Early Treatment with Risperidone for Subsyndromal Delirium after On-pump Cardiac Surgery in the Elderly

A Randomized Trial

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This article has been selected for the Anesthesiology CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

ABSTRACT

Background: The aim of this randomized, parallel-arm trial was to study the effect of treating subsyndromal delirium with risperidone on the incidence of clinical delirium in elderly patients who underwent on-pump cardiac surgery.

Methods: One hundred one patients aged 65 yr or older who experienced subsyndromal delirium after on-pump cardiac surgery were randomized using a computer-generated list to receive 0.5 mg risperidone (n = 51) or placebo (n = 50) every 12 h by mouth. Patients were assessed at 8 h by a blinded observer using the Intensive Care Delirium Screening Checklist, and those scoring more than 3 were evaluated by a blinded psychiatrist to confirm delirium. Patients in either group who experienced delirium were treated according to the same algorithm. Initially, risperidone was administered and if symptoms were not controlled, haloperidol was administered. The primary outcome was the proportion of patients who experienced delirium in either group.

Results: Seven (13.7%) patients in the risperidone group experienced delirium versus 17 (34%) in the placebo group (P = 0.031). Competing-risks regression analysis showed that failure to treat subsyndromal delirium with risperidone was an independent risk factor for delirium (subhazard ratio, 3.83; 95% CI, 1.63–8.98; P = 0.002). Two (3.9%) patients in the risperidone group experienced extrapyramidal manifestations versus one (2%) in the placebo group (P = 1.0).

Conclusion: Administration of risperidone to elderly patients who experienced subsyndromal delirium after on-pump cardiac surgery was associated with significantly lower incidence of delirium.

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ITH an aging world population and constantly improving anesthetic and surgical techniques, increasingly more elderly patients are expected to undergo cardiac surgery. Among sequels that could complicate the postoperative course of cardiac surgery, delirium is one of the most commonly encountered problems. In this respect, advanced age has been identified as an independent predictor for delirium after cardiac surgery, whereas younger age and off-pump surgery were shown to be associated with a lower risk for this complication.

Delirium is characterized by mental changes that develop over hours or days and tend to exhibit circadian variation. These typically comprise altered consciousness and attention and cognitive changes, including disturbed memory, language, orientation, and perception.

There is no formal definition for a subclinical phase of delirium. However, subsyndromal delirium (SSD) has been described in clinical reports as presence of some but not all features of delirium or more definitively as a score of 1–3 on the Intensive Care Delirium Screening Checklist (ICDSC), a tool validated for use in the intensive care unit (ICU) and demonstrated to have high sensitivity and acceptable specificity for detection of delirium.

Subsyndromal delirium seems to be associated with the same risk factors as those of delirium and may herald its imminent occurrence. Although SSD was shown to be associated with longer hospital and ICU length of stay, the implications of treating SSD with pharmacologic agents have not been elucidated.

Primarily used for schizophrenic disorders, atypical, newer or second-generation antipsychotics such as risperidone increasingly are being used for the prevention and treatment of delirium. There is evidence that these agents may have some role to play in the setting of delirium complicating cardiac surgery because a single dose of risperidone administered after cardiac surgery was shown to reduce the incidence of postoperative delirium. Because the administration of risperidone to all postoperative cardiac patients entails the disadvantage of treating subjects who would never become delirious, a more pertinent approach may be to administer this form of prophylaxis to those thought to be at particular risk for delirium, such as those with SSD. However, no data exist regarding the efficacy of administering risperidone or related antipsychotics to cardiac surgical patients with subsyndromal forms of delirium.

The aim of this trial was to test the hypothesis that administration of risperidone to elderly patients who developed SSD after cardiac surgery would result in reduction of the incidence of clinical delirium. In the absence of a formal definition for SSD, the condition was identified with a score of 1–3 on the ICDSC. A secondary aim was to study the impact of initiation of risperidone therapy during the subsyndromal, as opposed to the clinical, phase of delirium on ICU and hospital length of stay, duration of delirium, and highest score on the ICDSC. Lacking a validated tool for estimation of the severity of delirium, the highest score on the ICDSC was considered as a measure for rating severity of symptoms, making use of the graded framework of this assessment tool.

