

IN-HOSPITAL HALOPERIDOL USE AND PERIOPERATIVE CHANGES IN QTc-DURATION

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Abstract: *Objectives:* Haloperidol may prolong ECG QTc-duration but is often prescribed perioperatively to hip-fracture patients. We aimed to determine (1) how QTc-duration changes perioperatively, (2) whether low-dose haloperidol-use influences these changes, and (3) which clinical variables are associated with potentially dangerous perioperative QTc-prolongation (PD-QTc; increase >50 ms or to >500 ms). *Design:* Prospective cohort study. *Setting:* Tertiary university teaching-hospital. *Participants:* Patients enrolled in a randomized controlled clinical trial of melatonin versus placebo on occurrence of delirium in hip-fracture patients. *Measurements:* Data from ECGs made before and after hip surgery (1-3 days and/or 4-6 days post-surgery) were analyzed. QTc-duration was measured by hand, blinded for haloperidol and pre/post-surgery status. Clinical variables were measured at baseline. Mixed model analysis was used to estimate changes in QTc-duration. Risk-factors for PD-QTc were estimated by logistic regression analysis. *Results:* We included 89 patients (mean age 84 years, 24% male); 39 were treated with haloperidol. Patients with normal pre-surgery QTc-duration (male ≤430 ms, female ≤450 ms) had a significant increase (mean 12 ms, SD 28) in QTc-duration. A significant decrease (mean 19 ms, SD 34) occurred in patients with prolonged pre-surgery QTc-duration (male >450ms, female >470 ms). Haloperidol-use did not influence the perioperative course of the QTc-interval (p=0.351). PD-QTc (n=8) was not associated with any of the measured risk-factors. *Conclusion:* QTc-duration changed differentially, increasing in patients with normal, but decreasing in patients with abnormal baseline QTc-duration. PD-QTc was not associated with haloperidol-use or other risk-factors. Low-dose oral haloperidol did not affect perioperative QTc-interval.

Key words: QTc-prolongation, haloperidol, perioperative period.

Introduction

Haloperidol has for many years been a widely prescribed drug for the treatment of agitation, delirium, and psychoses. Although it is highly effective for these conditions, its use is hampered by concerns that it may cause lethal cardiac arrhythmias (Torsade de Pointes, TdP) (1-4). Such arrhythmias are caused by haloperidol's ability to block the delayed rectifier cardiac potassium channel (5-8) and heralded by QTc-prolongation on the ECG (9-14). Accordingly, clinicians are advised to monitor QTc-duration during haloperidol use (3, 12, 15). Also, identification of other risk factors for QTc-prolongation is relevant. Some risk factors are well-known, e.g., concomitant QT-prolonging drug use, and hypokalemia. We recently found indications in a cohort of older, hospitalized patients that other lesser-known stressors may have such great impact on QTc-duration that they mask the potential QTc-prolonging effects of haloperidol (16). In that cohort with multiple morbidities and co-medications, surgery was the factor most strongly associated with post-haloperidol QTc-prolongation. It is clinically relevant to establish in detail how surgery affects QTc-duration in this older, comorbid patient category, and how haloperidol use impacts on the course of perioperative QTc-duration, because these patients often

require haloperidol for delirium control (17).

In the present follow-up study, we therefore aimed to address the following questions: (1) how does QTc-duration change perioperatively? (2) does low-dose haloperidol influence these changes? (3) which clinical variables are associated with potentially dangerous QTc-prolongation?

Methods

Study population and design

For the current study we used data of patients from a randomized trial (N=452) of melatonin versus placebo on the occurrence of delirium in hip fracture patients (Trial registration number NTR1576) (18). This trial was carried out between November 2008 and May 2012 in one academic hospital and one non-academic hospital. Patients were selected for the present study if a pre-operative and at least one post-operative ECG were made. In all trial participants, a pre-operative ECG (T0) was performed. Prospective gathering of post-operative ECGs started in December 2011 at 1-3 days (T1) and/or 4-6 days (T2). To enlarge our study population, enrolled patients from the academic hospital before December 2011 were also included (retrospectively) if clinical post-operative ECGs had been performed.

