Preventing Postoperative Delirium After Major Noncardiac Thoracic Surgery—A Randomized Clinical Trial

Babar A. Khan, MD, MS[*,†,‡,§], **Anthony J. Perkins, MS**[¶], **Noll L. Campbell, PharmD**[†,‡,§,∥,**], **Sujuan Gao, PhD**[¶], **Sikandar H. Khan, DO**[*], **Sophia Wang, MD**[††], **Mikita Fuchita, MD**[*], **Daniel J. Weber, MD**[‡‡], **Ben L. Zarzaur, MD, MPH**[§§], **Malaz A. Boustani, MD, MPH**[*,†,‡,§], **Kenneth Kesler, MD**[§§]

[*] Department of Medicine, School of Medicine, Indiana University, Indianapolis, Indiana

[†] Department of Medicine, Center for Aging Research, Indiana University, Indianapolis, Indiana

[‡] Department of Medicine, Regenstrief Institute, Inc., Indianapolis, Indiana

[§] Department of Medicine, Center for Health Innovation and Implementation Science, Indiana Clinical and Translational Sciences Institute, Indiana University, Indianapolis, Indiana

[¶] Department of Statistics, School of Medicine, Indiana University, Indianapolis, Indiana

[∥] Eskenazi Health, Indianapolis, Indiana

[**] Department of Pharmacy Practice, College of Pharmacy, Purdue University, West Lafayette, Indiana

[††] Department of Psychiatry, School of Medicine, Indiana University, Indianapolis, Indiana

[‡‡] Department of Surgery, University of California, San Francisco, San Francisco, California

[§§] Department of Surgery, School of Medicine, Indiana University, Indianapolis, Indiana

Abstract

OBJECTIVES: To assess the efficacy of haloperidol in reducing postoperative delirium in individuals undergoing thoracic surgery.

DESIGN: Randomized double-blind placebo-controlled trial.

SETTING: Surgical intensive care unit (ICU) of tertiary care center.

PARTICIPANTS: Individuals undergoing thoracic surgery (N=135).

INTERVENTION: Low-dose intravenous haloperidol (0.5 mg three times daily for a total of 11 doses) administered postoperatively.

MEASUREMENTS: The primary outcome was delirium incidence during hospitalization. Secondary outcomes were time to delirium, delirium duration, delirium severity, and ICU and hospital length of stay. Delirium was assessed using the Confusion Assessment Method for the ICU and delirium severity using the Delirium Rating Scale-Revised.

RESULTS: Sixty-eight participants were randomized to receive haloperidol and 67 placebo. No significant differences were observed between those receiving haloperidol and those receiving placebo in incident delirium (n=15 (22.1%) vs n=19 (28.4%); p = .43), time to delirium (p = .43), delirium duration (median 1 day, interquartile range (IQR) 1–2 days vs median 1 day, IQR 1–2 days; p = .71), delirium severity, ICU length of stay (median 2.2 days, IQR 1–3.3 days vs median 2.3 days, IQR 1–4 days; p = .29), or hospital length of stay (median 10 days, IQR 8–11.5 days vs median 10 days, IQR 8–12 days; p = .41). In the esophagectomy subgroup (n = 84), the haloperidol group was less likely to experience incident delirium (n=10 (23.8%) vs n=17 (40.5%); p = .16). There were no differences in time to delirium (p = .14), delirium duration (median 1 day, IQR 1–2 days vs median 1 day, IQR 1–2 days; p = .71), delirium severity, or hospital length of stay (median 11 days, IQR 10–12 days vs median days 11, IQR 10–15 days; p = .26). ICU length of stay was significantly shorter in the haloperidol group (median 2.8 days, IQR 1.1–3.8 days vs median 3.1 days, IQR 2.1–5.1 days; p = .03). Safety events were comparable between the groups.

CONCLUSION: Low-dose postoperative haloperidol did not reduce delirium in individuals undergoing thoracic surgery but may be efficacious in those undergoing esophagectomy.

Keywords

delirium; esophagectomy; ICU; haloperidol; cognition

Delirium is a syndrome of disturbance of attention and awareness that develops quickly and fluctuates over the course of the day.[1] Individuals with delirium are vulnerable to hospital-acquired complications, leading to prolonged intensive care unit (ICU) and hospital stays, new institutionalization, higher healthcare costs, and greater mortality.[2–5] Postoperative delirium is also associated with long-term cognitive decline and dementia.[5,6]

Incidence of postoperative delirium ranges from 15% to 80%.[7–13] For noncardiac thoracic surgery, incidence of delirium could be as high as 50% in individuals undergoing esophagectomies.[14] Current theoretical models of delirium pathophysiology posit that a complex interaction between underlying vulnerabilities such as age and preexisting cognitive impairment coupled with an extensive external stressor such as esophagectomy predisposes to delirium.[15] As a response to surgery, peripheral macrophages produce pro-inflammatory cytokines such as interleukin (IL)-1 and tumor necrosis factor-alpha (TNF-α),[16,17] leading to blood–brain barrier disruption with infiltration of leukocytes into the central nervous system.[18–20] The resultant microglial activation produces local cytokines (TNF-α, IL-1 β) and reactive oxygen species and promotes cholinergic failure and dopaminergic excess.[21,22]

