**Effect of haloperidol on survival among critically ill adults with a high risk for delirium: the REDUCE randomized clinical trial**

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#### KEY POINTS (74 words, max 75-100)

**Question:** What is the effect of prophylactic haloperidol on survival among critically ill adults?

**Findings:** In this multicenter randomized clinical trial involving 1789 critically ill adults at high-risk for delirium, 28-day survival was 83.3% among patients receiving prophylactic haloperidol therapy and 82.7% among patients receiving a placebo, a non significant difference .

**Meaning:**  The use of prophylactic haloperidol therapy did not improve survival nor other delirium endpoints among critically ill adults with high-risk for delirium.

**Abstract (312 words, max. 350)**

**Importance**

Results of studies on use of prophylactic haloperidol in critically ill adults are inconclusive, especially in patients at high-risk for delirium.

**Objective**

To determine whether prophylactic use of haloperidol improve survival and other delirium outcomes of critically ill adults at high risk for delirium.

**Design, Setting, and Participants**

Randomized, double-blind, placebo-controlled investigator-driven study among 1789 critically ill adults conducted in 21 intensive care units (ICU) in the Netherlands. ICU patients without delirium, and with an expected length of stay in the intensive care unit of over one day, were included. Recruitment was from July 2013 to December 2016 and follow-up was conducted at 90 days with final follow-up on March 1, 2017.

**Interventions**

Patients received prophylactic treatment three times daily intravenously either 1 mg (n=350) haloperidol or 2 mg (n=732) haloperidol or placebo (n=707) administration of 0.9% sodium chloride.

**Main outcome and measures**

The primary outcome was 28-day survival. Secondary outcomes included 90-day survival, delirium incidence and number of delirium- and coma-free-days in 28-days.

**Results**

All randomized 1,789 patients (mean [SD] age 66.6 [12.6] years; 1,099 [61.4%] men) completed the study. The 1 mg haloperidol group was prematurely stopped because of futility. The 28-day survival rate in the 2 mg group was 83.3% and 82.7% in the placebo group (mean difference 0.6; 95% confidence interval -4.7 to 6.0) with an unadjusted hazard ratio of 0.91 and adjusted hazard ratio, 1.003 (95% confidence interval, 0.78 to 1.30). No differences between groups were found in delirium incidence, 33.0% vs. 33.3%, nor in any of the other delirium related outcomes.

**Conclusions and Relevance**

In this clinical trial involving critically ill adults with high-risk for delirium, the use of prophylactic haloperidol, compared to placebo, did not improve survival at 28 days and other delirium-related endpoints. These findings do not support the use of prophylactic haloperidol for reducing mortality in critically ill adults.

**Trial registration**

Clinicaltrials.gov: NCT01785290

**INTRODUCTION**

 Delirium is an acute brain disorder characterized by an acute onset of confusion, inattention, and a change in level of consciousness of which symptoms fluctuate during the day.[1](#_ENREF_1) Delirium is a frequently occurring acute brain disorder in intensive care unit (ICU) patients with incidence rates of approximately 30-50% and with prevalence rate up to 80%.[2](#_ENREF_2),[3](#_ENREF_3) It is associated with deleterious clinical outcomes, including prolonged duration of mechanical ventilation, increased ICU- and hospital length of stay (LOS),[2](#_ENREF_2),[3](#_ENREF_3) and increased mortality.[3](#_ENREF_3),[4](#_ENREF_4) Moreover, impaired cognitive functioning may persist when delirium resolves.[5](#_ENREF_5),[6](#_ENREF_6)

 It is important to first treat or remove delirium risk factors. Also the use of non-pharmacologic interventions focusing on potential risk factors like early mobilization, reducing use of sedatives and benzodiazepine play an important role in delirium management. When delirium occurs subsequently, often haloperidol is prescribed as pharmacologic delirium treatment[7](#_ENREF_7) and sometimes haloperidol is also prescribed as delirium prophylaxes.[8](#_ENREF_8),[9](#_ENREF_9) Interestingly, beneficial effects on delirium outcomes have been reported of prophylactic haloperidol in patients who were not critically ill,[10](#_ENREF_10),[11](#_ENREF_11) however, in ICU patients its role is inconsistent.[12-15](#_ENREF_12)

 The aim of this study was to determine the effects of two different doses of haloperidol given as prophylactic agent compared with placebo on 28-day survival in ICU patients. Also to determine the 90-day survival, delirium incidence, delirium-and-coma-free-days, and other delirium related outcome measures. In addition, we evaluated possible adverse effects of prophylactic haloperidol and determined the effects of prophylactic haloperidol in several predefined subgroups.

**METHODS**

**Design and setting**

The pRophylactic halopEriDol Use for delirium in iCu patiEnts at high risk for delirium (REDUCE) study, was a three-group, randomized, double-blind, placebo-controlled multicenter investigator-driven study performed in ICU patients with a high delirium risk. Twenty-one centers, including university hospitals, teaching and non-teaching hospitals, in the Netherlands participated. This study was conducted July 2013 and December 2016, and follow-up was conducted at 90 days with final follow-up on March 1, 2017. The medical ethical committee of Arnhem-Nijmegen, the Netherlands (CMO) approved this study including the deferred consent procedure (CMO-number 2012/424). The complete study protocol has been published previously.[16](#_ENREF_16)

**Study population and ethics**

Delirium-free ICU patients of ≥18 years, with an anticipated ICU stay of ≥two days as estimated by the attending intensivist, were considered as having a high risk for delirium and were eligible for study participation. Exclusion criteria were: delirium prior to inclusion, Parkinson disease, dementia or alcohol abuse, an acute neurological condition, history of a psychiatric disease and using anti-psychotics, history of clinically relevant ventricular arrhythmia in the last 12 months, QTc-time >500 msec, pregnant or breast feeding, or expected death within 2 days, known allergy or intolerance to haloperidol, and inability to obtain informed consent.