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The study was conducted according to the principles expressed in the Declaration of Helsinki. All participating patients were asked for written informed consent if additional investigations were made, and all data were analyzed anonymously. The medical ethics committee of the Academic Medical Center (Amsterdam, The Netherlands) approved the study.

ECG Measurements

All ECGs were analyzed separately by two researchers (MB and SJ), who were blinded for pre/post-surgery and haloperidol status. QT durations were measured by hand and corrected for heart rate using Bazett's formula (QTc) (19). All ECG measurements at T0, T1, and/or T2 were analyzed in the same lead for each patient, based on the best readable recording. If there was >10 msec difference in QTc-duration between the measurements of both researchers, the QT-interval was re-evaluated together. In case of atrial fibrillation or irregular heart rates, the mean of all RR-intervals in the recording was used for rate correction. Patients who had pacemaker beats or whose QTc-duration could not be reliably measured (typically due to flat T-waves) were excluded from further analysis.

To analyze whether the QTc-duration before surgery influenced the amount of change in QTc-duration, we stratified the patients into three subgroups of before-surgery QTc-duration, based on the European Society of Cardiology Guidelines (20): 1) Normal (male ≤ 430 ms, female ≤ 450 ms), 2) Borderline (male 431-450 ms, female 451-470 ms), and 3) Abnormal (male >450 ms, female >470 ms). Potentially dangerous QTc-prolongation was defined as an increase in QTc-duration (T0-T1 or T0-T2) by >50 ms or to a QTc-duration of >500 ms (13).

Haloperidol status

Of all patients, haloperidol status was determined at each ECG recording. Since the time interval between the ECG recordings was relatively short, and the elimination half-life of haloperidol long (21), all ECGs were considered as affected by haloperidol once haloperidol was administered (T0 and/or T1). The same applied for concomitant QT-prolonging medication.

Covariates

Of each patient, we collected age, sex, Charlson comorbidity index (CCI) (22), use of haloperidol, and delirium status from the trial's clinical research file. For the diagnosis of delirium, assessed daily, the DSM-IV criteria were used (23). The use of other QT prolonging drugs (24) at baseline, leukocyte count, and serum sodium, potassium and CRP level (measured within 72 hours before surgery) were derived from hospital records. Signs of an acute phase response or inflammation were defined as serum CRP level >100 mg/l, or leukocyte count $>10 \times 10^9/L$.

Data analysis

We used conventional ANOVA and chi-square statistics to evaluate differences per group (using Pearson and Fisher's Exact test where appropriate). In non-normally distributed data, we used Mann-Whitney U and Kruskal-Wallis non-parametric tests. The course of perioperative QTc-duration (T0-T1-T2), and differences in this course per subgroups (according to pre-surgery QTc-duration), was tested for significant change using a mixed model analysis assuming fixed effects, thereby accounting for changes in relevant clinical factors. We evaluated associations with age, sex, haloperidol use, concomitant use of QTc-prolonging medication, CCI, signs of inflammation, delirium status, serum sodium and potassium levels, and ECG parameters. As this study was set up as a substudy of an RCT studying the effect of melatonin on the incidence of delirium in patients admitted for hip-fracture, we also evaluated whether treatment arm was associated with QTc-duration.

Factors that were univariately associated ($p < 0.20$) with before-surgery QTc-duration, perioperative change in QTc-duration (T0-T1 or T0-T2), or baseline subgroup stratification (based on QTc-duration), were entered in the mixed model analysis. The final models estimated changes in perioperative QTc-duration while accounting for relevant variables (backward selection with $p < 0.05$). To test the possibility that an above normal QRS-width influenced observed QTc-duration, we performed a second analysis in which we used the QTc-duration minus excess QRS-duration (i.e., QRS width minus 110 ms) as the dependent variable.

To analyze whether haloperidol influenced the perioperative course of QTc-duration (T0-T1-T2), we compared patients who used no haloperidol at T0 but had used haloperidol shortly before T1, with patients who did not receive haloperidol at any time during our study period. The same methods as described above were deployed to test whether haloperidol significantly influenced the perioperative course of QTc-duration.

Risk factors for potentially dangerous QTc-prolongation were analyzed using logistic regression. If factors were associated with a $p < 0.20$ in the univariate analyses they were entered into a multivariate model. Effect sizes were expressed in odds ratios (OR) with their corresponding 95% confidence intervals (CI) and p-values.