Haloperidol is a typical antipsychotic that acts primarily by blocking dopamine receptors.[23,24] Haloperidol also inhibits production of pro-inflammatory cytokines IL-1

and TNF-α,[25] and increases levels of the IL-1 receptor antagonist (IL-1RA), an anti-inflammatory cytokine.[26] Haloperidol has been shown to reduce delirium burden in individuals undergoing abdominal surgery[27] and those who have had a hip facture,[28] but its role in reducing delirium in individuals undergoing thoracic surgery is unclear. Using the theoretical pathophysiological framework, we designed this randomized trial to assess the feasibility and efficacy of haloperidol prophylaxis in reducing delirium after major thoracic surgery, specifically esophagectomy.

MATERIALS AND METHODS

Study Design

The Indiana University institutional review board approved this randomized double-blind placebo-controlled single-center trial.

Study Setting

The trial was conducted at Indiana University Hospital Simon Cancer Center in Indianapolis, a 257-bed tertiary care center staffed by Indiana University School of Medicine faculty with a referral base from Indiana and neighboring states. Four surgeons from the thoracic surgery department participated in the study.

Enrollment, Eligibility, and Randomization

English-speaking individuals aged 18 and older undergoing thoracic surgery were included. Exclusion criteria were a history of schizophrenia, Parkinson's disease, severe dementia, alcohol abuse, neuroleptic malignant syndrome, haloperidol allergy, pregnancy, breast feeding, taking cholinesterase inhibitors or levodopa, or a corrected QT interval longer than 500 ms at the time of randomization. Eligible individuals were approached for informed consent before their surgery in the preoperative clinic.

Individuals who provided consent were randomized in a 1:1 ratio to haloperidol or placebo using a computer-generated randomization scheme (permuted block sizes of 6 and 8) stratified according to type of surgery (esophagectomy, pneumonectomy, other thoracic surgery). The investigational pharmacy executed the randomization scheme.

Study Procedures and Drug Administration

Participants underwent a thorough preoperative evaluation including neuropsychological testing. Those admitted for surgery received an order for blinded study drug, and the investigational pharmacist referred to the randomization list for treatment assignment. Apart from the investigational pharmacists, all study personnel, participants, and clinicians were blinded to each participant's treatment assignment.

Randomized participants underwent electrocardiography to confirm that their corrected QT interval was less than 500 ms. The first dose of the study drug was administered immediately postoperatively, followed by a 3-times-daily schedule, for a total of 11 doses. Haloperidol dose was 0.5 mg administered intravenously by bolus injection over 3 minutes. Placebo was identical in route, appearance, and volume.

A delirium rescue protocol was implemented to manage pain, agitation, and delirium in participants. The protocol focused on pain control using fentanyl, morphine, or hydromorphone and sedation and management of agitation using propofol in mechanically ventilated participants and dexmedetomidine in nonmechanically ventilated participants. Participants received a nonpharmacological delirium protocol including reorientation, eyeglasses and hearing aids, and sleep preservation through noise reduction, minimizing sleep interruptions, and illumination during daytime. Open-label antipsychotics were discouraged during the intervention phase, but the primary services were not otherwise restricted in their prescribing of haloperidol or other antipsychotics. An independent data safety monitoring board oversaw trial implementation.

Outcome Measures

The primary outcome measure was incidence of delirium during hospitalization. Secondary outcomes were time to delirium, delirium duration and severity, cognitive scores after surgery, and ICU and hospital lengths of stay. Trained, blinded research assistants collected all data.

Delirium Incidence and Duration—We used the Confusion Assessment Method for the ICU (CAM-ICU) to detect delirium.[29] Because delirium is a fluctuating disorder, research assistants conducted 2 delirium assessments each day, one in the morning (9:00–11:00 am) and one in the afternoon (3:00–5:00 pm), to maximize delirium identification. Delirium duration was defined as total number of days a participant was CAM-ICU-positive on the morning or afternoon assessment during their entire hospital stay. The Richmond Agitation Sedation Scale (RASS)[30] was used to assess eligibility for delirium assessment. Participants with a RASS score of −4 or −5 with lack of response to verbal or physical stimuli were characterized as comatose and were not eligible for CAM-ICU assessments. Participants with a RASS score of −3 to +4 were considered eligible to be assessed using the CAM-ICU.[30]

Delirium Severity—The Delirium Rating Scale—Revised (DRS-R-98)[31] was administered daily to measure delirium severity. The DRS-R-98 captures impairments in attention; short- and long-term memory; visuospatial ability and orientation; perceptual and sleep–wake cycle disturbances; abnormalities of language, thought process, and content; motor agitation or retardation; and mood lability.[31] It is a 16-item scale, with the severity scale having 13 items (rated 0–3 each, maximum 39 points) and higher scores indicating greater delirium severity.