 The informed consent process was initiated immediately after ICU admission and, in case this was not possible, a deferred consent procedure was used. Written consent was then necessary within 24 hours after the first administration of the study medication. If deferred informed consent was rejected, study medication was stopped immediately, and the patient was excluded from further analyses. Patients who provided consent and received at least one dose of study medication were considered as included and remained in the study. Patients in whom study medication had to be halved or stopped, e.g. due to adverse effects, remained allocated to their study-group and were analyzed on an intention to treat basis.

**Randomization and study medication**

Eligible patients were randomly assigned to one of the three groups: the intervention group of either 1 mg or 2 mg haloperidol, or the placebo group. Randomization was applied by the pharmacist of the Radboudumc using a permuted block randomization. The three groups were described as group A, group B and group C, patients were allocated to a 1:1:1 ratio. The randomization code was kept by this pharmacist, and together with members of the data safety management board they were the only people who were unblinded for this study. The pharmacist was not involved in clinical management of the patients. Each participating center had a stock of study medication of which the amount of study medication per study group (A, B and C) was equally divided for the three groups. The study medication was accompanied with a randomization list. Following randomization the numbers of study medication box were coupled with the randomization numbers. The numbered boxes consisted of 12 ampoules of study drug. If necessary, when a patient was admitted to the ICU for more than 4 days and did not develop delirium, a follow-up study medication box was assigned to this patient consisting of the same study regime as the previous box (A, B or C). The follow-up study medication was always delivered by a researcher or pharmacist, who was not involved in the study, using a shadow-list with code A-B or C ensuring the patients remained in the same study arm.

All study medication was manufactured by the Department of Pharmacy of the Radboudumc according to Good Manufacturing Practice regulations. All ampoules of study medication had a total volume of 1 ml, and ampoules and drug boxes had a fully identical appearance and label.

**Endpoints**

The primary endpoint was survival duration over 28-days (time to event). Secondary endpoints were 90-day survival, delirium incidence, number of delirium- and coma-free days in 28-day, duration of mechanical ventilation, length of ICU stay and hospital stay, incidence of unplanned removal of tubes and catheters, incidence of ICU re-admission, incidence of physical restraints. Furthermore, the incidence of all adverse effects was monitored for which study medication was halved or stopped. Exact definitions of the endpoints are shown in eMethods 1.

**Intervention and control group**

In the 21 participating centers the use of several non-pharmacologic delirium interventions is part of their daily ICU care, e.g. early mobilization, reduction of sedation and benzodiazepines and awakening trials; see eMethods 2. This pharmacologic study was conducted on top of the non-pharmacologic interventions.

The intervention groups received either 1 mg or 2 mg haloperidol and the placebo group received 0.9% sodium chloride, all three times daily and intravenously. To decrease the likelihood of adverse effects in specific cohorts, the dose of the study medication was halved in patients aged ≥80 years, a body weight of ≤50 kg, and in patients suffering from liver failure (serum bilirubin level >50 µmol/L) present at the time of inclusion or during the study.

 The first dose of the study medication was administered as soon as possible, always within 24 hours after ICU admission. Study medication was continued until day 28 or ICU discharge (whichever came first), or until delirium occurred. In the latter case, study medication was stopped and patients could be treated with open-label haloperidol. In agitated patients 2 mg haloperidol was prescribed intravenously three times daily, other delirium subtypes received 1 mg intravenously every 8 hours. Dosage could be increased up to a maximum of 5 mg every 8 hours in case of serious agitation or anxiety due to delirium. Escape medication was midazolam, clonidine, propofol or dexmedetomidine at the discretion of the attending physician. A similar treatment protocol including the administering of haloperidol intravenously, intramuscularly or orally dosed, was subscribed for the ward. In patients who were treated >3 days, haloperidol was halved once delirium resolved, the second delirium-free day the dose was halved again and haloperidol was stopped when the patient remained non-delirious. In case delirium re-occurred, the original dose was restarted. Study medication was not restarted once delirium subsided and therapeutic haloperidol was stopped or when a patient was re-admitted to the ICU within 28-days.

**Data collection**

Demographic data including age, sex, delirium prediction scores,[17](#_ENREF_17),[18](#_ENREF_18) APACHE-II score and diagnosis group were collected, together with data on all endpoints.