Materials and Methods

This randomized, double-blind, placebo-controlled, parallel-arm study included 101 consecutive elderly patients who experienced SSD after on-pump cardiac surgery. The study was conducted at the Cardiothoracic Surgery Unit, Ain Shams University Hospitals, Cairo, Egypt, during the period from December 2007 to November 2010. The study was approved by the institutional review board (Research Ethics Committee, Faculty of Medicine, Ain Shams University), and a written informed consent was obtained from the participants. The study was independently overseen by the local institutional Data and Safety Monitoring Board. Details of the trial protocol can be obtained from the Department of Anesthesiology, Faculty of Medicine, Ain Shams University.

Patient Selection

All patients 65 yr of age or older who were scheduled for on-pump cardiac surgery during the study period were consecutively approached and screened through the cardio-surgical preoperative assessment service to participate in this study if they had no history of neuropsychiatric disorders, alcoholism, substance abuse, or intake of psychotropic medications. A psychiatrist interviewed all patients the day before surgery using the Mini Mental State Examination, an 11-question tool encompassing five aspects related to cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score obtainable with this tool is 30, whereas a score of 23 or less is indicative of cognitive impairment. The Mini Mental State Examination has been validated as a screening tool for cognitive impairment.

In addition, the psychiatrist screened the patients for depression using the 15-item Geriatric Depression Scale, a yes-or-no questionnaire that has been shown to have a high level of internal consistency, with a score of 5 or more suggesting depression. Patients with a Mini Mental State Examination score of less than 25 or a score of more than 4 on the 15-item Geriatric Depression Scale were excluded, as were those with impaired hearing or visual acuity, speech difficulty, or contraindication to risperidone or haloperidol such as Parkinson’s disease, history of neuroleptic malignant syndrome, or prolonged QTc syndrome. Patients were also excluded if they had history of cerebrovascular disease or if other noncardiac procedures (e.g., carotid endarterectomy) were planned at the same setting.

Anesthetic Technique

A standardized balanced anesthetic technique was used for all participants. Patients were premedicated with 1 mg loraz-
A standard 12-lead electrocardiogram was obtained immediately between 35 and 45 mmHg and the pH between 7.35 and 7.45. Anesthesia was maintained with 1–5 μg · kg⁻¹ · h⁻¹ fentanyl infusion and isoflurane in 100% oxygen, and neuromuscular blockade was maintained with pancuronium infusion at 0.01 mg · kg⁻¹ · h⁻¹. During cardiopulmonary bypass, anesthesia and muscle relaxation were maintained using the same protocol. At the termination of cardiopulmonary bypass, propofol infusion was substituted for isoflurane at 25–75 μg · kg⁻¹ · min⁻¹, and fentanyl and pancuronium infusions were continued until the end of the procedure. Infusion rates of propofol and fentanyl varied according to clinical judgment regarding the rates deemed necessary to maintain adequate depth of anesthesia.

**Conduct of Cardiopulmonary Bypass**

Anticoagulation was effected with 300 IU/kg heparin to achieve an activated clotting time of more than 480 s. The oxygenator was primed with crystalloid solution, and hematocrit was kept between 25% and 27%. Extracorporeal circulation was conducted under moderate hypothermic (28°–32°C) circulatory arrest using nonpulsatile flow at 2–2.4 l · min⁻¹ · m⁻² and perfusion pressure between 50 and 70 mmHg. Myocardial preservation was provided with blood-enriched cold cardioplegic solution using a blood-to-crystalloid ratio of 1:4, which was repeated every 20–25 min throughout the ischemic period. Fractional concentration of inspired oxygen was adjusted to keep arterial oxygen tension between 150 and 250 mmHg, and gas flow was adjusted to maintain arterial carbon dioxide tension between 35 and 40 mmHg without temperature correction.