Cognitive Impairment—The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[32] was used to assess for cognitive impairment. The RBANS is a validated scale that yields scores for 5 cognitive domains (immediate memory, visuospatial construction, language, attention, delayed memory).[32] It was administered during the preoperative assessment and at postsurgery clinic follow-up.

ICU and Hospital Lengths of Stay—Electronic medical records were reviewed to determine ICU and hospital lengths of stay.

Other Data Collection

Information was collected on participant demographic characteristics, chronic comorbidities using the Charlson Comorbidity Index,[33] severity of illness using the Acute Physiology and Chronic Health Evaluation (APACHE) II,[34] depression using the Patient Health Questionnaire,[35] anxiety using the 7-item Generalized Anxiety Disorder Scale,[36] posttraumatic stress disorder symptoms using the Post Traumatic Stress Symptoms scale,[37] activities of daily living using the Katz scale,[38] and instrumental activities of daily living using the Lawton scales.[39] Information was also collected on daily sedative and analgesic exposure, duration of mechanical ventilation, and intraoperative data. Supplementary Table S1 describes the timing of data collection.

Drug-Related Adverse Events

Adverse effects related to haloperidol use, including QT prolongation and extrapyramidal symptoms, were monitored and reported to the data safety monitoring board.

Statistical Analysis

We assessed whether the proportion of participants developing delirium differed between the 2 groups using the Fisher exact test. To assess differences in the number of days in a coma or with delirium at discharge, we used a Poisson regression model that included an offset equal to the log (length of stay after randomization) to account for different lengths of stay between participants. Poisson regression was used to test for group differences in time in the ICU and on mechanical ventilation. Because there were no in-hospital deaths, Kaplan–Meier survival estimates were used to compare length of stay and differences in time to delirium. Time to delirium was calculated as days from the day of surgery until the first CAM-ICU positive result in patients with delirium. In delirium-negative participants, event time was censored at the day of last CAM-ICU screening. We used a mixed model to test whether delirium severity course differed over time. This model included all DRS-R-98 assessment days, a random effect for participant, and fixed effect for day and the interaction between day and randomization group. All other differences between groups were assessed using the Fisher exact test for categorical outcomes and the Wilcoxon rank sum test for continuous measures because the majority of these measures contained skewed data. Power analysis showed that a sample size of 53 individuals undergoing esophagectomy per group would achieve 80% power to detect a reduction of delirium incidence from 50% to 25% using a 1-tailed test at 5% significance. A power analysis for all thoracic surgeries was not performed because the study was designed a priori to answer the question in individuals undergoing esophagectomy. No interim analyses were planned, and there were no prespecified stopping guidelines. All analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Of 269 individuals undergoing major thoracic surgery screened from October 2013 to June 2015, 135 were enrolled in the trial. Sixty-eight were randomly assigned to haloperidol and 67 to placebo (Figure 1). Individuals undergoing esophagectomy constituted the largest group (n = 84), with 42 assigned to haloperidol and 42 to placebo (Supplementary

Figure S1). There were no differences in baseline participant characteristics between the haloperidol and placebo groups (Table 1) or in the intraoperative and postoperative factors except that more individuals undergoing esophagectomy in the placebo group received propofol (Table 2, Supplementary Tables S2 and S3).

Primary Outcomes

There was no difference in delirium incidence between the haloperidol (22.1%, 15/68) and placebo (28.4%, 19/67) groups (p = .43) (Table 3).

Secondary Outcomes

There were no differences in time to delirium (p = .43) (Figure 2) or median number of delirium days in participants with delirium (haloperidol: median 1 day, interquartile range (IQR) 1–2 days; placebo: 1 day, IQR 1–2 days; p = .71). There was a similar magnitude of reduction in delirium severity scores over time in both groups (Supplementary Figure S2).

There were no differences in ICU (haloperidol: median 2.2 days, IQR 1–3.3 days; placebo: median 2.3 days, IQR 1–4 days; p = .29) or hospital (haloperidol: median 10 days, IQR 8–11.5 days; placebo: median 10 days, IQR 8–12 days; p = .40) length of stay (Table 3, Supplementary Figure S3). When the analysis was limited to participants with delirium, the haloperidol group had a shorter hospital stay (median 10 days, IQR 8–14 days vs median 11 days, IQR 11–16 days; p = .03) (Supplementary Figure S4).

A small subset of participants underwent pre- and post-operative RBANS cognitive assessments (haloperidol, n = 17; placebo, n = 16). Postoperatively, the RBANS percentile change scores improved in the placebo group (haloperidol: median 6, IQR 0–23; placebo: median −9.25, IQR −17.5–0; p = .008).