Delirium was diagnosed using the confusion assessment method-ICU (CAM-ICU)[19](#_ENREF_19),[20](#_ENREF_20) or the intensive care delirium screening checklist (ICDSC)[21](#_ENREF_21), as having at least one positive delirium screening during the 28-days after inclusion. The number of delirium-and-coma-free days in 28 days was defined as the number of days alive without delirium and with a Richmond Agitation Sedation Scores (RASS) > -4 in 28-days.[13](#_ENREF_13),[22](#_ENREF_22)

In case a patient with delirium was discharged to the ward, a delirium day was defined according to the validated delirium observation scale score[23](#_ENREF_23) of 3 or more. The days following ICU discharge to the ward of non-delirium patients were considered as delirium-free-days. Participating centers who collected data on delirium, were all experienced in delirium assessment using either the CAM-ICU or, at one center, the ICDSC. Both validated assessment tools are recommended by critical care societies, demonstrating an approximately similar diagnostic performance[24](#_ENREF_24). In 14 out of the 21 participating centers delirium and coma days data were collected; mortality, safety data, and delirium incidence were collected in all centers. From 7 centers no data on delirium and coma days could be retrieved because of limited availability of research personnel.

 The following safety issues were specifically evaluated: QTc-time prolongation and drowsiness. Furthermore, the occurrence of extrapyramidal symptoms as dystonia, tremor, myoclonus, tics, rigidity, and akathisia,[25](#_ENREF_25) were determined daily by physical examination by the attending intensivist. In case a adverse effect occurred, the dose could be halved or be stopped, depending on the severity of the adverse effect and at the discretion of the attending physician. Only for prolonged QTc-time strict stopping rules were applied: study medication was temporarily stopped until normalization, after which study medication was restarted.

**Sample size calculation and Statistical analysis**

 Sample size was calculated based on the previous finding in a before-after study[14](#_ENREF_14), with a hazard ratio of 0.80 for 28-days mortality were the median survival time in the control group was 18 days. To be conservative, the effect size was set on a smaller effect size using a hazard ratio of 0.85, resulting in a total of 715 patients per group needed to have a power of 0.80, with an alpha of 0.05.

Data were analyzed according to the ‘intention to treat’ principle for patients in whom informed consent was obtained and who received at least one dose of study medication. A per-protocol analysis followed to compare the intervention groups with the placebo group for those who received study medication according to the study protocol, and as defined in the statistical analysis plan.

Imputation was only performed in case of missing data required for the delirium prediction models. Missing data for calculating the E-PRE-DELIRIC and PRE-DELIRIC prediction scores were imputed as in previous studies[17](#_ENREF_17),[18](#_ENREF_18),[26](#_ENREF_26) and as described in the statistical analysis plan. In total there were 10 missing values of the APACHE-II and 39 of the blood urea level which were subsequently imputed.

 For the descriptive statistics, continuous variables were presented as mean with standard deviation or median with inter quartile ranges, depending on their distribution. Normally distributed variables were tested using Student’s t-test for comparison and Mann–Whitney U-tests for non-normally distributed variables. Confidence intervals for the difference between two medians were calculated using Hodges-Lehmann estimates. Categorical (and binary) variables were presented as numbers with percentages and analyzed using Chi-square test. Confidence intervals of the differences between proportions were calculated using Yates’ correction for continuity.

Survival analyses with Kaplan-Meier curves were used for graphical presentation. Cox proportional hazard regression analyses were used to estimate the hazard ratio for survival in 28-days and 90-days with the use of haloperidol versus placebo. In addition to unadjusted comparisons, adjusted analyses were performed using prior set relevant covariates (APACHE-II score, age, sex, diagnosis group, sepsis, urgent admission, and center). Although confounding is unlikely in a randomized clinical trial of this size, the power of the study may increase by adjustments for covariates which were chosen prior to the study because these are all related to the primary endpoint[27](#_ENREF_27),[28](#_ENREF_28). Therefore we performed the Cox regression analyses both without and with these covariates.

 Prior to the study several subgroups were defined for sensitivity analyses. Subgroups were patients with a predicted delirium risk <20%, 20-30% and >30%, in different admission diagnosis groups, in severity of illness groups with APACHE-score <20, 20-25, >25, in groups receiving study medication up to 2 days, more than 2 days, 3 days or 5 days of prophylactic therapy, and patients that developed delirium and those who did not develop delirium. Per subgroup interaction was tested. The secondary endpoints and the sensitivity analyses were exploratory and therefore no correction for multiple testing was performed on these results.

An independent data safety management board, consisting of three members (one psychiatrist, one anesthesiologist, and one statistician) performed unblinded safety, futility and superiority interim analyses after the inclusion of 175, 350, 500 (safety and futility) and 1000 (safety and superiority) patients. For safety analyses the incidence of adverse and serious adverse events in the intervention and the placebo group were compared, and for futility or superiority of the intervention or placebo, the primary endpoint 28-day survival was used. Per analysis first the difference between the highest dose of haloperidol versus placebo was tested, and second the difference between lowest dose and placebo. Differences in adverse events between the groups were reviewed. The advice to drop a treatment group because of safety concerns or futility was given on discretion of the data safety management board. A time sequential to illustrate the increasing power of the study, leading to a trend towards benefit, harm or futility. The adaptive design allowed to drop one therapy group based on predefined futility definitions. After inclusion of 1000 patients, superiority was determined with a proven superiority (*p<0.003, two-sided)* of any dose of haloperidol over placebo resulting in an alpha of 0.049 (two-sided) for the final analysis. This alpha distribution was calculated by an independent statistician according to the method of Lan-DeMets cumulative alpha spending function of O’Brien-Fleming alpha spending.[29](#_ENREF_29) All statistical tests were two-sided and statistical significance was defined as a *P-*value <0.05. Statistical analyses were performed using SPSS version 23 (SPSS, Chicago, IL, USA) and R version 3.4.2. (R Foundation for Statistical Computing, Vienna, Austria).