Data are expressed as mean \pm standard deviation (SD), unless otherwise indicated. All data were analyzed using the statistical software package of SPSS (SPSS for Mac, version 20.0, SPSS Inc.).

Results

Between November 2008 and May 2012, 452 participants were enrolled in the trial (figure 1). In 96 participants, ECGs were performed both before and after surgery (58 with prospective after-surgery ECG). Patients in whom repeated ECG recordings were made did not differ regarding age

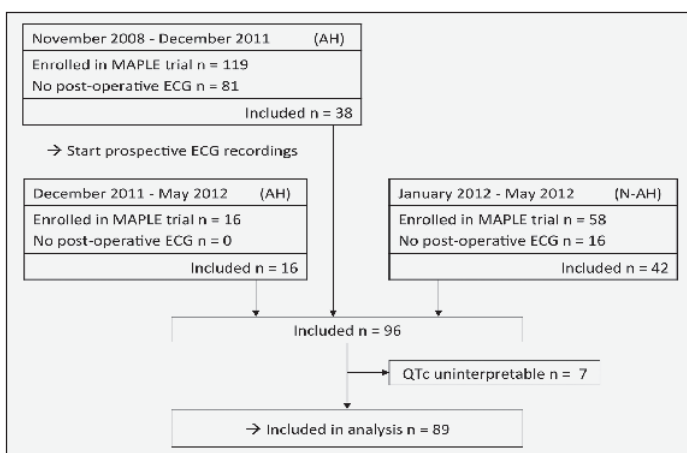
Table 1
Patient characteristics at T0

	All patients (n=89)	Normal (n=42)	Borderline (n=20)	Abnormal (n=27)	p-value
Male, n (%)	21 (23.6)	7 (16.7)	4 (20.0)	10 (37.0)	0.157
Age, years, mean (SD)	83.8 (13.5)	83.7 (8.7)	80.5 (24.1)	86.5 (7.4)	0.326
QTc-duration, ms, mean (SD)	445.0 (33.3)	416.5 (20.3)	455.8 (12.0)	481.3 (14.9)	<0.001
Heart rate, beats per minute, mean (SD)	78.0 (14.7)	79.6 (16.3)	76.6 (11.7)	76.6 (14.2)	0.621
QRS width, ms, mean (SD)	94.2 (20.1)	87.1 (14.7)	93.4 (17.0)	105.7 (24.5)	0.001
Atrial fibrillation, n (%)	12 (13.5)	6 (14.3)	2 (10.0)	4 (13.5)	1.000
Bundle branch blocks, n (%)	12 (13.5)	2 (4.8)	2 (10.0)	8 (29.6)	0.013
Haloperidol prescribed, n (%)	39 (43.8)	20 (47.6)	7 (35.0)	12 (44.4)	0.643
Other QT-prolonging drugs prescribed, n (%)	5 (5.6)	1 (2.4)	1 (5.0)	3 (11.1)	0.301
Charlson comorbidity index score, median (IQR)	1 (0, 2)	1 (0, 2)	1 (0.25, 2)	1 (1, 2)	0.366
Delirium during study period, n (%)	33 (37.1)	17 (40.5)	5 (25.0)	11 (40.7)	0.446
Signs of inflammation, n (%)	38 (42.7)	21 (50.0)	7 (35.0)	10 (37.0)	0.416
Serum sodium level, mmol/l, mean (SD)	139.2 (4.5)	138.3 (4.4)	139.0 (4.4)	140.9 (4.5)	0.068
Serum potassium level, mmol/l, mean (SD)	4.0 (0.5)	4.1 (0.6)	4.0 (0.5)	4.0 (0.6)	0.291

IQR: Inter quartile range, SD: Standard deviation. Normal: T0 QTc-interval male ≤ 430 ms, female ≤ 450 ms. Borderline: T0 QTc-interval male 431-450 ms, female 451-470 ms. Abnormal: T0 QTc-interval male >450 ms, female >470 ms; P-values were calculated with Pearson chi-square test or Fischer's Exact test where appropriate for dichotomous data, and with ANOVA for continuous data. P-value for Charlson Comorbidity Index was calculated with Kruskal Wallis test.

and sex to those in whom no repeated ECGs were made. Included patients had slightly lower Charlson Comorbidity index than excluded patients (mean=1.3, median=1.0 vs. mean=1.6, median=1.0 respectively, $p=0.022$). In seven of these 96 participants, ECG abnormalities hindered a reliable measurement of QT duration; these participants were excluded, yielding a study population of 89 patients for final analysis. Treatment arm of the RCT was not associated with QTc-duration ($p=0.772$).