Esophagectomy Subgroup

Primary Outcome—Delirium incidence was lower in the haloperidol (23.8%, 10/42) than the placebo (40.5%, 17/42) group, but the difference was not statistically significant (p = .16) (Table 3).

Secondary Outcomes—There was no difference in time to delirium between the groups (p = .14) (Figure 2) and no difference in number of days with delirium in participants with delirium (haloperidol: median 1 day, IQR 1–2 days, placebo median 1 day, IQR 1–2 days; p = .70). Delirium severity reduction was similar in both groups (Supplementary Figure S5).

ICU stay was significantly shorter in the haloperidol (median 2.8 days, IQR 1.1–3.8 days) than the placebo (median 3.1 days, IQR 2.1–5.1 days) group (p = .03) (Table 3). No differences were found in hospital length of stay (haloperidol: median 11 days, IQR 10–12 days; placebo: median 11 days, IQR 10–15 days; p = .25) (Table 3). When the analysis was limited to participants with delirium, the haloperidol group had a trend toward significantly fewer hospital days (haloperidol: median 11 days, IQR 10–14 days; placebo: median 12 days, IQR 11–16 days; p = .06] (Supplementary Figure S6).

A small subset of participants underwent pre- and post-operative RBANS cognitive assessments (haloperidol, n = 9; placebo, n = 9). Postoperatively, RBANS percentile change scores improved in the placebo group (haloperidol: median 13, IQR 0–24; placebo: median –2, IQR –18–0; p = .05).

Esophagectomy Versus Other Thoracic Surgeries

Individuals undergoing esophagectomy were slightly older (median 62, IQR 53–69 vs median 61 IQR 45–67; p = .16), were more likely to undergo preoperative chemotherapy (75.3% vs 30.0%, p <.001), had greater severity of illness (APACHE 11 score: median 17, IQR 13.5–24.5 vs median 14, IQR 11–20; p = .008), had longer surgeries (median 4.9 hours, IQR 4.1–5.4 hours vs median 2.1 hours, IQR 1.4–3 hours; p <.001), and received a higher intraoperative volume (median 3,000, IQR 2,500–3,775 mL vs median 1,400, IQR 1,000–2,000 mL; p <.001) and more benzodiazepines (diazepam equivalents: median 20 mg, IQR 11.3–62.5 mg vs median 12.5, IQR 5–22.5 mg; p = .003) than those undergoing other thoracic surgeries.

Individuals undergoing esophagectomy had higher delirium incidence (32.1%, 27/84), than those undergoing other thoracic surgeries (13.7%, 7/51) (p = .02), longer duration of mechanical ventilation (median 1 day, IQR 0.4–1.2 days vs median 0.2 days, IQR 0.1–0.8 days; p = .01), and longer ICU (median 2.9 days, IQR 2–4 days vs median 1.1 days, IQR 0–2.2 days; p < .001) and hospital (median 11 days, IQR 10–13 days vs median 7 days, IQR 5–8 days; p < .001) stays and were less likely to be discharged home (84.5% vs 96.1%, p = .048).

Safety

There were no differences in adverse events between the groups (Supplementary Tables S4–S6).

DISCUSSION

Our results demonstrate the feasibility of conducting a randomized, placebo-controlled clinical trial in individuals undergoing major thoracic surgery. The low-dose postoperative haloperidol intervention did not reduce delirium incidence, duration, or severity in the overall population, although prespecified esophagectomy subgroup experienced modest benefits; the haloperidol intervention reduced the incidence of delirium by 17% and reduced ICU length of stay. Similar to the overall group, hospital length of stay was shorter, although not statistically significant, in the esophagectomy subgroup when the analysis was limited to participants with delirium.

Our study results had similarities to and differences from those of other delirium prevention studies in the surgical literature[27,28]. One study[27] showed a decrease in delirium incidence, delirium duration, and ICU length of stay with haloperidol prophylaxis in elderly individuals —predominantly individuals undergoing abdominal surgery. The other study[28] did not show a reduction in delirium incidence in elderly individuals undergoing hip surgery, but prophylaxis reduced delirium duration, severity, and hospital length of stay in individuals with delirium. Both studies used low-dose haloperidol (1.2 mg/d for 3 days,[28] 1.7-mg 1-time

