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QTc prolongation after haloperidol administration in critically ill patients post cardiovascular surgery: A cohort study and review of the literature

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Abstract

Objective. From case reports, haloperidol administration has been associated with QTc prolongation, *torsades de pointes*, and sudden cardiac death. In a vulnerable population of critically ill patients after cardiac surgery, however, it is unclear whether haloperidol administration affects the QTc interval. Thus, the aim of this study is to explore the effect of haloperidol in low doses on this interval.

Method. This retrospective cohort study was performed on a cardio-surgical intensive care unit (ICU), screened 2,216 patients and eventually included 68 patients with delirium managed with oral and intravenous haloperidol. In this retrospective analysis, electrocardiograms were taken prior and within 24 h after haloperidol administration. The effect of haloperidol on QTc was determined with a Person correlation, and inter-group differences were measured with new long QT comparisons.

Results. In total, 68 patients were included, the median age was 71 (64–79) years and predominantly male (77%). Haloperidol administration followed ICU admission by three days and the cumulative dose was 4 (2–9) mg. As a result, haloperidol administration did not affect the QTc ($r = 0.144$, $p = 0.23$). In total, 31% (21/68 patients) had a long QT before and 27.9% (19/68 patients) after haloperidol administration. Only 12% (8/68 patients) developed a newly onset long QT. These patients were not different in the route of administration, cumulative haloperidol doses, comorbidities, laboratory findings, or medications.

Significance of results. These results indicated that low-dose intravenous haloperidol was safe and not clinically relevant for the development of a newly onset long QT syndrome or adverse outcomes and support recent findings inside and outside the ICU setting.

Introduction

Delirium, also called acute confusional state, is an unspecific manifestation of acute illness occurring in post cardio-surgical patients (Rudiger et al., 2016) and characterized by disturbances in consciousness or attention and cognition, an abrupt onset and fluctuating course caused by underlying etiologies (DSM 5) (American Psychiatric Association, 2013). Delirium is common in the intensive care units (ICUs) reaching an incidence of 80% and causes significant distress for patients, families, and caregivers. The management of delirium is controversial. Whereas the outdated American Psychiatric Associations Guidelines (Practice guideline for the treatment of patients with delirium, American Psychiatric Association, 1999) recommended the use of antipsychotics, in particular haloperidol as the gold standard, the newer National Institute for Clinical Excellence (NICE) guidelines (Royal College of Physicians (UK), 2010) advocate the cautious use of antipsychotics only for patients in distress caused by delirium. Further, previous reviews supported the use of antipsychotics, whereas a later review disapproved of their use (Barbateskovic et al., 2016; Kishi et al., 2016; Neufeld et al., 2016; Burry et al., 2018; Nikooie et al., 2019; Riviere et al., 2019).

The management schedule implemented in this study compromised between these approaches, administering haloperidol for delirious patients in distress and experiencing hallucinations.

Haloperidol is a typical antipsychotic with primarily inverse agonism on the dopamine (D)-2 to -4 receptors, silent agonism on the alpha-1a and negligible effects on the histaminergic and muscarinergic receptors. Like all enteral antipsychotics, haloperidol can prolong the QTc in a dose-dependent manner likely caused by hERG inhibition (Crumb et al., 2006) causes QTc prolongation, *torsades de pointes*, and sudden cardiac death. In particular, the

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parenteral formulation has been associated with QTc prolongation and *torsades de pointes* (Metzger and Friedman, 1993). In the 1980s, sudden cardiac death may have been caused by very high doses of haloperidol (Henderson et al., 1991). As shown in deaths caused by methadone, another aspect of parenteral formulations is the use of additives: Chlorobutanol, a preservative, caused substantial QTc prolongation by inhibition of the human ether-a-go-go related gene responsible for cardiac potassium channels and reduced potassium elimination causing a prolongation of the repolarization (Kornick et al., 2003). For parenteral haloperidol, some generic formulations contain chlorobutanol, whereas, e.g., the brand formulation does not. Additionally, recent evidence suggests that QTc prolongation is clinically less important than previously assumed (Tables 1 and 2). Further, QRS morphology might be more relevant to QTc prolongation, *torsades de pointes*, and sudden cardiac death (Attin and Davidson, 2011).

Hence, it remains unclear, whether haloperidol administration prolongs the QTc interval in a vulnerable population after cardiac surgery. We hypothesize that the current formulation of haloperidol has no clinically relevant adverse effect on the QTc time. The aim of this study is to assess the risk of QTc prolongation after haloperidol administration in ICU patients after cardiac surgery and to compare our results with reports from the literature.

Methods

Patients and procedures

This retrospective cohort study was reported according to STROBE guidelines (von Elm et al., 2014) and conducted on the cardio-surgical ICU at the University Hospital Zurich, Switzerland. From January 1 to December 31, 2014, 1,181 patients were managed on this 12-bed unit, mostly post cardiovascular surgery. The ICU is led by certified specialists in intensive care medicine. The treatment goals of our cardio-surgical ICU patients have been summarized (Hauffe et al., 2015, 2016). Neurologists and psychiatrists are available for expert consultation at all hours. The daily records of all patients admitted to the ICU were screened in order to identify patients with delirium managed with enteral and/or parenteral haloperidol. Inclusion criteria were age >18 years, management with haloperidol intravenously, orally or either, and an electrocardiogram (ECG) prior and after haloperidol administration. Exclusion criteria were the absence of ECG in the given time frame within 24 h after haloperidol administration and a pacemaker ECG. Patients were only once included in the analysis, repeated occurrences were omitted.

This study was approved by the ethics committee of the Canton of Zurich (KEK-ZH-Nr. 2012-0263).