**RESULTS**

During the study period 15,882 eligible ICU adults with an expected length of ICU stay of ≥2 dayswere admitted to the participating ICU’s. A total of 11,898 patients were excluded, most frequently due to an acute neurological condition (35.7%), in 2188 (13.8%) patients no informed consent and in 7 patients no confirmation of a deferred consent was obtained (Figure 1). A total of 732 patients were included in the 2 mg haloperidol group of which 46 (6.3%) patients via deferred consent procedure, and 707 in the placebo group of which 52 (7.4%) via deferred consent. No safety issues occurred in all interim analyses, and during the fourth interim-analysis, after 1000 included patients, the data safety management board advised to prematurely terminate the inclusion of patients in group C due to futility, as reflected in the time sequential analysis (eFigure 1). For this reason only 350 patients were included in this group, that after unblinding turned out to be the 1 mg haloperidol group. A post-hoc power calculation was performed, the power for the 1mg haloperidol group to demonstrate a significant effect, after the inclusion of 1000 patients was 6.1%. As a consequence and per statistical analysis plan, only the effects of the 2 mg haloperidol group were compared to the placebo group in the primary analyses. The demographic and patient characteristics between both groups were comparable (Table 1).

**Primary outcome**

The 28-day survival rate between the 2 mg haloperidol group (610 out of 732; 83.3%) and the placebo group (585 of 707; 82.7%), proportion difference 0.6 (95%CI: -3.4 to 4.6)(Table 2). The adjusted hazard ratio (HR) for survival in 28 days for the 2 mg haloperidol group was 1.003 (95%CI: 0.78 to 1.30), and the unadjusted hazard ratio was 0.91 (95% CI: 0.67 to 1.24) compared with the placebo group, Figure 2.

**Secondary outcomes**

*90-day survival, delirium incidence, delirium-and-coma-free days*

The survival rate at 90-day also did not differ between the haloperidol group (579 out of 732 patients; 79.1%) and the in the placebo group (556 of 707 patients; 78.6%), proportion difference 0.5% (95%CI: -3.9 to 4.8)respectively , Figure 2.

The delirium incidence between the haloperidol and placebo groups was not statistically different, 33.3% versus 33.0%; proportion difference 0.4% (95%CI -4.6 to 5.4). The number of days till delirium developed also did not differ between the groups. Patients that developed delirium and subsequently received open label haloperidol according to the study protocol, were treated for a similar duration, in both groups the median number of days of open label delirium treatment was 2 days [IQR 1-5]. The dose of open label haloperidol was also not significant different between both groups, both median 3.0 mg [IQR 2.0-4.6]. From in total 1506 (84.2%) patients data on delirium and coma days could be retrieved. There were no significant differences in number of delirium free-days, coma free-days and delirium-and-coma-free-days alive in 28 days (Table 2).

*Delirium-related outcome measures*

No differences were found between both groups regarding the duration of mechanical ventilation, incidence of unplanned removal of tubes, incidence of ICU re-admission, length of ICU stay and in-hospital stay, and other delirium related outcomes (Table 2). In both groups, physical restraints were used in a no significant different proportion of 191 patients (27.0%) versus 169 patients (24.8%) proportion difference 2.2% (-2.4 to 6.8).

**Per-protocol analysis**

All patients who did not receive the study medication according to the study protocol[16](#_ENREF_16) (6.8% in 2mg haloperidol group and 5.5% in the placebo group) were subsequently excluded from the per-protocol analysis. Again, no statistically significant differences were found between groups in the per-protocol analysis for any of the outcome measures (eTable 1).

**Safety issues**

Five serious adverse events (SAE) were reported. Three patients died, one in each group (Table 2). All SAE’s were judged to be unlikely related to the study medication. Three patients had a monomorphic ventricular tachycardia and one patient suffered from a refractory shock. In one patient, who was assigned to the placebo group, a suspected malignant neuroleptic syndrome was reported. The number of reported adverse events was not statistically different between the groups.

**Subgroup analysis**

Sensitivity analyses were performed for all predefined subgroups in strata according to delirium prediction scores, admission diagnosis, severity of illness, duration of prophylactic therapy, and patients that developed delirium and those who did not develop delirium. No significant interaction between any of the subgroups and treatment were found (Table 3, and eFigure 2a-c). Day-28 and day-90 survival, as well as on delirium incidence, across all tested subgroups showed no differences between patients who received 2 mg haloperidol and those who received placebo (Table 3).

**DISCUSSION**

In this large multicenter double-blinded randomized clinical trial no differences were found in critically ill adults at high risk for delirium at 28-days survival between patients that received prophylactic haloperidol therapy and patients that received placebo. Also no differences were found at 90-days survival as well as for all other secondary endpoints. Furthermore, across predefined subgroups, the lack of a prophylactic effect was very consistent. Prophylactic haloperidol therapy was not associated with haloperidol-induced adverse effects.