postoperative infusion[27]). We used a similar low-dose strategy based on the evidence from the aforementioned studies and prior work from our group[40] demonstrating that low-dose haloperidol conferred efficacy similar to that of higher haloperidol doses with less risk of extrapyramidal symptoms. Our results were similar to those of the Hope-ICU[41] and (REDUCE) trials.[42] Both compared haloperidol with placebo in traditional medical and surgical ICU populations and used delirium- and coma-free days as one of the outcomes. They tested a slightly higher dose of haloperidol (Hope-ICU: 2.4 mg every 8 hours, REDUCE: 2 mg 3 times daily) than the 0.5 mg 3 times daily that we used. No differences in delirium- or coma-free days were observed in either trial between the intervention and placebo groups. REDUCE also evaluated the effect of haloperidol on delirium incidence and did not find any difference between the intervention and placebo groups. The incidence rate was 33% in both groups. Our low-dose haloperidol approach could not reduce delirium incidence either, but we were able to reduce the length of ICU stay in individuals undergoing esophagectomy, in contrast to the Hope-ICU and REDUCE studies. Because there were no differences in delirium duration between the intervention and control groups, the reduction in the ICU length of stay could not be attributed to shorter delirium duration. Other factors, although statistically nonsignificant, such as high benzodiazepine use in the placebo group and ondansetron in the intervention group, may have contributed to these results. A potential protective effect of haloperidol that could have been mediated through its antiinflammatory and immunomodulatory properties could not be discounted[25]; especially in individuals undergoing esophagectomy, who may have a higher cytokine burden.

The esophagectomy subgroup differed from participants undergoing other thoracic surgeries in multiple aspects. Individuals undergoing esophagectomy had higher APACHE II scores and poorer function at baseline. Surgery was twice as long in the esophagectomy group (mean 5 hours), and participants undergoing esophagectomy had twice the blood loss during surgery and received higher doses of opioids and benzodiazepines intraoperatively. The high risk profile explains the higher delirium incidence of 32.1% in esophagectomy subgroup than the 13.7% in other thoracic surgeries. In addition, the duration of ICU stay was twice as long in the esophagectomy subgroup. These differences suggest a targeted strategy of low-dose haloperidol for the high-risk esophagectomy subgroup and do not justify use of prophylaxis in all individuals undergoing thoracic surgery, especially uncomplicated cases with short ICU stays. The mechanisms for a potential therapeutic benefit are unclear, but the extent of surgery combined with the severity of illness predisposing to high cytokine levels might respond better to the antiinflammatory properties of haloperidol. Larger studies with serial biomarkers focusing on high-risk subgroups such as individuals undergoing esophagectomy could elucidate the efficacy of haloperidol prophylaxis and underlying pathogenic mechanisms.

One of the main lessons we learned from our pilot investigation is the inherent difficulty in conducting longitudinal postsurgical follow-up. We could not achieve adequate postdischarge follow-up to collect the neurocognitive outcomes. Hence, improvements in cognitive scores in the placebo group could represent a lack of regression of the scores to the mean given the small sample size. Many of our participants were referred from out of the hospital system and did not return for follow-up and in-person cognition assessments. In designing future studies, researchers should consider allocating extra resources for study

personnel travel to conduct these assessments at homes of trial participants. With the increasing availability of Internet-connected telephones, better options could be to use Telehealth for cognitive assessments (Skype, Zoom, Face Time) or conduct assessments that could be performed over the telephone.

Our study had several limitations. We had a small sample size for a prevention study. We were unable to achieve the target of 106 esophagectomies as specified in our power calculation because of the limited resources afforded to us through a small local grant. We observed lower delirium incidence rate in the low dose haloperidol group (23.8%) compared to delirium incidence in the placebo group (40.5%) in esophagectomy patients. We estimate that a larger study with 266 total participants would have 80% power to detect the effect size observed in our study. It was a single-site study with results shaped by local practice patterns, which may not be replicable at other institutions. The CAM-ICU was used throughout hospitalization, which may have resulted in missing cases of delirium outside the ICU.

Our study had several strengths. We used a double-blind placebo-controlled design with validated data assessment tools. Trained research staff monitored for delirium twice daily. Information on all relevant baseline, intraoperative, and postoperative variables was collected, including baseline cognitive and psychological assessments, information not routinely collected. We achieved high fidelity to our intervention, with a mean of 10 administered postoperative doses. Inclusion of a prespecified esophagectomy subgroup provides relevant contrast and comparison with individuals undergoing other types of thoracic surgery, which could allow development of surgery-specific approaches.

In conclusion, use of low-dose haloperidol postoperatively does not reduce delirium incidence, duration, or severity in individuals undergoing major thoracic surgery. Low-dose haloperidol prophylaxis may be efficacious in reducing delirium incidence in individuals undergoing esophagectomy, but this finding needs to be confirmed in a multiinstitutional randomized trial with adequate sample size.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

Conflict of Interest:

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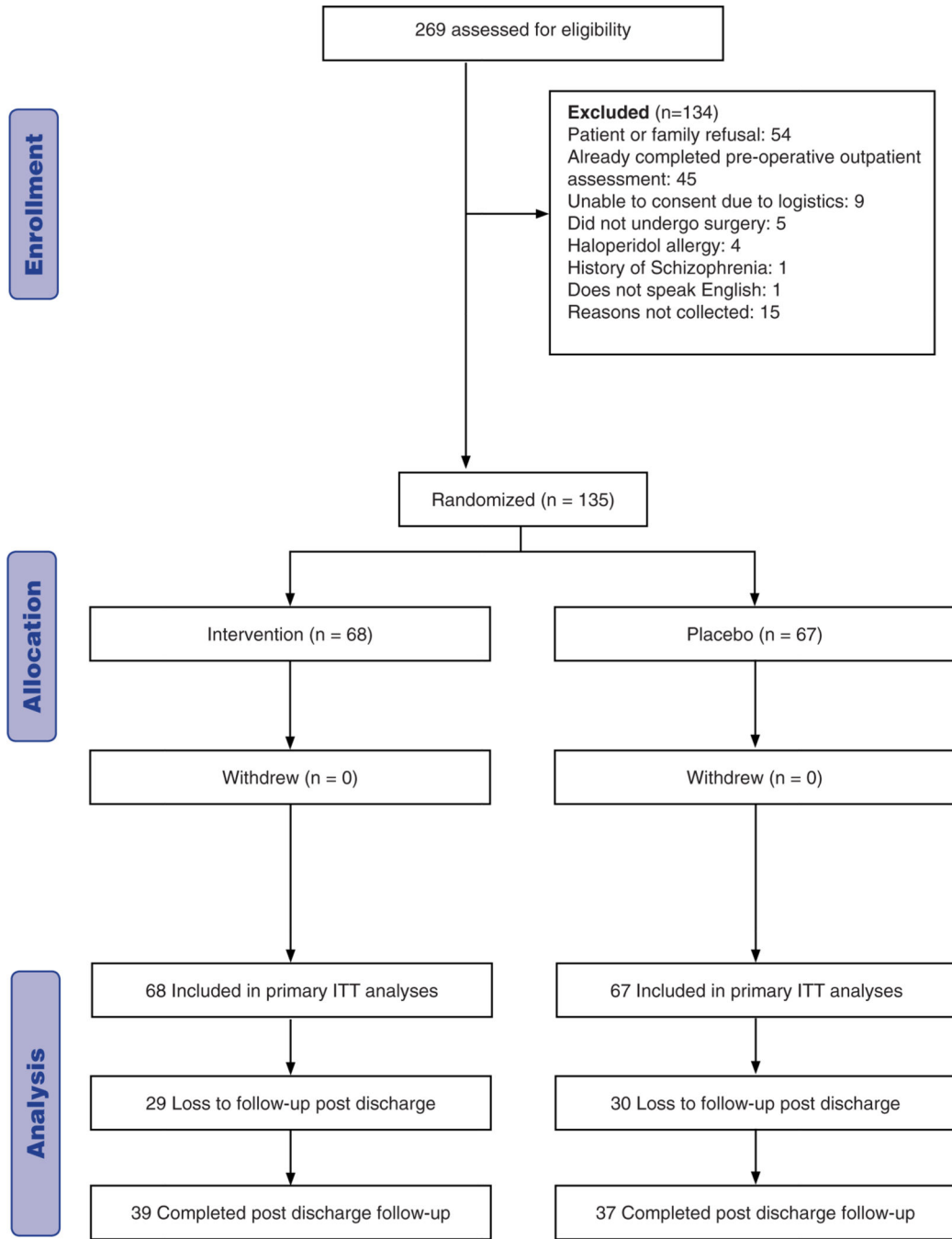
Figure 1.
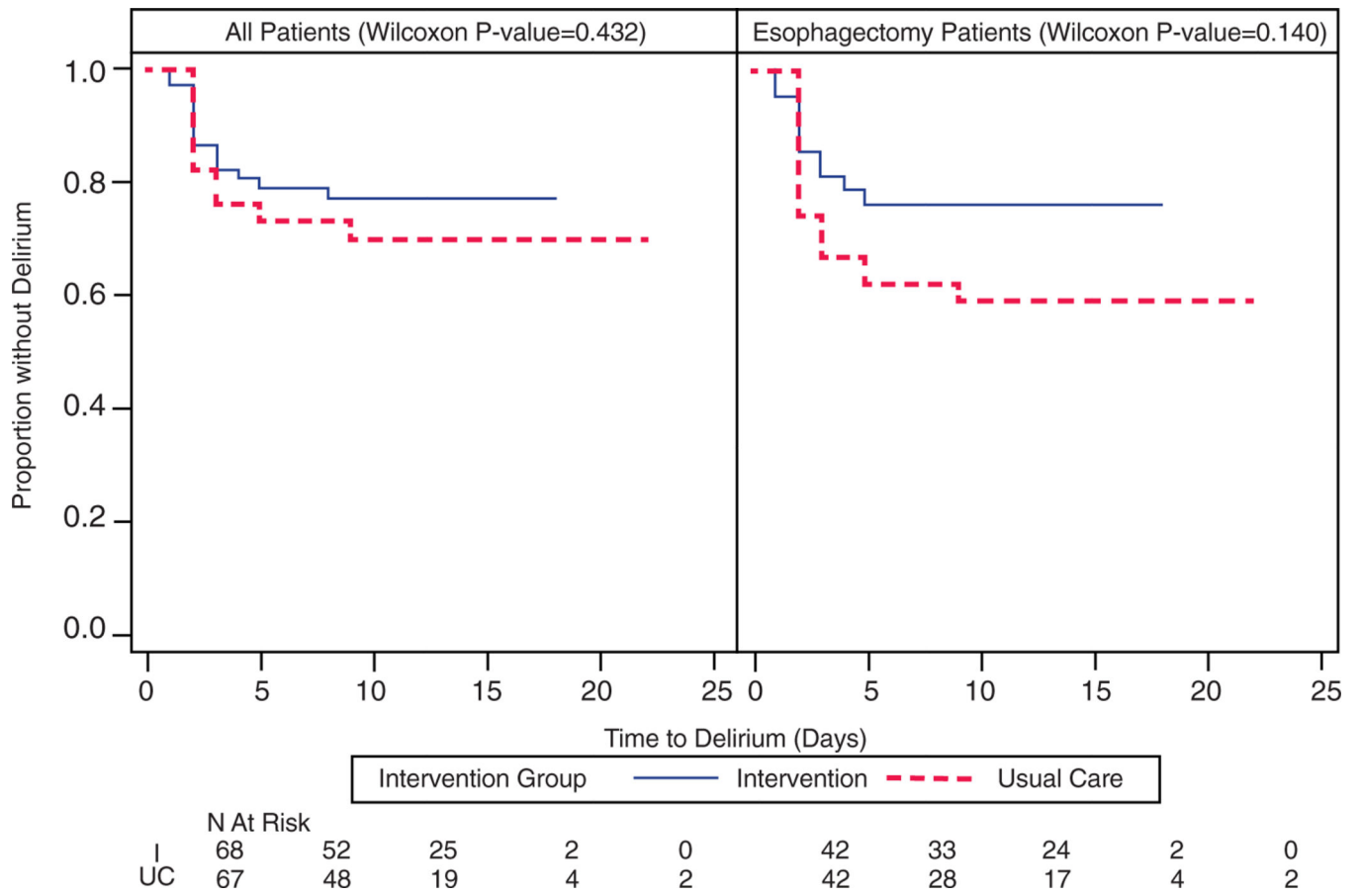Flow of participants through study.