Variables

The severity of disease at the ICU was calculated with the Simplified Acute Physiology Score (SAPS) II (Le Gall et al., 1993). The ECG after haloperidol administration was performed within 24 h and compared with the ECG recorded at ICU admission. The QT time was measured by the electrocardiograph Cardiovit AT 10 (Schiller, Baar, Switzerland) and by manual analysis. QT times were corrected with the Bazett formula: $QTc = QT/\sqrt{\text{heart rate}}$. Long QT was defined according to the American Heart Association as QTc >450 ms for men and QTc >460 ms for women (Rautaharju et al., 2009).

Delirium management schedule

The delirium management schedule (DelirPath) (Schubert et al., 2018) consists of a screening and a management algorithm. All patients on the ICU are regularly screened thrice daily with the Intensive Care Delirium Screening Checklist (ICDSC) and on suspicion of incident delirium, the Confusion Assessment Method for the ICU (CAM-ICU) was performed.

The ICDSC (Devlin et al., 2007) is a screening instrument including eight items based on the DSM-IV TR criteria specifically designed for the intensive care setting with two points: absent or present. This scale was designed for patients with limited communication abilities such as intubated patients. The maximum score is eight; scores of more than three indicate the presence of delirium. Each item is rated on the patient's behavior over the previous 24 h, and the inter-rater reliability between intensive care staff was considered adequate (Bergeron et al., 2001).

The CAM-ICU (Ely et al., 2001) is based on the CAM (Inouye et al., 1990) reflecting the DSM-III-R criteria (American Psychiatric Association, 1987) and designed for patients with limited communication abilities. This scale contains four features with two levels: absent and present. The nonverbal items achieve a lower sensitivity than the verbal items. The inter-rater reliability ranges from 0.79 to 0.95 (McNicoll et al., 2005).

Once delirium was determined with the ICDSC and CAM-ICU, the management algorithm (Schubert et al., 2018) was initiated. In patients with hyperactive delirium, pipamperone was administered orally. In delirious patients with hallucinations or aggressive behavior, enteral and/or parenteral administration of haloperidol was added. Oral haloperidol (Haldol® 2 mg/ml, Janssen-Cilag AG, Zug, Switzerland) containing the preservative E 218 was administered as drops in doses of 0.5 or 1 mg. Intravenous haloperidol (Haldol® 5 mg/ml, Janssen-Cilag AG, Zug, Switzerland) containing *acidum lacticum* and *aqua ad iniectabilia q.s. ad solute* was injected in steps of 0.5–1 mg iv. The cumulative dose was adjusted by the physician according to the clinical condition. Neither enteral nor intravenous haloperidol contained the preservative chlorobutanol.

Vegetative symptoms were blunted with the α-2 agonists clonidine (as short or continuous infusions) or dexmedetomidine (continuous infusions only). In individuals with nocturnal agitation, insomnia or a risk of a nonconvulsive epilepsy, intravenous midazolam was continuously infused at doses of 0.05–0.1 mg/kg/h and interrupted daily at 6 am.

Data sources

Physiological variables were collected from the hand-written ICU charts and transferred into an electronic database. Results from patient history and clinical examination, the surgical reports, the ECG, as well as the results from laboratory analyses were extracted from the electronic patient documentation system. Physiological and laboratory variable were collected on the day haloperidol was started. No additional study-specific interventions were performed.

Statistical analysis

All analyses were performed with the use of IBM SPSS Statistics (IBM Corp, Armonk, NY). Baseline characteristics were determined for all included patients and described as medians and

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Table 1. Studies with significant QTc prolongation