 The pathophysiological mechanism of delirium is poorly understood. Delirium is considered a multifactorial disorder and many different pathways to its occurrence have been postulated[30](#_ENREF_30),[31](#_ENREF_31) resulting in many hypotheses.[31](#_ENREF_31) The fact that the average of 11 risk factors present at the same time in ICU delirium patients[2](#_ENREF_2) suggests the involvement of multiple pathways in its development. Therefore, it seems plausible that a mediator that alters delirogenic causal pathways may helpful. Haloperidol is an antipsychotic agent with antidopaminergic, anti-adrenergic, limited anticholinergic properties, and possibly anti-inflammatory effects[32](#_ENREF_32) that potential antagonists multiple delirogenic pathways.

 Haloperidol has been the first drug of choice to treat delirium[7](#_ENREF_7) for decades despite the lack of evidence that haloperidol is effective. For this reason the Society of Critical Care Medicine in its last guideline on pain, agitation and delirium[33](#_ENREF_33) did not recommend its use for treatment and neither for delirium prevention in critically ill adults. However, several ICU studies have evaluated possible prophylactic effects of haloperidol but demonstrating contradictory effects[12-15](#_ENREF_12). One randomized clinical trial in postoperative, moderate severe ICU patients receiving a maximum of 1.2 mg haloperidol showed a reduced delirium incidence and more delirium-free-days[12](#_ENREF_12). Another randomized clinical trial in severely ill medical ICU patients receiving 2.5 mg three times daily, showed no beneficial effect.[13](#_ENREF_13) and also no effect was found in reducing subsyndromal delirium with prophylactic haloperidol.[15](#_ENREF_15) Although a previous before-after study[14](#_ENREF_14) showed clinical relevant and favorable effects in a similar group of high risk and critically ill adults, these beneficial effects could not be replicated in the current randomized clinical trial. However, the findings of this study corroborate the findings of other randomized clinical trials in critically ill adults.[13](#_ENREF_13),[15](#_ENREF_15) The large sample size of this study allowed us to perform several sensitivity analyses, confirming the lack of effect across the different subgroups.

 This study has several limitations. First, one may argue that the early stopping of the 1mg haloperidol group is a limitation, however, it was a predefined consequence of our adaptive design which we consider as a strength of our study. Second, the duration of prophylactic therapy (median 2 days) could be too short to prevent delirium and its deleterious outcome. It cannot be excluded that longer exposure to haloperidol is may be needed to influence patient outcome. However, subgroup analysis in patients treated for more than two days also did not show any beneficial effect. Third, the used dose of haloperidol may have been too low. In a before-after study[14](#_ENREF_14) a 1 mg dose every 8 hours demonstrating beneficial effects without relevant adverse effects. For this reason it was chosen to also use a higher dose, similar as Page et al..[13](#_ENREF_13) In both haloperidol dosage groups no beneficial effects were found. Fourth, it was not feasible to collect data for all secondary outcome measures in some centers due to research staff limitations. However, the median number of delirium and coma free days between both groups did not differ, therefore collecting these data in a somewhat smaller group did not affect our results.

A fifth limitation of our study could be that in severely ill ICU adults the brain is already too affected for haloperidol to exert a prophylactic effect, since in non-ICU adults prophylactic haloperidol may have beneficial effects.[10](#_ENREF_10),[11](#_ENREF_11) But in the subgroup of patients with a low severity of illness score also no beneficial effects could be not demonstrated . Nevertheless, it cannot be ruled out that delirium is may be more easily and favorably affected in non-ICU adults compared to critically ill ICU adults.

**CONCLUSIONS**

This large multicenter double-blinded randomized clinical trial showed that prophylactic haloperidol therapy does not influence survival, delirium incidence nor related complications in critically ill adults. These findings do not support the use of prophylactic haloperidol in critically ill adults.

**List of abbreviations**

APACHE-II: Acute Physiology and Chronic Health Evaluation-II

CAM-ICU: Confusion Assessment Method-Intensive Care Unit

ICDSC: Intensive Care Delirium Screening Checklist

ICU: Intensive Care Unit

(E-)PRE-DELIRIC: (Early) Prediction delirium in ICU patients

RASS: Richmond Agitation Sedation Scale

SAE: Serious Adverse Event

SUSAR: Sudden Unexpected Serious Adverse Reaction

**Competing interests**

All authors declare that they have no competing interests related to this study.

**Authors’ contributions**

Drs. Mark van den Boogaard and Peter Pickkers had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Mark van den Boogaard, Arjen Slooter and Peter Pickkers designed the study and wrote the protocol. Mark van den Boogaard is the principal investigator. Peter Pickkers is project leader and Arjen Slooter and Johannes van der Hoeven are sub investigators. Arjen Slooter, Peter Pickkers, Lisette Schoonhoven, supervised the conduct of the study. Saskia Houterman and Gerjon Hannink supported the study design and protocol with statistical advises and performed the statistical analysis. Roger Brüggemann supported the study protocol with regard to study drug advises. Mark van den Boogaard, Arjen Slooter, Albertus Beishuizen, Wytze Vermeijden, Danie Pretorius, Jan de Koning, Koen Simons, Paul Dennesen, Peter van der Voort, Meta van der Woude, Anna Besselink, Lieuwe Hofstra, Peter Spronk, Walter van den Bergh, Dirk Donker, Malaika Fuchs, Attila Karakus, Mirelle Koeman and Mirella van Duijnhoven are responsible for conducting the study in their hospital. JvdH co-supervised and corrected the manuscript. All authors gave input and approved the final manuscript.