Figure 1
Patient inclusion



AH: academic hospital, N-AH: non-academic hospital

Table 1 presents baseline characteristics of the study population. Mean age was 83.8 ± 13.5 years, and 24% was male. Thirty-seven percent of patients suffered a delirium during

enrollment and 43% showed signs of inflammation. Forty-four percent of patients received haloperidol in the perioperative period at median daily dose of 1 mg (Interquartile range 0.78-1.29), all administered orally. Six percent used other QTc prolonging drugs: citalopram (n=5), sotalolol (n=4), flecainide (n=3) and amiodarone (n=3).

In our overall study population, we found no difference in QTc-duration between T0, T1 and T2 (Figure 2, panel A). However, patients with normal QTc-duration at T0 exhibited significant QTc-prolongation post-surgery (12 ± 28 ms [$p=0.009$]); in 10% of these patients, QTc-interval rose to abnormal levels. In contrast, patients with prolonged QTc-duration at T0 showed significant QTc-shortening post-surgery (-19 ± 34 ms [$p=0.006$]), although 56% retained abnormal levels. Patients with borderline prolonged QTc-duration at T0 exhibited no change in QTc-duration post-surgery.

Overall, after adjusting for relevant covariates (sex and QRS-duration), the interaction between baseline QTc-subgroup and time of ECG measurement (T0, T1 and T2) was significant ($p<0.001$), indicating that pre-surgery QTc-interval (normal, borderline and abnormal) significantly impacts the course of the perioperative QTc-interval. Repeating the analysis with QRS-duration subtracted from the measured QTc-duration did not yield different results. Also, the course of perioperative QTc-changes was not affected by the nature of the source population (ECG made for research or clinical purposes).

Supplemental table 1 shows baseline characteristics according to haloperidol use at T1. We excluded patients who used haloperidol at T0, and those who started haloperidol use at T2 (instead of T1), resulting in n=76. Patients receiving haloperidol were older (88 vs. 81 years, $p=0.046$), and had, as

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Table 2
Odds Ratios for potentially dangerous QTc-prolongation

	Potentially dangerous QTc-prolongation		OR	Univariate OR	
	Yes (n=8)	No (n= 81)		95% CI	p-value
Male, n (%)	1 (13%)	20 (25%)	0.4	0.05 – 3.8	0.450
Age, years, mean (SD)	86.7 (10.0)	83.5 (13.8)	1.0	0.9 – 1.1	0.493
QTc-duration, ms, mean (SD)	454.5 (46.2)	444.0 (32.0)	1.01	0.99 – 1.03	0.395
QTc group before surgery					
Normal, n (%)	3 (38%)	39 (48%)	Reference		
Borderline, n (%)	2 (25%)	18 (22%)	1.4	0.2 – 9.4	0.701
Abnormal, n (%)	3 (38%)	24 (30%)	1.6	0.3 – 8.7	0.571
Heart rate, beats per minute, mean (SD)	74.5 (10.1)	78.4 (15.1)	0.98	0.98 – 1.04	0.476
QRS width, ms, mean (SD)	92.5 (16.2)	94.4 (20.5)	1.00	0.96 – 1.03	0.804
Atrial fibrillation, n (%)	2 (25%)	10 (12%)	2.4	0.4 – 13.4	0.330
Right or left bundle branch block, n (%)	1 (13%)	11 (14%)	0.9	0.1 – 8.1	0.909
Charlson comorbidity index score, median (IQR)	1.0 (1,3)	1.0 (0,2)	1.1	0.7 – 1.8	0.666
Delirium during study period, n (%)	3 (38%)	30 (37%)	1.02	0.2 – 4.6	0.979
Haloperidol prescribed, n (%) (T1 or T2)	5 (63%)	32 (40%)	2.6	0.6 – 11.4	0.221
QT-prolonging drugs, n (%) (T1 or T2)	0 (0%)	5 (6%)			0.617
Serum sodium level, mmol/l, mean (SD)	138.0 (5.0)	139.4 (4.5)	0.94	0.8 – 1.09	0.417
Serum potassium level, mmol/l, mean (SD)	4.1 (0.6)	4.0 (0.5)	1.2	0.3 – 4.6	0.766
Signs of inflammation, n (%)	4 (50%)	34 (42%)	1.4	0.3 – 5.9	0.663