Author (Reference)	Population (Number of patients, setting)	Haloperidol (Dose, administration)	Main findings
(Harvey et al., 2004) Intramuscular haloperidol or lorazepam and QT intervals in schizophrenia[a,b]	Schizophrenic patients, treated with haloperidol or lorazepam ($n = 12$ per group), blinded, randomized, placebo-controlled crossover design, emergency services	7.5 mg haloperidol im or 4 mg lorazepam im	- Haloperidol increased the QTc an average of 5.1 ms using Bazett's correction - Effects of lorazepam on QTc were nullified by correction for the heart rate elevation
(Harrigan et al., 2004) A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition[a,b,c]	Prospective, randomized study, in which patients with psychotic disorders reached steady-state, haloperidol ($n = 27$), thioridazine ($n = 30$), ziprasidone ($n = 31$), quetiapine ($n = 27$), olanzapine ($n = 24$), and risperidone ($n = 25$). QTc interval at the time of estimated peak plasma/serum concentrations in the absence and presence of metabolic inhibition	15 mg/d haloperidol po, thioridazine 300 mg/d po, ziprasidone 160 mg/d po, quetiapine 750 mg/d po, olanzapine 20 mg/d po, risperidone 6–8 mg/d increased to 16 mg/d po. ECGs were done at steady-state on monotherapy and after concomitant administration of appropriate cytochrome P450 (CYP450) inhibitors	- The presence of metabolic inhibition did not significantly augment QTc prolongation associated with any agent - Each of the antipsychotics studied was associated with measurable QTc prolongation at steady-state peak plasma concentrations, which was not augmented by metabolic inhibition - Haloperidol was associated with mean changes of 7.1 ms in QTc - No patient had a QTc interval ≥ 500 ms - Mean QTc changes from baseline were similar in the presence of metabolic inhibition to those changes observed during monotherapy
(Lindborg et al., 2003) Effects of intamuscular olanzapine vs. haloperidol and placebo on QTc intervals in acutely agitated patients[a,b,c]	Four double-blind trials were compared. Databases included: placebo-controlled, haloperidol-controlled, and geriatric placebo-controlled patients with schizophrenia ($n = 482$)	Haloperidol 7 mg im, vs. placebo im, or olanzapine im 2.5, 5, 7.5, or 10 mg	- The report showed that for acutely agitated patients with schizophrenia, bipolar mania and dementia, QTc interval changes during treatment with the newly developed intramuscular formulation of olanzapine were no greater than during treatment with intramuscular haloperidol or intramuscular placebo
(Desai et al., 2003a) Variability of heart rate correction methods for the QT interval[a,c]	Randomized, double-blind, placebo-controlled, crossover trial, healthy subjects ($n = 16$) to compare the variability of heart rate-corrected QT intervals (QTc) using different methods in a study of low-dose oral haloperidol	Single doses of haloperidol 10 mg po. Heart rate correction of the QT interval was performed using Bazett's, Fridericia's and subject-specific correction methods	- Haloperidol caused a statistically significant mean QTc prolongation using the three correction methods - At 10 h post-haloperidol administration, the mean QTc on haloperidol was 425.4 ms and was statistically significantly greater than the mean QTc on the placebo of 403.1 ms using Bazett's correction
(Desai et al., 2003b) Pharmacokinetics and QT interval pharmacodynamics of oral haloperidol in poor and extensive metabolizers of CYP2D6[a]	Randomized, double-blind, placebo-controlled, crossover trial of healthy poor (PMs) and extensive (EMs) metabolizers of CYP2D6 ($n = 16$)	Single 10 mg dose of haloperidol po	- There was a statistically significantly greater mean QTc on haloperidol 421.6 ± 20.1 ms than on placebo 408.4 ± 18.5 ms
(Su et al., 2003) A pilot crossover design study on QTc interval prolongation associated with sulpiride and haloperidol[a,b]	Four-week, crossover study to evaluate QTc intervals in patients with schizophrenia during drug-free, sulpiride-treated, and haloperidol-treated periods	Patients received 15 mg/kg of body weight of sulpiride in divided dosing for two weeks and the received 0.25 mg/kg of body weight of haloperidol in divided dosing for another two weeks	- QTc intervals in the sulpiride-treated period lengthened significantly when compared with drug-free and haloperidol-treated periods - All cases in this study were under therapeutic dose of haloperidol, and there was no significant QTc prolongation

(*Continued*)

Table 1. (*Continued.*)

Author (Reference)	Population (Number of patients, setting)	Haloperidol (Dose, administration)	Main findings
(Kane et al., 2002) Efficacy and safety of aripiprazole and haloperidol vs. placebo in patients with schizophrenia and schizoaffective disorder[b]	Patients with schizophrenia or schizoaffective disorder ($n = 414$)	Aripiprazole 15 or 30 mg/d compared to placebo 10 mg/d haloperidol as an active control	- Haloperidol was associated with significant extrapyramidal symptoms, prolongation in QTc interval and prolactin elevation at endpoint compared with placebo and compared to aripiprazole
(Czekalla et al., 2001) Analysis of the QTc interval during olanzapine treatment of patients with schizophrenia and related psychosis[a,b,c]	Four trials comparing olanzapine with placebo, haloperidol, and risperidone in acutely psychogenic patients ($n = 2,700$)	15 ± 5 mg/d haloperidol per day	- These analyses suggest that olanzapine in patients with schizophrenia and related psychoses does not contribute to QTc prolongation resulting in potentially fatal ventricular arrhythmias - There was no significant increase in QTc in the haloperidol group

Clinical studies in PubMed were searched using the following terms.
[a]Haloperidol and QT prolongation (16 studies).
[b]Haloperidol and long QT (13 studies).
[c]Haloperidol and QTc prolongation (19 studies).

interquartile ranges based on their parametric properties, in addition to percentages for categorical variables. Subsequent group comparisons were made between patients who developed a new long QT after haloperidol administration and patients who did not. Values are given as median (interquartile range) or numbers (percentages), as appropriate. Groups were compared using the Mann–Whitney *U* test or the Fisher's exact test, as appropriate. Pearson or Spearman correlations were chosen to determine the dose-dependent effect of haloperidol on QTc. The null hypothesis was rejected with a two-sided p-value < 0.05.

Literature review

A limited literature search was conducted on key resources, including PubMed, as well as focused internet search. PubMed was searched with the filter for clinical trials using the terms "haloperidol AND QT prolongation," "haloperidol AND QTc prolongation," "haloperidol AND long QT," and "haloperidol AND delirium AND critical illness." The search was also limited to English language documents published between March 2001 and February 2019.

Results

Study population

During the 24-month study period, 2,216 patients were admitted to the cardio-surgical ICU. The patients were rather sick, as evidenced by a median SAPS and ICU mortality of 31 and 4.3%, respectively. On hospital admission, 129 patients had objected to the scientific use of their medical data and, therefore, were not screened. Overall, 169 patients had an incomplete documentation and were, therefore, not screened, too. Of the 1,918 patients screened, 146 received haloperidol. Of these, on 72, no ECG was performed and another six had a pacemaker rhythm and were consequently excluded (Figure 1). In the end, 68 patients were included in this analysis. The median age of patients was 71 years, and 77% were male. All patients underwent cardiac surgery and both median SAPS and ICU LOS were 41 and 6 days, respectively, and mortality did not occur. The interval between ICU admission and haloperidol administration was three days, and the cumulative haloperidol dose was 4 mg. Haloperidol was administered enterally in 7.4%, intravenously in 84%, and both enterally and intravenously in 8.8%.