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Figure 1. Patient enrollment and flow through study

Figure 2. Kaplan-Meier Survival curve 28-day and 90-day

Table 1. Demographic and patient characteristics

|  |  |  |  |
| --- | --- | --- | --- |
|  | 1 mg haloperidol(N=350) | 2 mg haloperidol(N=732) | placebo(N=707) |
| Age, mean (SD) | 66.1 (12.6) | 66.7 (12.7) | 67.0 (12.6) |
| Male, n (%) | 206 (58.9) | 459 (62.7) | 434 (61.4) |
| Admission type, n (%)* Surgical
* Medical
* Trauma
 | 163 (46.6)171 (48.9)16 (4.6) | 337 (46.0)365 (49.9)30 (4.1) | 328 (46.4)357 (50.5)22 (3.1) |
| Urgent admission, n (%) | 285 (81.4) | 600 (82.0) | 572 (80.9) |
| Mechanical ventilated, n (%) | 247 (70.6) | 498 (68) | 457 (64.6) |
| APACHE-II score, mean (SD)\*History of cognitive disturbance, n (%)Use of corticosteroids before ICU admission, n (%)Acute respiratory failure, n (%)Blood urea level at time of ICU admission, median (IQR)Mean arterial blood pressure in mmHg, mean (SD) | 20.1 (7.1)6 (1.7)69 (19.7)136 (38.9)7.2 (5.0-12.0)75 (30) | 19.2 (6.9)12 (1.6)186 (25.4)304 (41.5)7.8 (5.5-12.4)78 (27) | 19.0 (6.8)17 (2.4)194 (27.4)296 (41.9)7.7 (5.5-13.0)79 (26) |
| Sepsis, n (%) | 107 (30.6) | 274 (37.4) | 234 (33.1) |
| PRE-DELIRIC [17](#_ENREF_17),[18](#_ENREF_18) score, mean (SD)#E-PRE-DELIRIC [26](#_ENREF_26) score, median (IQR)# | 26.3 (12.4)18 (11-31) | 26.1 (11.9)19(11-29) | 25.6 (11.8)19 (12-30) |
| QTc-time at time of inclusion, median (IQR) | 440 (410-469) | 447 (422-466) | 443 (420-468) |

\* APACHE-II score ranges from 0 -71; the higher score, the more severely ill the patient and the higher the hospital mortality risk

# (E-)PRE-DELIRIC score ranges from 0-100, representing the percentage chance that delirium may occur during the complete ICU length of stay

Table 2. Primary and secondary outcomes **[intention to treat analysis]**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | 2 mg haloperidol (N=732) | placebo (N=707) | *Difference (95%CI)* *2 mg haloperidol -placebo\*\** | 1 mg haloperidol (N=350)  |
| Survival in 28-day, n (%)Survival in 90-day, n (%)Delirium incidence, n (%) | 610 (83.3)579 (79.1)244 (33.3) | 585 (82.7)556 (78.6)233 (33.0) | *0.6 (-3.4 to 4.6)**0.5 (-3.9 to 4.8)**0.4 (-4.6 to 5.4)* | 286 (81.7)275 (78.6)139 (39.7) |
| Number of delirium-coma-free days in 28-days, median [IQR]\*Number of delirium-free days in 28-days, median [IQR]\*Number of coma-free days in 28-days, median [IQR]\* | 26 (17-28)28 (22-28)27 (22-28) | 26 (19-28)28 (23-28)27 (23-28) | *0.0 (0 to 0)\*\***0.0 (0 to 0)\*\***0.0 (0 to 0)\*\** | 26 (17-28)28 (21-28)27 (21-28) |
| Number of days to occurrence delirium, median [IQR]\*Duration of mechanical ventilation in days, median [IQR] | 3 (2-6)2 (0-6) | 3 (2-6)2 (0-5) | *0.0 (0 to 0)\*\***0.0 (0 to 0)\*\** | 4 (2-6)2 (0.3-7) |
| Length of stay ICU, median [IQR]Length of stay hospital, median [IQR]Incidence of ICU re-admission, n (%)Incidence of physical restraints, n (%) Incidence of unplanned removal of tubes, catheters, n (%)Incidence of re-intubation, n (%)Number of days treated with open-label haloperidol, median [IQR]Dose of open-label haloperidol in mg/day, median [IQR]**Safety issues**Maximum QTc-time in msec., median [IQR]* number of QTc-time prolongations, n (%)