95% CI: 95% confidence interval, IQR: inter quartile range, OR: odds ratio, SD: standard deviation. QT-prolonging drugs: citalopram, sotalol, flecainide, amiodarone; P-value for QT-prolonging drugs was calculated with Fisher's Exact test.

expected, more often a delirium (70.8 vs. 19.2%, $p < 0.001$).

Mean QTc-duration did not differ per haloperidol status for ECGs made at T0 and T1 (figure 2, panel B and C, all patients). Although mean QTc-duration was different for patients with or without haloperidol use at T2, this difference was not statistically significant ($p = 0.178$). When stratifying according to pre-operative QTc-interval (normal, borderline, abnormal) the pattern of perioperative QTc-change was not different for patients with or without haloperidol use. However, at T2, numbers per group after stratification were too small to make meaningful comparisons.

Mixed models analysis showed that, after adjusting for relevant covariates (sex and QRS-duration), the course of changes in QTc-duration was not significantly different between patients with or without haloperidol use ($p = 0.351$). Use of other QTc-prolonging medication also did not significantly influence the perioperative course of QTc-duration.

Eight patients (9%) developed potentially dangerous QTc-prolongation post-surgery, three (38%) of whom had a normal before-surgery QTc-duration. In five patients, QTc-duration increased to >500 ms. No TdP episodes were documented. We analyzed factors associated with dangerous QTc-prolongation (Table 2). No risk factors showed significant ORs in the

univariate analysis. Therefore, a multivariate analysis was not performed.