QTc measurements

There were no differences between machine and manual measurements of the QTc time (data not shown). The median QTc time difference between follow-up and baseline was 3 (−23 to 32) ms. In total, 53% experienced QTc prolongation after haloperidol administration with 31 (12–47) ms.

At baseline, 31% (21/68 patients) had a long QT, and following, after haloperidol administration, 28% (19/68 patients). Only 17% with QTc within normal limits at baseline had a newly onset long QT after haloperidol administration. Patients with and without a newly onset long QT were compared, and the results are displayed in Tables 3 and 4. Inter-group analyses did not reveal significant risk factors. Further, haloperidol was not associated with a dose-dependent QTc prolongation as displayed in Figure 2.

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Table 2. Studies without significant QTc prolongation

Author (Reference)	Population (Number of patients, setting)	Haloperidol (Dose, administration)	Main findings
(Girard et al., 2018) Haloperidol and ziprasidone for treatment of delirium in critical illness[a]	566 critically ill patients with delirium treated with placebo ($n = 184$), haloperidol ($n = 192$), or ziprasodine ($n = 190$)	20 mg daily haloperidol iv or 40 mg daily ziprasidone iv or placebo iv or 14 days	- The use of haloperidol or ziprasidone compared with placebo did not significantly alter the duration of delirium
(van den Boogaard et al., 2018) Effect of haloperidol on survival among critically ill adults with a high risk of delirium: The REDUCE randomized clinical trial[a]	Critically ill adults with a high risk of delirium ($n = 1,789$)	Three times daily 1 mg iv or 2 mg haloperidol iv or placebo iv	- The use of prophylactic haloperidol compared with placebo did not improve survival at 28 days - These findings do not support the use of prophylactic haloperidol for reducing mortality in critically ill adults
(Spellmann et al., 2018) QTc prolongation in short-term treatment of schizophrenia patients: Effects of different antipsychotics and genetic factors[b,c,d]	10 schizophrenic adults ($n = 10$)	Treatment for five weeks	- QTc measured before treatment and once a week - QTc using the Bazett formula - Long QT (men 450 ms, women 470 ms) - QTc prolongation women > men - Significant more QTc prolongation with amisulpride, olanzapine, and quetiapine than with aripiprazole, haloperidol, and risperidone - No association between the genetic factors and the QTc duration at baseline and during treatment
(Duprey et al., 2016) The use of low-dose IV haloperidol is not associated with QTc prolongation: Post hoc analysis of a randomized, placebo-controlled trial[b,c,d]	ICU patients with subsyndromal delirium treated with haloperidol ($n = 34$) and placebo ($n = 34$)	1 mg haloperidol iv	- The QTc was similar between the two groups - Low-dose haloperidol intravenous was not associated with QTc prolongation
(Al Qadheeb et al., 2016) Preventing ICU subsyndromal delirium conversion to delirium with low-dose IV haloperidol: A double-blind, placebo-controlled pilot study[b]	ICU patients treated with haloperidol ($n = 34$) and placebo ($n = 34$)	1 mg haloperidol iv	- Low-dose haloperidol did not prevent delirium - No difference in QTc prolongation between groups
(Gaffigan et al., 2015) A randomized controlled trial of intravenous haloperidol vs. intravenous metoclopramide for acute migraine therapy in the emergency department[b,c]	Patients with headache treated with haloperidol ($n = 31$) or metoclopramide ($n = 33$)	5 mg haloperidol iv or 10 mg metoclopramide iv after 25 mg diphenhydramine iv	- Intravenous haloperidol was as safe and effective as metoclopramide - Mean QTc was equal and normal in the two groups and did not change after treatment
(Blom et al., 2015) In-hospital haloperidol use and perioperative changes in QTc-duration[c]	Hip-fracture patients with delirium ($n = 89$)	39 patients were treated with haloperidol po	- Haloperidol use did not influence the perioperative course of the QTc interval - QTc duration changed differentially, increasing in patients with normal but decreasing in patients with abnormal baseline QTc duration - Dangerous perioperative QTc prolongation was not associated with haloperidol use or other risk factors - Low-dose oral haloperidol did not affect perioperative QTc interval
(Page et al., 2013) Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): A randomised, double-blind, placebo-controlled trial[c]	ICU patients treated with haloperidol ($n = 71$) or placebo ($n = 70$)	2.5 mg haloperidol iv or placebo iv every 8 h	- Haloperidol did not modify the duration of delirium in critically ill patients - Although haloperidol can be used safely in this population the use of iv haloperidol should be reserved for the short-term management of acute agitation

(*Continued*)

Table 2. (*Continued.*)