Incidence of extra-pyramidal symptoms* dystonia, n (%)
* tremor, n (%)
* myoclonus, n (%)
* tics, n (%)
* rigidity, n (%)
* akathasia, n (%)
 | 5 (2-9)15 (9-28)65 (8.9)191 (27.0)81 (11.1)71 (9.7)2 (1-5)3.0 (2.0-4.6)465 (446-483)33 (4.5)1 (0.1)6 (0.8)4 (0.5)4 (0.5)3 (0.4)4 (0.5) | 4 (2-9)15 (9-26)68 (9.6)169 (24.8)73 (10.3)62 (8.8)2 (1-5)3.0 (3.0-4.6)463 (440-486)36 (5.1)3 (0.4)7 (1.0)4 (0.6)6 (0.8)6 (0.8)4 (0.6) | *0 (-0.0 to 1.0)\*\***1.0 (0 to 2.0)\*\***0.7 (-3.4 to 2.4)**2.2 (-2.4 to 6.8)**0.7 (-2.5 to 4.1)**0.9 (-0.2 to 4.1)**0.0 (0 to 0)\*\***0 (-0.4 to 0.3)\*\***1.0 (-2.0 to 5.0)\*\***-0.5 (-2.9 to 1.8)**0.3 (-0.1 to 4.0)**-1.7 (-1.2 to 0.9)**-0.1 (-0.8 to 0.8)**-0.3 (-1.3 to 0.6)**-0.5 (-1.4 to 5.2)**-0.0 (-0.8 to 0.7)* | 4 (2-9)16 (9-31)36 (10.3)102 (30.0)42 (12.0)32 (9.1)2 (1-5)3.0 (2.0-4.3)465 (440-489)31 (8.9)3 (0.9)6 (1.7)4 (1.1)4 (1.1)3 (0.9)6 (1.7) |
| Reported Serious Adverse Events, n (%) | 2 (0.3) | 1 (0.1) | *0.1 (-0.5 to 0.7)* | 2 (0.6) |

\* Data collected in smaller group of patients:

N=608 (83.1%) in 2 mg haloperidol group, N=599 (84.7%) in placebo group, and N=299 (85.4%) in 1 mg haloperidol group.

\*\* Differences between medians are described as absolute difference in ranking following order