**Postoperative Management**

After surgery, all patients were admitted to the cardiosurgical ICU, where a standard protocol was implemented for sedation, analgesia, and management of mechanical ventilation. Patients initially were kept on mechanical ventilation until they were stabilized and eligible for weaning from mechanical ventilation. Unless otherwise indicated, the initial ventilator setting comprised synchronized intermittent mandatory ventilation mode, tidal volume 8–10 ml/kg, ventilator rate 8–10 breaths/min, fractional concentration of inspired oxygen 1.0, positive end-expiratory pressure 2.5–5 cm H₂O, and pressure support 5–8 cm H₂O. Arterial blood gas analysis was done within 15 min after admission to the ICU, and the fractional concentration of inspired oxygen was reduced gradually to 0.4 in decrements of 0.1 every 30 min with serial checking of arterial blood gases after each decrement to maintain an arterial oxygen tension of ≥95 mmHg and/or an arterial oxygen saturation of ≥97%. The ventilator rate was adjusted to keep the arterial carbon dioxide tension between 35 and 45 mmHg and the pH between 7.35 and 7.45. A standard 12-lead electrocardiogram was obtained immediately after initial stabilization in the ICU. Unless otherwise indicated, 12-lead electrocardiography was repeated every 12 h during ICU stay and every 24 h thereafter until patients were discharged from the hospital. Serially obtained electrocardiograms were examined for abnormalities, including those of the ST segment and QTc interval.

Patients initially were sedated with propofol infusion at 25–75 μg · kg⁻¹ · min⁻¹. The infusion rate was adjusted to keep a score of 2 (i.e., responsive to touch or name) to 3 (i.e., calm and cooperative) on the Motor Activity Assessment Scale. This scale provides a score of 0–6 and has been shown to be both valid and reliable for assessment of sedation in mechanically ventilated surgical patients. The Motor Activity Assessment Scale was used to assess patients exhibiting recovery of muscle power enough to allow employment of this tool. For patients with significant neuromuscular blockade, infusion of propofol was titrated according to clinical judgment. Analgesia was provided with intravenous morphine infusion at 10 μg · kg⁻¹ · h⁻¹, 1 g intravenous paracetamol every 6 h, and 15 mg intravenous ketorolac every 6 h.

Weaning and extubation were carried out according to a standard institutional protocol. Once patients were eligible for weaning, residual neuromuscular blockade was reversed with neostigmine and glycopyrrolate, propofol infusion was discontinued, and patients were allowed to awaken. Morphine infusion was continued after extubation until patients were discharged from the ICU. Unless required to stay in the ICU, patients were transferred to the intermediate care unit after 24 h from extubation then shifted to the regular cardiosurgical ward after another 24 h. Criteria for ICU discharge were withdrawal of inotropic and/or vasopressor support, discontinuation of invasive monitoring, absence of significant arrhythmia, adequate ventilation (arterial oxygen tension more than 60 mmHg and arterial oxygen saturation more than 90% on fractional concentration of inspired oxygen less than 0.5 by facemask; arterial carbon dioxide tension less than 45 mmHg or within 5 mmHg of preoperative value in patients with chronic obstructive pulmonary disease), urine output more than 0.5 ml · kg⁻¹ · h⁻¹, and chest tube drainage less than 50 ml/h for at least 2 h.

**Screening for SSD and Randomization**

Four intensivists and three ward physicians, who were blinded to the patients’ groups, were charged with screening patients for SSD using the ICDSC. All clinicians involved in SSD screening were trained systematically by a senior instructor in using the ICDSC on postoperative cardiac surgery patients. The ICDSC provides a total score of 0–8 obtained by assessing eight items: altered level of consciousness; inattention; disorientation; hallucination, delusion or psychosis; psychomotor agitation or retardation; inappropriate speech or mood; sleep–wake cycle disturbance; and symptom fluctuation. The ICDSC has been shown to have a sensitivity of 99% and a specificity of 64% for detection of...
delirium with excellent concordance among critical care physicians and psychiatrists as well as among critical care physicians and nurses using this tool.\textsuperscript{10} Moreover, the ICDSC has good agreement, on the order of 80%, with the Confusion Assessment Method for the ICU (CAM-ICU), an assessment tool in common use.\textsuperscript{18}

Screening for SSD was started 4 h after extubation and performed regularly at the beginning of each 8-h nursing shift thereafter. Subjects who experienced SSD, as evidenced by a score of 1–3 on the ICDSC,\textsuperscript{9} were randomized in a 1:1 ratio to receive either 0.5 mg risperidone or placebo every 12 h by mouth. Randomization was carried out by a clinical pharmacist using a computer-generated random number list created with GraphPad StatMate v.1.01i software (GraphPad Software Inc., San Diego, CA) using permuted blocks of size 4.