Author (Reference)	Population (Number of patients, setting)	Haloperidol (Dose, administration)	Main findings
(van den Boogaard et al., 2018) Haloperidol prophylaxis in critically ill patients with a high risk for delirium[c]	High-risk ICU patients for delirium treated prophylactically with haloperidol ($n = 177$)	1 mg/8 h haloperidol iv	- Haloperidol was stopped in 12 patients because of QTc time prolongation - Patients who were not treated during the intervention period showed the similar result compared to the untreated control group
(Wang et al., 2012) Comparison of dexamethasone with ondansetron or haloperidol for prevention of patient-controlled analgesia-related postoperative nausea and vomiting: A randomized clinical trial[c]	Female patients with risk of PONV ($n = 135$), randomized in three groups, randomized trial	Dexamethasone 5 mg iv, dexamethasone plus 2 mg haloperidol im, or ondansetron 4 mg iv	- The incidences of total PONV in the first 24 h in the dexamethasone and haloperidol group were significantly lower than those of dexamethasone alone - There was no clinically relevant prolongation of the QTc interval in any group
(Kane et al., 2011) A double-blind, randomized study comparing the efficacy and safety of sertindole and risperidone in patients with treatment-resistant schizophrenia[c]	Treatment of 321 patients with haloperidol, 216 of them with sertindole, and 105 of them with risperidone ($n = 321$)	Haloperidol 10–30 mg/d (screening period) vs. risperidone 2–6 mg/d (titration phase) and 6–12 mg/d maintenance phase vs. sertindole 4–12 mg/d (titration phase) and 12–24 mg (maintenance phase)	- Prolongation of the QTc interval was observed significantly more often with sertindole than with haloperidol
(Lin et al., 2010) A randomized, double-blind comparison of risperidone vs. low-dose risperidone plus low-dose haloperidol in treating schizophrenia[d]	Efficacy and safety of risperidone monotherapy ($n = 42$) vs. low-dose risperidone plus low-dose haloperidol ($n = 46$) in schizophrenia	2 mg/d risperidone plus 2 mg/d haloperidol or monotherapy with 4 mg/ risperidone	- There were no significant differences in changes in corrected QT interval
(Miceli et al., 2010) Effects of high-dose ziprasidone and haloperidol on the QTc interval after intramuscular administration: a randomized, single-blind, parallel-group study in patients with schizophrenia or schizoaffective disorder[b,c,d]	Randomized, single-blind study, hospitalized patients with schizophrenia or schizoaffective disorder, treated with haloperidol ($n = 27$), or ziprasidone ($n = 31$)	Two high-dose injections of ziprasidone im (20 and 30 mg) or haloperidol 7.5 and 10 mg), separated by 4 h	- None of the patients had a QTc interval $\geq$ 480ms - QTc changes from the baseline were clinically modest with both drugs
(Devlin et al., 2010) Efficacy and safety of quetiapine in critically ill patients with delirium: A prospective, multicentre, randomized, double-blind, placebo-controlled pilot study[c]	Adult ICU patients with delirium ($n = 36$)	Quetiapine 50 mg bd or placebo bd. Pretreated patients with haloperidol	- Quetiapine added to as-needed haloperidol results in faster delirium resolution, less agitation, and a greater rate of transfer to home or rehabilitation. - The incidence of QTc prolongation and extrapyramidal symptoms was similar between groups
(Garcia et al., 2009) The efficacy and safety of blonanserin compared with haloperidol in acute-phase schizophrenia: A randomized, double-blind, placebo-controlled, multicentre study[b]	Randomized, double-blind study in patients with schizophrenia ($n = 307$), who were randomized into one of five treatment groups	Blonanserin 2.5, 5, or 10 mg or haloperidol 10 mg od or placebo od	- Haloperidol caused persistent elevation in prolactin - There was a lower incidence of the extrapyramidal syndrome with blonanserine 10 mg than with haloperidol 10 mg - Haloperidol and QTc were not studied
(Reade et al., 2009) Dexmedetomidine vs. haloperidol in delirious, agitated, intubated patients: a randomised open-label trial[c]	Randomized, open-label, parallel-group pilot trial in the medical and surgical intensive care unit. 20 patients with delirium	Infusion of either haloperidol 0.5–2 mg/h or dexmedetomidine 0.2–0.7 mcg/kg/h, with or without loading doses of 2.5 mg	- Only one patient prematurely discontinued haloperidol due to QTc interval prolongation

		haloperidol or 1 mcg/kg dexmedetomidine.	- Dexmedetomidine is a promising agent for the treatment of ICU-associated delirious agitation
(Chu et al., 2008) The prophylactic effect of haloperidol plus dexamethasone on postoperative nausea and vomiting in patients undergoing laparoscopically assisted vaginal hysterectomy[b]	Women ($n = 80$ in each five groups) undergoing laparoscopic-assisted vaginal hysterectomy, randomized, double-blind study	After the anesthesia, patients received: 2 mg haloperidol iv or saline or 1.25 mg droperidol or 5 mg dexamethasone or 2 mg haloperidol plus 5 mg dexamethasone to prevent PONV	- No differences were found among the five groups in the side effects of QTc prolongation - Prophylactic haloperidol 2 mg plus dexamethasone 5 mg produced a greater reduction in the incidence of PONV than did either drug used alone, placebo or droperidol
(Grecu et al., 2008) Haloperidol plus ondansetron vs. ondansetron alone for prophylaxis of postoperative nausea and vomiting[c]	Patients undergoing general anesthesia ($n = 260$). Haloperidol plus ondansetron vs. ondansetron alone for prophylaxis of postoperative nausea and vomiting. Randomized, double-blind protocol	Haloperidol 1 mg iv plus ondansetron 4 mg iv or ondansetron 4 mg plus saline iv	- Postoperative nausea and vomiting prophylaxis with both drugs are significantly more effective and longer-lasting than ondansetron alone - QTc prolongation was not different - There is no detectable increase in side effects
(Lee et al., 2007) Haloperidol is as effective as ondansetron for preventing postoperative nausea and vomiting[b,c]	Double-blinded study, patients treated with haloperidol ($n = 45$) or ondansetron ($n = 45$), hospitalized, before the end of surgery	2 mg haloperidol iv, 4 mg ondansetron iv to prevent PONV	- Haloperidol 2 mg iv given 30 min before the end of surgery is effective in preventing PONV - No prolongation of the QTc interval was observed in either group
(Park et al., 2006) Combined effects of itraconazole and CYP2D6*10 genetic polymorphism on the pharmacokinetics and pharmacodynamics of haloperidol in healthy subjects[b,c,d]	19 healthy volunteers whose CYP2D6 genotypes were predetermined were enrolled. The study combined effects of the CYP3A4 inhibitor itraconazole and the CYP2D6*10 genotype on the pharmacokinetics and pharmacodynamics of haloperidol	5 mg haloperidol od po following pretreatment of placebo or itraconazole at 200 mg/d for 10 days in a randomized crossover manner	- QTc prolongation was statistically insignificant in both groups

Clinical studies in PubMed were searched using the following terms.
[a]Haloperidol and delirium and critical illness (10 studies).
[b]Haloperidol and QT prolongation (16 studies).
[c]Haloperidol and QTc prolongation (19 studies).
[d]Haloperidol and long QT (13 studies).