Table 3. Sensitivity analyses **[intention to treat analyses]**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | 2 mg haloperidol(N=732) | placebo(N=707) | *Difference (95% CI) between 2 mg haloperidol and placebo* |  *Interaction effects* *(p-value)* | 1 mg haloperidol(N=350) |
| **Surgical group (N=828)**Survival in 28-days, n (%)Survival in 90-days, n (%)Delirium incidence, n (%) | 295 (87.5)280 (83.1)139 (41.2) | 285 (86.9)273 (83.2)122 (37.2) | *0.6 (-4.7-6.0)**0.1 (–6.0-5.7)**4.1 (-3.4-11.8)* | *Admission group**28-days: 0.73**90-days: 0.82* *Delirium incidence: 0.67* | 142 (87.1)135 (82.8)72 (44.2) |
| **Medical group (N=893)**Survival in 28-days, n (%)Survival in 90-days, n (%)Delirium incidence, n (%) | 288 (78.9)272 (74.5)97 (26.6) | 279 (78.2)262 (73.4)103 (28.9) | *0.7 (-5.5-7.0)**1.1 (-5.5-7.8)* *2.3 (-9.0-4.5)*  |  | 131 (76.6)127 (74.3)59 (34.5) |
| **Trauma group (N=68)**Survival in 28-days, n (%)Survival in 90-days, n (%)Delirium incidence, n (%) | 27 (90.0)27 (90.0)8 (26.7) | 21 (95.5)21 (95.5)8 (36.4) | *5.5 (-23.0-12.3)* *5.5 (-23.2-12.3)* *9.7 (-39.2-19.8)*  |  | 13 (81.3)13 (81.3)8 (50.0) |
| **APACHE-II score <20 (N=1006)**Survival in 28-days, n (%)Survival in 90-days, n (%)Delirium incidence, n (%) | 376 (91.5)364 (88.6)119 (29.0) | 367 (90.0)355 (87.0)111 (27.2) | *1.6 (-2.7-5.8)* *1.6 (-3.1-6.3)* *1.7 (-4.7-8.1)*  | *APACHE –II group* *28-days: 0.64* *90-days: 0.63* *Delirium incidence: 0.62* | 169 (90.4)166 (88.8)62 (33.2) |
| **APACHE-II score 20-25 (N=398)**Survival in 28-days, n (%)Survival in 90-days, n (%)Delirium incidence, n (%) | 129 (79.6)122 (75.3)63 (38.9) | 121 (78.6)114 (74.0)56 (36.4) | * 1. *(-8.5-10.7)*
	2. *1.3 (-8.9-11.5)*
	3. *2.5 (-8.8-13.8)*
 |  | 61 (74.4)58 (70.7)38 (46.3) |
| **APACHE-II score >25 (N=385)**Survival in 28-days, n (%)Survival in 90-days, n (%)Delirium incidence, n (%) | 105 (66.0)93 (58.5)62 (39.0) | 97 (66.9)87 (60.0)66 (45.5) | 1. *(-12.3-10.2)*
2. *-1.8(-13.5-9.9)*
3. *-6.2 (-17.9-5.5)*
 |  | 56 (69.1)51 (63.0)39 (48.1) |
| **PRE-DELIRIC score <20 (N=600)**Survival in 28-days, n (%)Survival in 90-days, n (%)Delirium incidence, n (%) | 220 (95.2)217 (93.9)45 (19.5) | 233 (92.5)227 (90.1)49 (19.4) | *2.8 (-1.9-7.5)* *3.9 (-1.3-9.1)* *-0.0 (-7.2-7.1)*  | *PRE-DELIRIC group**28-days: 0.42**90-days: 0.56* *Delirium incidence: 0.34* | 108 (92.3)107 (91.5)26 (22.2) |
| **PRE-DELIRIC score 20-30 (N=578)**Survival in 28-days, n (%)Survival in 90-days, n (%)Delirium incidence, n (%) | 213 (85.9)202 (81.5)85 (34.3) | 198 (88.0)186 (82.7)71 (31.6) | *2.1 (-8.6-4.4)* *-1.2 (-8.6-6.1)* *2.7 (-6.2-11.6)*  |  | 87 (82.9)85 (81.0)46 (43.8) |
| **PRE-DELIRIC score >30 (N=611)**Survival in 28-days, n (%)Survival in 90-days, n (%)Delirium incidence, n (%) | 177 (70.0)160 (63.2)114 (45.1) | 154 (67.0)143 (62.2)113 (49.1) | *2.9 (-5.8-11.6)* *1.0 (-8.1-9.9)* *-4.0 (-13.2-5.5)* |  | 91 (71.1)83 (64.8)67 (52.3) |
| **Duration of preventive treatment ≤2 days (N=967)**Survival in 28-days, n (%)Survival in 90-days, n (%)Delirium incidence, n (%) | 333 (85.6)315 (81.0)121 (31.1) | 320 (82.5)303 (78.1)130 (33.5) | *3.1 (-2.2-8.5)* *2.9 (-3.0-8.8)* *-2.4 (-9.2-4.4)*  | *Prevention 2days group* *28-days: 0.43* *90-days: 0.39**Delirium incidence: 0.61* | 162 (85.3)157 (82.6)68 (35.8) |
| **Duration of preventive treatment >2 days (N=822)**Survival in 28-days, n (%)Survival in 90-days, n (%)Delirium incidence, n (%) | 277 (80.8)264 (77.0)123 (35.9) | 265 (83.1)253 (79.3)103 (32.3) | *-2.3 (-8.5-3.8)* *-2.3 (-8.9-4.3)* *3.6 (-3.9-11.1)*  |  | 124 (77.5)118 (73.8)71 (44.4) |
| **Duration of preventive treatment ≤3 days (N=1,176)**Survival in 28-days, n (%)Survival in 90-days, n (%)Delirium incidence, n (%) | 412 (86.4)394 (82.6)151 (31.7) | 396 (83.5)376 (79.3)147 (31.0) | *2.8 (-1.9-7.6)* *3.3 (-1.9-8.5)* *0.6 (-5.5-6.7* | *Prevention 3 days group**28-days: 0.27* *90-days: 0.21**Delirium incidence: 0.62* | 192 (85.3)187 (83.1)80 (35.6) |
| **Duration of preventive treatment >3 days (N=613)**Survival in 28-days, n (%)Survival in 90-days, n (%)Delirium incidence, n (%) | 198 (77.6)185 (72.5)93 (36.5) | 189 (81.1)180 (77.3)86 (36.9) | *-3.5 (-11.0-4.1)* *-4.7 (-12.8-3.4)* *-0.4 (-9.4-8.5)*  |  | 94 (75.2)88 (70.4)59 (47.2) |
| **Duration of preventive treatment ≤5 days (N=1,431)**Survival in 28-days, n (%)Survival in 90-days, n (%)Delirium incidence, n (%) | 495 (85.2)470 (80.9)187 (32.2) | 483 (83.6)461 (79.8)184 (31.8) | *1.6 (-2.7-6.0)* *1.1 (-3.6-5.9)* *0.4 (-5.2-5.9)*  | *Prevention 3 days group* *28-days: 0.50**90-days: 0.67* *Delirium incidence: 0.64* | 225 (82.7)220 (80.9)104 (38.2) |
| **Duration of preventive treatment >5 days (N=358)**Survival in 28-days, n (%)Survival in 90-days, n (%)Delirium incidence, n (%) | 115 (76.2)109 (72.2)57 (37.7) | 102 (79.1)95 (73.6)49 (38.0) | *-2.9 (-13.4-7.6)* *-1.5 (-12.6-9.7)* *-0.2 (-11.9-11.4)*  |  | 61 (78.2)55 (70.5)35 (44.9) |
| **Non-delirium patients (N=1,173)**Survival in 28-days, n (%)Survival in 90-days, n (%) | 407 (83.4)389 (79.7) | 396 (83.5)377 (79.5) | *-0.1 (-5.0-4.7)**0.2 (-5.1-5.4)* | *Non-delirium group**28-days: 0.91**90-days: 0.98* | 175 (82.9)172 (81.5) |
| Number of delirium-coma-free days in 28-days, median [IQR] | 27 (25-28) | 28 (26-28) | *0.0 (0 to 0)\*\** | *Delirium incidence: n.a.* | 27 (26-28) |
| **Delirium patients (N=616)**Survival in 28-days, n (%)Survival in 90-days, n (%) | 203 (83.2)190 (77.9) | 189 (81.1)179 (76.8) | *2.1 (-5.2-9.4)**1.0 (-6.9-9.0)* | *Delirium group**28-days: 0.55**90-days: 0.75* | 111 (79.9)103 (74.1) |
| Number of delirium-coma-free days in 28-days, median [IQR] | 20 (13-24) | 21 (13-25) | *0 (-19.9-9.9)\*\** | *Delirium incidence: n.a.* | 20 (8-24) |

\*\* Differences between medians are described as absolute difference in ranking following order

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