary.

Table 3. Factor Association with Change in Physical Component Summary and Mental Component Summary Scores

	Physical Component Summary Score (n = 579)		Mental Component Summary Score (n = 579)	
	β ± SE	*P* Value	β ± SE	*P* Value
Age	−0.23 ± 0.07	0.002	−0.31 ± 0.09	0.001
Male sex	−0.35 ± 1.53	0.821	−0.29 ± 1.97	0.884
Surgical admission	Reference		Reference	
Medical admission	−5.14 ± 1.67	0.002	−7.16 ± 2.14	0.001
Trauma admission	−10.55 ± 3.86	0.006	−4.24 ± 4.95	0.392
Baseline component summary score	−0.54 ± 0.06	< 0.001	−0.46 ± 0.08	< 0.001
Days mechanically ventilated	0.09 ± 0.18	0.624	0.06 ± 0.23	0.804
Daily haloperidol dose	−0.41 ± 0.48	0.396	−0.14 ± 0.62	0.818
Hospital length of stay	0.01 ± 0.03	0.590	0.04 ± 0.03	0.285
APACHE II score	−0.15 ± 0.16	0.346	−0.11 ± 0.20	0.586
Sedation < 24 h after admission	2.15 ± 2.40	0.372	2.09 ± 3.13	0.504
Sepsis	−2.78 ± 1.74	0.088	−2.37 ± 2.26	0.293
PRE-DELIRIC score	−0.27 ± 0.13	0.033	−0.28 ± 0.17	0.094
Delirium days	0.37 ± 0.25	0.135	0.58 ± 0.32	0.070
Days of sedation induced coma	−1.04 ± 0.28	< 0.001	−1.07 ± 0.36	0.003

APACHE II, Acute Physiology and Chronic Health Evaluation II; PRE-DELIRIC, prediction of ICU delirium; SE, standard error.

1.17; Supplemental Digital Content 5, http://links.lww.com/ALN/B971).

Discussion

The REDUCE study, a large multicenter double-blind randomized clinical trial involving ICU patients at high risk for delirium, recently showed that prophylactic haloperidol use had no effects on survival and incidence and duration of delirium in critically ill patients. In the present study, we evaluated the effect of prophylactic haloperidol use in the ICU on long-term quality of life 6 months after ICU admission. Although no effects of prophylactic haloperidol use were demonstrated, statistically significant differences in physical and mental function were observed over time in the total study group, and several factors other than delirium were found to be associated with a decline in long-term quality of life.

As ICU mortality rates decrease over the years, the focus is shifting from preventing short-term mortality toward improving long-term quality of life after ICU stay.[8,17,18] Long-term effects of prophylactic haloperidol use were not investigated previously. The REDUCE study showed no effects of prophylactic haloperidol treatment on short-term outcomes,[11] and this secondary analysis reveals that long-term quality of life is not affected either. These results are in accordance with the recent prophylactic rosuvastatin study.[19] The current guideline of the Society of Critical Care Medicine[20] does not recommend pharmacologic interventions to prevent delirium in ICU patients, and our findings support this recommendation.[11]

In the total study group, the summarized physical and mental quality-of-life scores differed statistically significant over time. As one might expect, we found that older age is associated with a decline in physical and mental functioning 6 months after ICU admission. Interestingly, and possibly of importance for clinical practice, is the independent association between the number of sedation-induced coma days and a decline in long-term quality of life. One day of sedation-induced coma was associated with a 15% decline of the physical functioning score and a 9% decline point of mental functioning score at 6 months after ICU admission. However, this was an exploratory analysis that should be interpreted cautiously, because bias cannot be excluded. Nevertheless, this finding supports the recommendation to use light sedation levels with Richmond agitation sedation scores between 0 and −2, instead of deep sedation or coma with Richmond agitation sedation scores of −3 to −5, as stated in the current Society of Critical Care Medicine guideline.[20] Mean scores of quality of life at baseline and at 6 months were similar for the total study population, although individual scores for physical and mental functioning over time varied considerably. The association between baseline and long-term quality of life scores was highly significant. This finding illustrates that population means may lead to the false conclusion that patients' functional status recovers in the long-term to levels comparable with those found before ICU admission, whereas our analyses show that large differences between subgroups are present. As a consequence, and to reduce the impact of ICU care on physical and mental functioning,[18,21] preventive interventions should be focused on subgroups of patients with low quality-of-life scores at ICU admission.

Several limitations of this study need to be addressed. First, only patients at high risk for delirium were included, which may limit the generalizability of the results. In the REDUCE study, an anticipated ICU length of stay of 2 days or more was used as a surrogate parameter to identify patients at high risk of developing delirium, but several of these patients were misclassified as carrying a high risk when assessed using a delirium prediction model with a higher accuracy (PRE-DELIRIC).[15]

Second, the number of patients lost to follow-up was considerable; despite a high response rate of 71% at baseline, the response rate at 1 and 6 months was 52% and 47%, respectively. It needs to be acknowledged that these response rates are still relatively high when considering the mortality rate of 15% at 1 month and 20% at 3 months. Nevertheless, although being similar to comparable studies,[22–24] the loss to follow-up may have introduced bias.

Third, unfortunately more detailed data on sedation use was not collected. Therefore, it was not possible to evaluate the possible contribution to the decline in quality of life of separate sedatives like propofol or midazolam, the dosage of the administered sedation, or the indication for sedation. The association between sedatives and decline in quality of life remained present, also after adjusting for several sedation-related factors such as severity of illness and admission type. Although the effects of no sedation *versus* sedation with daily interruption were previously studied,[25] including long-term outcome measures,[26] only psychologic outcomes were assessed, not quality of life.

In conclusion, prophylactic haloperidol use in critically ill patients exerts no beneficial effect on long-term quality of life in ICU survivors. The factors age, medical, and trauma admission, baseline quality of life, risk for delirium, and the number of sedation-induced coma days are associated with the decline in long-term outcome parameters. These associations can be used to inform patients and should be taken into account both during treatment in the ICU and during the post-ICU period.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: mark.vandenboogaard@radboudumc.nl. Raw data available at: mark.vandenboogaard@radboudumc.nl.

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