\textbf{Interventions and Allocation Concealment}

The test drugs were prepared by the hospital’s pharmacy and were identical in appearance and odor. The drugs were dispensed in identical containers sealed and numbered according to the computer-generated random number list. Codes signifying allocated groups were typed and kept at the pharmacy in sealed envelopes. In the case of emergency, the envelopes could be accessed and broken upon the request of the attending team. Otherwise, treatment concealment was maintained until recruitment, data collection, and analysis were completed.

\textbf{Assessment for Delirium}

In the ICU, the intensivist in charge continued screening for delirium using the ICDSC at the beginning of each 8-h nursing shift until patients were discharged to the cardiosurgical ward or until the occurrence of a competing event, such as second operation, reintubation, or death. After patient discharge to the cardiosurgical ward, screening was done by the ward physician, who continued 8-h assessments until patients were discharged from the hospital or the occurrence of a competing event.

The test drugs were continued for 24 h after subsidence of SSD (consistent with a score of 0 on the ICDSC) or until a score of more than 3 on the ICDSC was obtained. Patients who scored more than 3 on the ICDSC were labeled as possibly delirious,\textsuperscript{9} and the diagnosis of delirium was confirmed by the same psychiatrist who performed the preoperative assessment. The psychiatrist who attended to patients in the 4 h after identification of the condition with the ICDSC was blinded to the patient groups and used the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for diagnosis.\textsuperscript{8} When delirium was diagnosed, the pharmacy staff were told to break the sealed envelope containing the patient’s code to identify the patient’s allocation group and dispense rescue medication. Patients in the placebo group who experienced delirium were given 0.5 mg oral risperidone every 12 h, and if symptoms were not controlled, the dose could be increased to a daily dose of 4 mg. In patients belonging to the risperidone group who experienced delirium, the dose of risperidone was incrementally increased until symptoms were controlled or a dose of 4 mg/day was attained. In either group, haloperidol was used as a second-line rescue medication if symptoms were not controlled with risperidone in a daily dose of 4 mg. Haloperidol administration was begun orally at 0.5 mg every 8 h and could be escalated to 10 mg/day if needed. Rescue medications were started once the diagnosis of delirium was confirmed, and the dosage could be escalated by doubling the dose at 24-h intervals, if needed, until symptoms were controlled or the maximum dosage limit was attained. Rescue medications were continued for 24 h after a score of 0 was achieved on the ICDSC.

\textbf{Outcome Measures}

The primary outcome measure was the occurrence of clinical delirium. Secondary outcome measures were the duration and severity of delirium, length of ICU and hospital stay, and occurrence of side effects such as extrapyramidal manifestations.

\textbf{Statistical Analysis}

The required sample size was estimated using the Power Analysis and Sample Size software 2005 (PASS©; NCSS, Kaysville, UT). Based on retrospective local institutional data, it was expected that approximately 25% of those who experienced SSD would progress to overt delirium if untreated, and that the incidence would be on the order of 5% if treated. Thus, it was estimated that a sample size of 50 patients in each study group would achieve 85% power to detect a difference of 0.2 between the group proportions of 0.25 and 0.05. The test statistic used was the two-sided likelihood ratio chi-square test, and significance was targeted at an $\alpha$-error of 0.05.

Statistical analysis was done on a personal computer using Stata® version 11.1 (StataCorp LP, College Station, TX) for Windows® (Microsoft, Redmond, WA). Normally distributed numerical data were presented as mean (SD), and between-group differences were compared using the independent-samples Student $t$ test. Nonnormally distributed numerical data were presented as median (interquartile range), and intergroup differences were compared using the Mann–Whitney U test. Nominal data were presented as ratio or as number (percentage), and the differences between the two groups were compared using the Pearson chi-square test with Yates correction or Fisher exact test if more than 20% of cells in a cross-tabulation had expected count of less than 5. Agreement between the ICDSC and the DSM criteria for diagnosis of delirium was tested using Cohen’s $\kappa$ statistic.

All statistical analyses were based on the intention to treat. This approach requires that patients be analyzed according to the group to which they are randomly assigned regardless of...
subsequent withdrawal or deviation from protocol.19 Thus, all patients randomized to either treatment were analyzed, including those who did not complete the study protocol because of events such as death, second operation, or reintroduction of mechanical ventilation. Patients who initially were randomized to receive placebo and subsequently received risperidone for clinical delirium were analyzed according to their initial randomization group (i.e., placebo group). Likewise, patients who were randomized to receive risperidone and subsequently received haloperidol as a second-line rescue medication were analyzed as randomized.