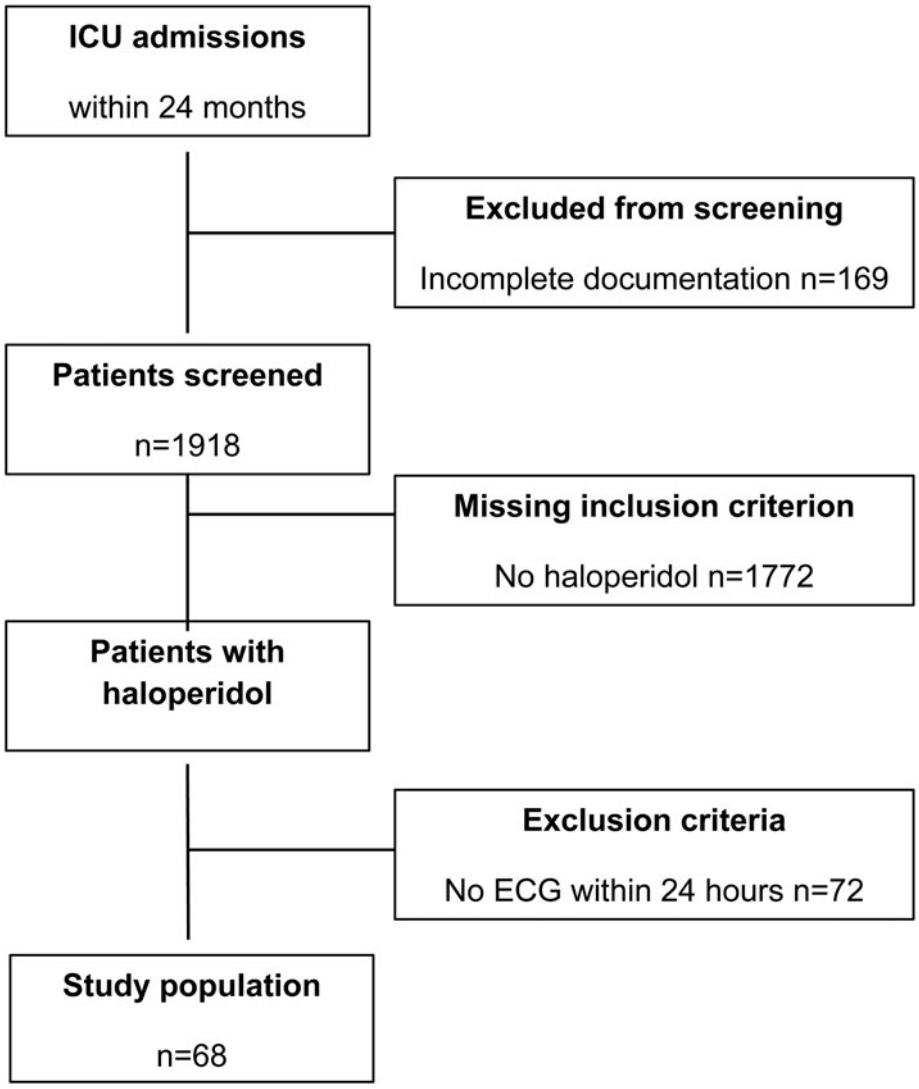

Fig. 1. Exclusion process.

Discussion

Summary of main findings

In this clinical observation study performed in a cardio-surgical ICU, we investigated the relationship between haloperidol administration for delirium and QTc prolongation. First, one-third of patients had a long QT prior to haloperidol administration, and this number did not increase with haloperidol. Second, there was no correlation between haloperidol dose and QTc time, suggesting that haloperidol by itself does not cause relevant QTc prolongations. Third, a detailed analysis between patients with and without a newly onset long QT revealed no significant risk factors. Of note, the time interval between the first dose of haloperidol and the ECG was not different between the two groups. In addition, inter-group differences between the patient with and without a new long QT, the route of haloperidol administration and cumulative haloperidol doses did not exist.

Review of the literature and comparison to the existing literature

The search strategy in PubMed for clinical trials and with the terms "haloperidol and QT prolongation" yielded 16, "haloperidol and QTc prolongation" 19, and "haloperidol and long QT" 13 publications. Further, using the search terms, "haloperidol AND delirium AND critical illness" returned 10 clinical publications. A summary of the 32 retrieved publications is given in Tables 1 and 2. In the more recent studies published between April 2006 and June 2018 (Table 2), the QTc prolongation after haloperidol was considered not significant and across studies, doses were low (between 1 and 5 mg/d). The findings in these studies (Table 2) are comparable with our results. One study (Wang et al., 2012) investigated intramuscular haloperidol at 7.5 and 10 mg separated by 4 h: the changes in QTc from baseline were modest and eventually, no patient displayed a QTc interval ≥480 ms. Another study (van den Boogaard et al., 2013) used haloperidol at 10–30 mg/d; however, the route of administration is unknown, and the effect on QTc was not compared vs. placebo.