Figure 2.
Time to delirium in all participants undergoing thoracic surgery and the subgroup undergoing esophagectomy.

Table 1.

Baseline Characteristics of All Participants Undergoing Thoracic Surgery and the Subgroup Undergoing Esophagectomy

Characteristic	Overall, N = 135		Esophagectomy, n = 84	
	Haloperidol, n= 68	Placebo, n = 67	Haloperidol, n= 42	Placebo, n= 42
Age, median (IQR)	60 (51.8–68)	62.3 (52.6–69.2)	61.0 (52.1–67.9)	64 (57.2–70.5)
African American, n (%)	2 (3.0)	3 (4.5)	0 (0.0)	3 (7.1)
Female, n (%)	22 (32.4)	13 (19.4)	12 (28.6)	6 (14.3)
Education				
High school graduate, n (%)	36 (55.4)	32 (51.6)	24 (60.0)	21 (55.3)
Some college, n (%)	16 (24.6)	22 (35.5)	8 (20.0)	12 (31.6)
Bachelor's degree or more, n (%)	13 (20.0)	8 (12.9)	8 (20.0)	5 (13.2)
Preoperative chemotherapy, n (%)	33 (50.8)	40 (64.5)	27 (69.2)	31 (81.6)
Acute Physiology and Chronic Health Evaluation II score, median (IQR)	16 (13–24)	17 (11–24)	16.5 (13–24)	18 (14–25)
Charlson Comorbidity Index, median (IQR)	2 (2–3)	3 (2–4)	2 (2–3)	3 (2–4)
Activity of daily living score, median (IQR)	6 (6–6)	6 (6–6)	6 (6–6)	6 (6–6)
Instrumental activity of daily living score, median (IQR)	8 (7–8)	8 (7–8)	8 (7–8)	8 (7–8)
Preoperative RBANS score, median (IQR)	88.5 (78.5–101)	90 (84.5–98)	95 (76–102)	90 (87–100)
Preoperative RBANS percentile, median (IQR)	22 (8–52.5)	25 (15–45)	37 (7–55)	25 (19–50)
Preoperative Patient Health Questionnaire score, median (IQR)	3.7 (1–7)	2 (1–5)	4 (1–7)	3 (1–5)
Preoperative 7-item Generalized Anxiety Disorder Scale score, median (IQR)	2 (0–6)	2 (0–5)	3 (0–6)	1.5 (0–5)
Preoperative Post-Traumatic Symptom Scale score, median (IQR)	16.5 (12–22)	14 (11–20)	16.5 (12–22)	13 (11–20)
Body mass index, kg/m^2, median (IQR)	27.7 (23.7–32.2)	29.1 (25.1–32.1)	25 (22.6–31.5)	28.5 (24.4–32)
Type of surgery				
Esophagectomy, n (%)	42 (61.8)	42 (62.7)		
Ivor Lewis, n	32	39		
Other, n	10	3		
Left pneumonectomy, n (%)	1 (1.5)	2 (3.0)		
Thoracotomy, n (%)	25 (36.8)	23 (34.3)		
Lobectomy or bilobectomy with mediastinal dissection, n	11	10		
Lobectomy or bilobectomy, n	6	1		
Mediastinal dissection, n	2	7		