Patients experiencing delirium at any time during the follow-up period were considered to have experienced a “failure event” at that time. Patients experiencing events such as death, second operation, or reinitiation of mechanical ventilation were considered to have experienced a “competing-risk event.” A competing-risk event is one that would prevent the failure event of interest from occurring or fundamentally alters the probability of that event occurring rather than delaying its occurrence. Because time to a competing-risk event was defined, occurrence of such an event was regarded as “informative censoring” of data. Patients who did not experience delirium or any other competing-risk event during the follow-up period were regarded as “noninformatively censored” observations because time to occurrence of an event, if any, could not be defined.20

Competing-risks regression analysis was performed to compare the “cumulative incidence function” of the failure event of interest (i.e., delirium) in the two study groups adjusting for competing-risk events and for other possible confounding factors. The cumulative incidence of delirium at a given time is the probability that an individual has experienced delirium before that time. Because competing-risks analysis does not require that competing-risk events be independent of the failure event (i.e., independence assumption) or that subjects have the same value of covariate predictors (i.e., homogeneity assumption), no such untestable assumptions were made before analysis.20

Covariates entered in the regression model included randomization group and the Rudolph Risk Score,21 which was derived at the time of data analysis from data all of which had been obtained and recorded during the preoperative workup. At this stage, all information used for risk stratification was available through our database, and no information had to be collected retrospectively. This score comprised four predictors of delirium: previous stroke or transient ischemic attacks, Mini Mental State Examination score,14 15-item Geriatric Depression Score,19 and abnormal albumin. Assigning a total score of 0–5, this risk prediction rule was validated for preoperative risk stratification of elderly patients undergoing cardiac surgery.21

Constrained by the observed event rate, we used a rather parsimonious regression model to adjust for only two relevant covariates in keeping with the rule of thumb that to obtain adequately precise estimates, 10 events should be observed for each predictor to be included in a survival model.22 The competing-risks regression model provided an adjusted estimate for the hazard of subdistribution of the failure event known as the “subhazard ratio.”23

All reported P values are two-sided. P values < 0.05 are considered statistically significant.

Results

During the period from December 2007 to November 2010, 243 subjects 65 yr of age or older underwent open-heart procedures with cardiopulmonary bypass. Forty-seven (19.3%) patients did not fulfill eligibility criteria, and 19 (7.8%) declined to participate. One hundred seventy-seven (72.8%) patients were enrolled, 101 (51.7%) of whom experienced SSD and were randomized to receive risperidone (n = 51) or placebo (n = 50).

All statistical analyses were based on the intention to treat. Two (3.9%) patients in the risperidone group and one (2%) in the placebo group died of cardiogenic shock. Mechanical ventilation had to be reinitiated in three (5.9%) patients in the risperidone group and in two (4%) in the placebo group. One (1.96%) patient in the risperidone group and two (4%) in the placebo group underwent a second operation because of cardiac tamponade. Ninety patients (45 in each group) completed the study protocol (fig. 1).

Demographic and preoperative characteristics of the studied population are shown in table 1 and relevant operative and postoperative data in table 2.

Primary and secondary outcome measures are displayed in table 3. Eight (15.7%) patients in the risperidone group and 19 (38%) in the placebo group had scores of 4 or more on the ICDSC (P = 0.011) and were labeled as possibly delirious. The diagnosis of delirium was confirmed by DSM criteria in 7 (13.7%) patients in the risperidone group compared with 17 (34%) patients in the placebo group (P = 0.031). This comprised an absolute risk reduction of 0.20 (95% CI, 0.04–0.37) with a number needed to treat of 4.9 (95% CI, 2.7–24.4). There was excellent agreement between the ICDSC and the DSM criteria with regard to the diagnosis of delirium (Cohen’s κ = 0.921, P < 0.001).

Intensive care unit and hospital lengths of stay were comparable in both groups (P = 0.517 and 0.056, respectively). Two (3.9%) patients in the risperidone group experienced extrapyramidal manifestations versus one (2%) patient in the placebo group to whom risperidone was administered to treat delirium (P = 1.0). These side effects, which developed during risperidone therapy, were mild and responded to reduction of the dosage. None of the patients studied experienced abnormality of the QTc interval. The attending team requested emergency breaking of the concealment envelopes in none of the patients.
Table 4 shows the competing-risks regression model as adjusted for randomization group and the Rudolph Risk Score, whereas figure 2 shows the cumulative incidence function curves based on this model. Failure to treat SSD with risperidone was associated independently with a sub-hazard ratio of 3.83 (95% CI, 1.63–8.98; *P* < 0.002).