Conversely, throughout the publications between March 2001 and October 2004 (Table 1), significant QTc prolongations were reported after haloperidol administration. However, the administration of lower doses of haloperidol (up to 0.25 mg/kg) in split doses was not associated with significant QTc prolongations (Desai et al., 2003a). Similarly, another study was not able to replicate significant QTc prolongation after 15 ± 5 mg/d haloperidol vs. other antipsychotics (Kane et al., 2002).

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Table 3. Reviews and meta-analysis

Author (Reference)	Population (Number of patients, setting)	Haloperidol (Dose, administration)	Main findings
(Wu et al., 2019) Association of delirium response and safety of pharmacological interventions for the management and prevention of delirium: A network meta-analysis[a]	Meta-analysis comparing outcomes (n = 1,435)	Haloperidol plus lorazepam vs. placebo/control group for delirium treatment	- Haloperidol plus lorazepam might be the best treatment - None of the pharmacological interventions for treatment increased the all-cause mortality
(Meyer-Massetti et al., 2010) The FDA extended warning for intravenous haloperidol and torsades de pointes: How should institutions respond?[b]	Patients (n = 70) with iv haloperidol-associated QTc prolongation (QTP) and/or *torsades de pointes* (TdP). Of 54 reports of TdP, 42 events were reportedly preceded by QTP	When post-event QTc data were reported, QTc was prolonged >450 ms in 96% of cases. Three patients experienced sudden cardiac arrest. 68 (97%) had additional risk factors for TdP/QTP, most commonly concomitant proarrhythmic agents	- Patients experiencing TdP received a cumulative dose of haloperidol 5–645 mg iv - Patients with QTP alone received a cumulative dose of 2–1,540 mg iv - While administration of iv haloperidol can be associated with QTP/TdP, this complication most often took place in the setting of concomitant risk factors - Importantly, the available data suggest that a total cumulative dose of iv haloperidol of <2 mg is safe without ongoing electrocardiographic monitoring in patients without concomitant risk factors

ICU, Intensive Care Unit; iv, Intravenously; po, per os; im, Intramuscular; od, once daily; bid, bis in die (twice daily); PONV, Postoperative Nausea and Vomitus.
Clinical studies in PubMed were searched using the following terms.
[a]Haloperidol and delirium and critical illness (10 studies).
[b]FDA haloperidol QTc.

Table 4. Baseline and medical characteristics of patients with new long QT and controls

Parameters	New long QT (QTc) n = 8	Controls n = 60	p
Baseline characteristics			
Age (years)	70 (64–81)	71 (64–78)	0.703
Male gender	8/8 (100%)	44/60 (73%)	0.183
Weight (kg)	77 (72–84)	81 (70–90)	0.549
Height (cm)	172 (164–176)	168 (164–175)	0.727
BMI (kg/m^2)	27 (24–31)	28 (25–31)	0.587
SAPS	39 (33–55)	41 (31–49)	0.607
Delirium diagnosis (ICU day)	2 (1–3)	2 (1–3)	0.358
ICU management at haloperidol start			
On mechanical ventilation	0/8 (0%)	5/60 (8.3%)	1.000
Hemodynamics			
Heart rate (1/min)	90 (66–103)	80 (75–94)	0.848
MAP (mmHg)	73 (70–96)	70 (65–75)	0.133
On noradrenaline	4/8 (50%)	34 (57%)	0.724
Dose (mcg/kg/min) — (n = 34)	0.10 (0.05–0.12)	0.10 (0.05–0.13)	0.924
On inotropes	1/6 (13%)	9/60 (15%)	1.000
On renal replacement therapy	0/8 (0%)	3/60 (5.0%)	1.000
Infections (suspected or proven)	2/6 (25%)	16/60 (27%)	1.000
Laboratory values at the start of haloperidol			
Lactate (mmol/l)	1.15 (0.93–2.68)	1.00 (0.80–1.43)	0.276
Base excess (mmol/l)	−0.80 (−2.43 to 0.05)	−0.65 (−3.03 to 0.53)	0.985

(*Continued*)

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Table 4. (*Continued.*)

Parameters	New long QT (QTc) $n = 8$	Controls $n = 60$	p
$ScvO_2$ (%)	65 (57–68)	69 (62–74)	0.189
Hemoglobin (g/l)	82 (80–91)	88 (80–100)	0.360
White blood cell count (G/l)	8.0 (6.5–11.5)	10.1 (7.6–11.8)	0.223
C-reactive protein	154 (90–205)	89 (30–154)	0.069
Creatinine	92 (74–113)	101 (82–137)	0.282
GOT (U/L)	49 (41–80)	49 (33–84)	0.939
GPT (U/L)	25 (19–33)	26 (19–44)	0.668
Creatinine kinase (U/l)	443 (200–834)	398 (189–883)	0.805
Myoglobine (mcg/l)	209 (126–293)	279 (155–640)	0.196
Troponine (mcg/l)	0.68 (0.48–1.12)	0.57 (0.32–1.21)	0.596
Calcium ionized (mmol/l)	1.17 (1.16–1.23)	1.20 (1.17–1.22)	0.640
Sodium (mmol/l)	139 (138–141)	140 (137–142)	0.472
Potassium (mmol/l)	4.75 (4.6–5.0)	4.90 (4.6–5.0)	0.766
Magnesium (mmol/l)	0.93 (0.87–1.05)	0.99 (0.90–1.14)	0.230
Haloperidol			
Administration			
Enteral	0/8 (0%)	5/60 (8.3%)	0.417
Intravenous	8/8 (100%)	49/60 (82%)	
Enteral and intravenous	0/8 (0%)	6 (10%)	
Cumulative dose (mg)	7 (3–13)	4 (2–7)	0.165
Interval between first and last dose (h)	8.7 (1.1–16)	5.6 (0.8–15)	0.661
Interval between first dose and ECG follow-up (h)	6.9 (3.5–17)	6.7 (2.0–13)	0.549
QTc interval			
QTc baseline (ms)	432 (408–439)	434 (414–462)	0.253
QTc after haloperidol (ms)	468 (455–481)	433 (415–449)	**0.001**
QTc prolongation (ms)	50 (21–63)	−1 (−26 to 27)	**<0.001**
Anti-delirant medication			
Pipameron	6/8 (75%)	36/60 (60%)	0.701
Dose (mg) — ($n = 42$)	70 (55–130)	60 (40–115)	0.292
Drugs with effects on QTc time			
Amiodarone	1/8 (13%)	10/60 (17%)	1.000
Dose (mg)	150	450 (263–1200)	0.187
Antibiotics	8/8 (100%)	53/60 (88%)	0.587
Other QT prolonging drugs	0/8 (0%)	8 (13%)	0.582
Outcome			
ICU LOS	6 (4–9)	7 (4–10)	0.723
ICU survival	8/8 (100%)	60/60 (100%)	1.000