Characteristic	Overall, N = 135		Esophagectomy, n = 84	
	Haloperidol, n= 68	Placebo, n = 67	Haloperidol, n= 42	Placebo, n= 42
Other, n	6	5		
American Society of Anesthesiologists class, n (%)				
I	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
II	3 (4.4)	0 (0.0)	1 (2.4)	0 (0.0)
III	65 (95.6)	66 (98.5)	41 (97.6)	42 (100.0)
IV	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)

IQR=interquartile range; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status.

Table 2.

Intra- and Postoperative Data of All Participants Undergoing Thoracic Surgery and the Subgroup Undergoing Esophagectomy

Variable	Haloperidol	Placebo	P-Value
All thoracic surgeries, n (N = 135)	68	67	
Intraoperative data, median (IQR)			
Duration of surgery, hours	4.1 (2.3–5.0)	4.0 (2.6–5.1)	.91
Duration of anesthesia, hours	5.7 (4.0–6.4)	5.4 (3.8–6.7)	.99
Estimated blood loss, mL	150 (100–300)	150 (100–300)	.71
Volume infused intraoperatively, mL, median (IQR)			
Total	2,507 (1,400–3,500)	2,500 (1,500–3,100)	.67
Crystalloid	2,050 (1,350–3,000)	2,000 (1,410–2,500)	.51
Colloid	500 (0–500)	500 (0–850)	.50
Postoperative transfusion, n (%)	3 (4.4)	4 (6.0)	.72
Esophagectomies, n (n = 84)	42	42	
Intraoperative data, median (IQR)			
Duration of surgery, hours	5.0 (4.2–5.2)	4.7 (4.1–5.6)	.70
Duration of anesthesia, hours	6.3 (5.7–6.8)	6.4 (5.5–7.1)	.93
Estimated blood loss, mL	200 (100–300)	300 (100–300)	.48
Volume infused intraoperatively, mL, median (IQR)			
Total	3,225 (2,514–3,800)	3,000 (2,500–3,500)	.30
Crystalloid	2,550 (2,100–3,300)	2,200 (1,900–3,000)	.10
Colloid	500 (250–750)	500 (500–1,000)	.11
Postoperative transfusion, n (%)	2 (4.8)	3 (7.1)	>.99

IQR = interquartile range.

Table 3.

Outcomes of All Participants Undergoing Thoracic Surgery and the Subgroup Undergoing Esophagectomy

Outcome	Haldol	Placebo	P-Value
All participants, n (N = 135)	68	67	
Delirium incidence, n (%)	15 (22.1)	19 (28.4)	.43
Delirium or coma duration, days, median (IQR)	1 (0–2)	1 (0–2)	.94
Delirium duration, days, median (IQR)[1]	1 (1–2)	1 (1–2)	.71
Delirium or coma duration, days, median (IQR)[1]	2 (2–3)	2 (2–4)	.14
Length of mechanical ventilation, days, median (IQR)	0.8 (0.2–1.1)	1.0 (0.2–1.1)	.67
ICU length of stay, days, median (IQR)	2.2 (1.0–3.3)	2.3 (1.0–4.0)	.29
Hospital length of stay, days, median (IQR)	10 (8–11.5)	10 (8–12)	.40
Discharged home, n (%)	61 (89.7)	59 (88.1)	.79
In-hospital mortality, n (%)	0 (0.0)	0 (0.0)	
Esophagectomy, n (N = 84)	42	42	
Delirium incidence, n (%)	10 (23.8)	17 (40.5)	.16
Delirium or coma duration, days, median (IQR)	1 (1–2)	1 (1–2)	.58
Delirium duration, days, median (IQR)[1]	1 (1–2)	1 (1–2)	.70
Delirium or coma duration, days, median (IQR)[1]	2 (2–3)	3 (2–4)	.36
Length of mechanical ventilation, days, median (IQR)	1.0 (0.3–2.2)	1.1 (0.9–1.2)	.46
ICU length of stay, days, median (IQR)	2.8 (1.1–3.8)	3.1 (2.1–5.1)	.03
Hospital length of stay, days, median (IQR)	11 (10–12)	11 (10–15)	.25
Discharged home, n (%)	35 (83.3)	36 (85.7)	>.99
In-hospital mortality, n (%)	0 (0.0)	0 (0.0)	

[1] In participants with delirium.

IQR=interquartile range; ICU=intensive care unit.