The model provided an adjusted estimation for the cumulative incidence probability of delirium that was statistically significant ($\text{Wald chi-square} = 21.94, P < 0.0001$).

Characteristics of clinical delirium in affected patients in both groups are shown in table 5. There were no statistically significant differences between the two groups with regard to duration of clinical delirium ($P = 0.664$), highest score on the ICDSC ($P = 0.234$), need for haloperidol ($P = 0.608$), highest doses of risperidone and haloperidol ($P = 0.318$ and...
Table 1. Demographic and Preoperative Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risperidone Group (n = 51)</th>
<th>Placebo Group (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 65 to 70 yr</td>
<td>36 (70.6%)</td>
<td>39 (78%)</td>
</tr>
<tr>
<td>&gt;70 yr</td>
<td>15 (29.4%)</td>
<td>11 (22%)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>33/18</td>
<td>36/14</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>32 (62.7%)</td>
<td>35 (70%)</td>
</tr>
<tr>
<td>Single, divorced, or widow(er)</td>
<td>19 (37.3%)</td>
<td>15 (30%)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or above</td>
<td>40 (78.4%)</td>
<td>43 (86%)</td>
</tr>
<tr>
<td>Less than high school</td>
<td>11 (21.6%)</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non- or ex-smoker</td>
<td>36 (70.6%)</td>
<td>31 (62%)</td>
</tr>
<tr>
<td>Active smoker</td>
<td>15 (29.4%)</td>
<td>19 (38%)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non- or ex-consumer</td>
<td>44 (86.3%)</td>
<td>45 (90%)</td>
</tr>
<tr>
<td>Active consumer</td>
<td>7 (13.7%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>17 (33.3%)</td>
<td>14 (28%)</td>
</tr>
<tr>
<td>Past cardiac surgery</td>
<td>10 (19.6%)</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA class II</td>
<td>20 (39.2%)</td>
<td>18 (36%)</td>
</tr>
<tr>
<td>NYHA class III or IV</td>
<td>31 (60.8%)</td>
<td>32 (64%)</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥0.3</td>
<td>42 (82.4%)</td>
<td>43 (86%)</td>
</tr>
<tr>
<td>≤0.3</td>
<td>9 (17.6%)</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>11 (21.6%)</td>
<td>12 (24%)</td>
</tr>
<tr>
<td>Anemia*</td>
<td>12 (23.5%)</td>
<td>10 (20%)</td>
</tr>
<tr>
<td>Albumin &lt;35 g/l</td>
<td>10 (19.6%)</td>
<td>12 (24%)</td>
</tr>
<tr>
<td>MMSE score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28 to 30</td>
<td>30 (58.8%)</td>
<td>31 (62%)</td>
</tr>
<tr>
<td>25 to 27</td>
<td>21 (41.2%)</td>
<td>19 (38%)</td>
</tr>
<tr>
<td>GDS-15 score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to 2</td>
<td>25 (49%)</td>
<td>26 (52%)</td>
</tr>
<tr>
<td>3 to 4</td>
<td>26 (51%)</td>
<td>24 (48%)</td>
</tr>
<tr>
<td>Rudolph Risk Score&lt;sup&gt;31&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>23 (45.1%)</td>
<td>25 (50%)</td>
</tr>
<tr>
<td>1</td>
<td>22 (43.1%)</td>
<td>21 (42%)</td>
</tr>
<tr>
<td>2</td>
<td>6 (11.8%)</td>
<td>4 (8%)</td>
</tr>
</tbody>
</table>

Data are presented as number (percentage) or ratio.

* Defined as hemoglobin <130 g/l in men or <120 g/l in women.
† All four items comprising the score were individually evaluated and recorded during preoperative workup. Total score was derived at the time of data analysis from these data. No data used were collected retrospectively.
GDS-15 = 15-item Geriatric Depression Scale; MI = myocardial infarction; MMSE = Mini Mental State Examination; NYHA = New York Heart Association.

0.757, respectively), or length of ICU or hospital stays (P = 0.576 and 0.901, respectively).