Results are represented as median (interquartile range). Controls are patients preexisting long QT at baseline ($n = 21$) and normal QTc time after haloperidol administration ($n = 39$).

In addition, a cumulative dose of haloperidol <2 mg intravenously was safely administrated in patients without concomitant risk factors without ongoing electrocardiographic monitoring (Lin et al., 2010).

This might support the notion as shown in mortalities on methadone that an additive in addition to high dosing might have been responsible for the past reports on QTc prolongation, *torsades de pointes*, and sudden cardiac death (Kornick et al., 2003). Commonly overseen, haloperidol, like most first-generation antipsychotics, has multiple neurotoxic effects vs. second-generation antipsychotics (Nasrallah and Chen, 2017) and the *in vivo* extent of this neurotoxicity remains understudied.

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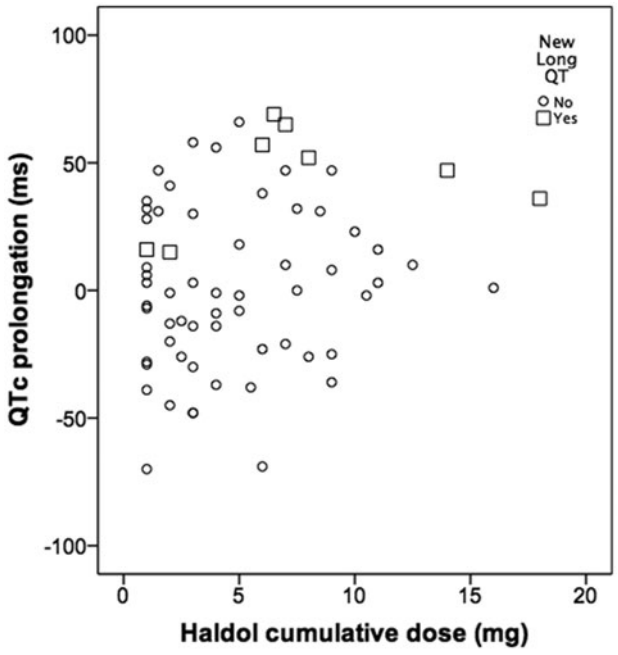

Fig. 2. Correlation between haloperidol dose and QTc intervals. Pearson correlation coefficient: new long QT (squares, $n = 8$): $r = 272$, $p = 0.515$; Controls (circles, $n = 60$): $r = 0.082$, $p = 0.536$.

Strengths and limitations of the study

This study had few strengths and limitations: over 2 years, 2,216 patients were screened and systematically assessed. Eventually, few patients could be included, preventing the meaningful use of multivariate testing. Apparently, haloperidol was not the first-line treatment of delirium in this ICU — vs. the α-2 agonists clonidine and dexmedetomidine — but reserved for delirious patients with predominant hallucinations and/or aggressive behavior. Further, it was not possible to collect all relevant parameters relevant to QTc interval prolongation; however, this effect might be negligible. Of note, one-third of patients had a long QT before starting haloperidol. Further with a randomized controlled design are required to confirm these findings.

Interpretation

Low-dose intravenous haloperidol is not clinically relevant as risk factor for the development of a newly onset long QT syndrome: For (1) the number of patients with long QT did not increase with haloperidol administration; (2) there was no dose-dependent effect of haloperidol on QTc intervals; and (3) no inter-group differences between the oral and intravenous formulation existed. These results are supported by recent publications inside and outside the ICU setting, and hence, the requirement of ECG monitoring when administering intravenous haloperidol might be unnecessary.

Generalizability

One strength of this study was its setting, the daily clinical practice. However, only ICU patients post major cardiovascular surgery, a vulnerable population for the development of arrhythmia, was included. Underlying cardiac diseases, as well as the cardiac surgery by themselves, represent risk factors for the development of long QT. Hence, these findings may overestimate the frequency of long QT syndromes vs. other critically ill patients. Further studies may benefit from the inclusion of other clinical settings.

Conclusions

In this clinical observation study performed in a cardio-surgical ICU, we investigated the relationship between haloperidol administration for delirium and QTc prolongation. These results indicate the safety of low-dose intravenous haloperidol in the management of delirium; thus, haloperidol did not represent a clinically relevant risk factor for the development of a new long QT syndrome and further support recent publications investigating the safety of low-dose haloperidol inside and outside the ICU setting. Hence, the requirement of cardiac monitoring when administering intravenous haloperidol is questionable for delirious patients suffering from hallucinations and aggressive behavior.

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Conflict of interest. There are no conflicts of interest.

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