Discussion

The current study showed that administration of risperidone to elderly patients who experienced SSD, as diagnosed by a score of 1–3 on the ICDSC, after on-pump cardiac surgery was associated with significantly lower incidence of clinical delirium.

Although the clinical implications of SSD are not clear, the condition was shown to be associated with the same risk factors as delirium. In addition, patients with SSD were reported to exhibit more delirium symptoms and to have more prolonged ICU and hospital length of stay.9,11

The current study showed that 57.1% of patients experienced SSD after surgery. Data on the incidence of SSD after cardiac surgery is scant. Nonetheless, one study indicated that approximately 34% of patients undergoing cardiac surgery exhibited manifestations compatible with SSD.24 That study used the Confusion Assessment Method, which comprises four features: acute onset and fluctuation, inattention,
Table 3. Outcome Measures in Both Study Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risperidone Group (n = 51)</th>
<th>Placebo Group (n = 50)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score ≥3 on the ICDSC</td>
<td>8 (15.7%)</td>
<td>19 (38%)</td>
<td>0.011</td>
</tr>
<tr>
<td>Clinical delirium by DSM criteria</td>
<td>7 (13.7%)</td>
<td>17 (34%)</td>
<td>0.031</td>
</tr>
<tr>
<td>Length of ICU stay, days</td>
<td>2 (2 to 3)</td>
<td>3 (2 to 3)</td>
<td>0.517</td>
</tr>
<tr>
<td>Length of hospital stay, days</td>
<td>6 (5 to 7)</td>
<td>6 (5 to 8)</td>
<td>0.056</td>
</tr>
<tr>
<td>Extrapyramidal side effects</td>
<td>2 (3.9%)</td>
<td>1 (2%)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Data are presented as number (percentage) or median (interquartile range).

DSM = Diagnostic and Statistical Manual of Mental Disorders; ICDSC = Intensive Care Delirium Screening Checklist; ICU = intensive care unit.

Table 4. Competing-risks Regression Model for Incidence of Clinical Delirium as Adjusted for Treatment Group and the Rudolph Risk Score

<table>
<thead>
<tr>
<th>Covariate</th>
<th>SHR</th>
<th>Robust SE</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
<th>z</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to treat SSD with risperidone</td>
<td>3.83</td>
<td>1.67</td>
<td>1.63</td>
<td>8.98</td>
<td>3.08</td>
<td>0.002</td>
</tr>
<tr>
<td>Rudolph Risk Score²¹*</td>
<td>2.62</td>
<td>0.73</td>
<td>1.51</td>
<td>4.53</td>
<td>3.43</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* All four items comprising the score were individually evaluated and recorded during preoperative workup. Total score was derived at time of data analysis from these data. No data used were collected retrospectively.

95% CI = 95% confidence interval; SE = standard error; SHR = subhazard ratio; SSD = subsyndromal delirium; z = z statistic.
those who experienced SSD would progress to overt delirium if untreated and that the incidence would be on the order of 5% if treated. Our premise was that reduction in incidence of delirium of this magnitude could be a plausible effect size to pursue in a randomized controlled trial.

One weakness in the current study is that the dosage of risperidone used has not been validated previously for SSD. Because data on the use of antipsychotics to treat SSD are lacking, we used a dosage shown by a previous report to be effective for the treatment of delirium.34

Because of apparent logistic difficulties related to the extended period over which the study was conducted and the frequency of evaluations needed, screening for delirium was not performed by the same clinician. No attempt was made to test interobserver agreement, so this should be regarded as a limitation of the study.

Another limitation is that many categories of patients were primarily excluded from the current study. These patients had physical problems that would render assessment for delirium difficult (e.g., hearing loss) or put them at exceptionally high risk for delirium (e.g., depression or significant cognitive impairment). The previously unexplored aim of the current study was to investigate the relevance of treating SSD in patients who, on account of their age and the type of surgery they underwent, are at risk for delirium. It was thought that the inclusion of patients at especially high risk for delirium could result in failure of the study to demonstrate an effect that might be beneficial for those at lower degrees of risk for this untoward outcome. The implication of this shortcoming is that extrapolation of current results to such high-risk groups should be exercised with caution and that other trials are needed to determine whether risperidone can improve delirium outcomes in high-risk patient groups.

In the current study, risperidone was administered to patients who experienced clinical delirium in both groups. Al-

**Fig. 2.** Cumulative incidence function curves for delirium in both study groups based on competing-risks regression analysis. Failure to treat subsyndromal delirium with risperidone was associated independently with a subhazard ratio of 3.83 (95% CI, 1.63 to 8.98; \( P = 0.002 \)).

**Table 5.** Characteristics of Clinical Delirium in Affected Patients in Both Study Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risperidone Group (n = 7)</th>
<th>Placebo Group (n = 17)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of clinical delirium, days</td>
<td>3 (2 to 4)</td>
<td>3 (3 to 4)</td>
<td>0.664</td>
</tr>
<tr>
<td>Highest score on the ICDSC</td>
<td>6 (5 to 7)</td>
<td>5 (4 to 5)</td>
<td>0.234</td>
</tr>
<tr>
<td>Highest risperidone dose, mg/day</td>
<td>3 (2 to 4)</td>
<td>3 (2.25 to 3.5)</td>
<td>0.318</td>
</tr>
<tr>
<td>Need for haloperidol</td>
<td>2 (28.6%)</td>
<td>3 (17.6%)</td>
<td>0.608</td>
</tr>
<tr>
<td>Highest haloperidol dose, mg/day</td>
<td>0 (0 to 1.5)</td>
<td>0 (0 to 0)</td>
<td>0.757</td>
</tr>
<tr>
<td>Length of ICU stay, days</td>
<td>3 (2 to 4)</td>
<td>3 (3 to 4)</td>
<td>0.576</td>
</tr>
<tr>
<td>Length of hospital stay, days</td>
<td>9 (7 to 10)</td>
<td>9 (8 to 10)</td>
<td>0.901</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range) or number (percentage).

ICDSC = Intensive Care Delirium Screening Checklist; ICU = intensive care unit.
though this may have served to confound the assessment of secondary outcome measures, it was judged to be more appropriate to use risperidone as a first-line treatment and to preserve haloperidol for a second-line rescue medication in view of the latter drug’s potential to prolong the QTc interval and to precipitate malignant dysrhythmias.

Likewise, the administration of glycopyrrolate along with neostigmine to antagonize residual neuromuscular blockade may have influenced the incidence of delirium or extrapyramidal side effects. Nonetheless, a comparable number of patients in both groups received these medications. Finally, there has been growing concern regarding residual neuromuscular blockade after cardiac surgery. In this respect, one editorial has recommended that a train-of-four ratio of less than 0.9 be antagonized pharmacologically before extubation.

A pertinent issue is that no a priori power analysis was conducted in the current study for secondary outcome measures. Thus, it is probable that the study had low power to detect a statistically significant difference between the two groups with regard to ICU and hospital length of stay. In fact, because of the small number of patients who experienced delirium, the study apparently had low power to detect a relevant difference among delirious patients in both study groups with regard to duration of delirium, highest score on the ICDSC, or consumption of antipsychotic medications. This may be viewed as a limitation to the current study, the results of which should be regarded as quite preliminary. In this respect, larger studies specifically designed to evaluate whether early administration of risperidone during SSD versus later initiation of risperidone at time of development of clinical delirium would make a difference regarding the clinical course of patients.

Ideally, a standard definition should be coined for SSD and a validated diagnostic tool developed for SSD according to that definition. Consequently, a large randomized multi-arm study may determine whether it is best with regard to prevention of clinical delirium to administer risperidone to all elderly heart surgery patients after surgery or whether it is similarly effective to administer the prophylactic medication selectively to those who experience SSD. Such a trial may include the following arms: a group that receives placebo immediately after surgery and gets risperidone only if clinical delirium develops, a group that receives risperidone after surgery regardless of the development of SSD, a group that receives risperidone if SSD is diagnosed, and a group that receives placebo if SSD is diagnosed and receives risperidone only if clinical delirium occurs. Such a study design may give the best sense of what postoperative timing and what clinical targeting for risperidone administration would be most effective for avoiding the occurrence of postoperative delirium in this patient population.

Conclusion

The administration of risperidone to elderly patients who experienced SSD after on-pump cardiac surgery was associated with a significantly lower incidence of clinical delirium. Larger studies are required to validate the results of this study and to determine what timing and clinical targeting for risperidone administration would be most effective for avoiding this untoward outcome.

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References