Discussion

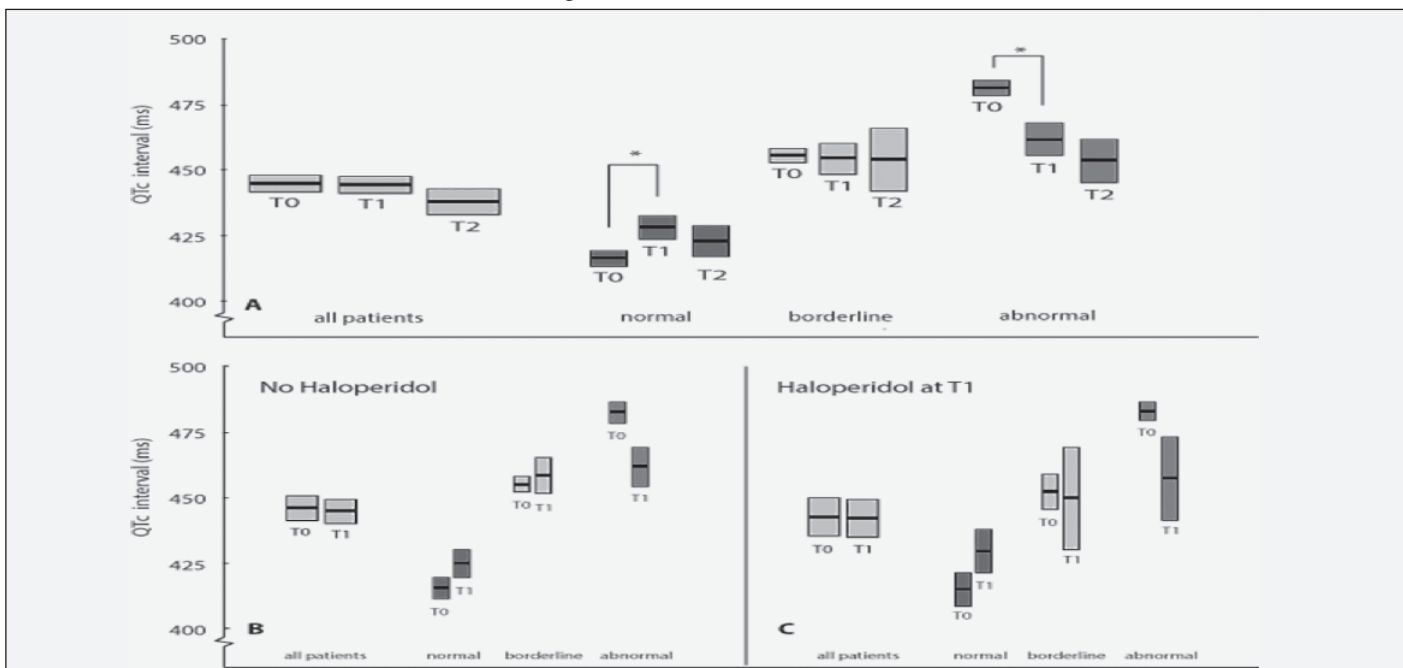
Main findings

In this real-life study among old-age hospitalized patients with multiple co-morbidities undergoing hip surgery, perioperative QTc-durations changed differentially. Substantial QTc-prolongation occurred predominantly in patients with normal before-surgery QTc-duration. Conversely, in most patients with abnormal before-surgery QTc-duration, QTc-shortening occurred. Changes in perioperative QTc-duration were not influenced by low-dose haloperidol use.

Perioperative QTc-prolongation

There are few studies that have analyzed QTc-intervals in the perioperative period. Nagele et al. (25) found that 80% of patients undergoing non-cardiac surgery experienced a significant prolongation of QTc-interval during surgery (with an average increase of 23 ms), whereas 18% of patients had a shortening of QTc-interval. However, age and gender distribution was different (with the present study concerning older patients), and patients were not stratified according to

Figure 2
Perioperative course of QTc-duration



Bars represent mean \pm standard error. Normal: T0 QTc-interval male \leq 430 ms, female \leq 450 ms. Borderline: T0 QTc-interval male 431-450 ms, female 451-470 ms. Abnormal: T0 QTc-interval male $>$ 450 ms, female $>$ 470 ms. Panel A) All patients; T0: n=89, T1: n=88, T2: n=45. Normal subgroup; T0: n=42, T1: n=42, T2: n=23. Borderline subgroup; T0: n=20, T1: n=19, T2: n=11. Abnormal subgroup; T0: n=27, T1: n=27, T2: n=11. Panel B) Patients without haloperidol during study period. All patients; T0: n=52, T1: n=52. Normal subgroup; T0: n=23, T1: n=23. Borderline subgroup; T0: n=13, T1: n=13. Abnormal subgroup; T0: n=16, T1: n=16. Panel C) Patients with haloperidol prescribed at T1 (and no haloperidol at T0). All patients; T0: n=24, T1: n=23. Normal subgroup; T0: n=12, T1: n=12. Borderline subgroup; T0: n=5, T1: n=4. Abnormal subgroup; T0: n=7, T1: n=7.

baseline QTc-duration, which hinders a good comparison with our results.

The results of our study are, however, in line with the results of our previous (retrospective) study in which we analyzed QTc-intervals of patients before, during and after low-dose haloperidol use (16). In that study, we found that the course of change in QTc-duration depends primarily on baseline QTc-duration. Surgery and baseline QTc-interval were independently associated with potentially dangerous QTc-prolongation. In the present prospective study, too, we found that (perioperative) QTc-intervals changed differentially, increasing in patients with normal pre-surgery QTc-intervals and decreasing in patients with abnormal pre-surgery QTc-intervals.

A possible explanation for these observations is the 'regression-to-the-mean' phenomenon (26), as, in the course of time, shorter QTc-intervals increased and longer intervals normalized. This phenomenon is known to occur in randomly distributed data. However, since the QTc-interval is generally not regarded as a random value, we do not expect that our results can be solely attributed to regression-to-the-mean, although we do expect intrinsic variability in QTc-interval to play an important role in our findings. It has been argued that the mean of at least three QTc-measurements at different times during the day should be used when studying QTc-changes (27). In clinical practice, however, decisions regarding the

QTc interval are usually based on a measurement from a single ECG recording. Arguably, the importance of intrinsic QTc-variability is underestimated in many studies, but exceptionally difficult to establish within observational study designs.

Haloperidol and QTc-interval

In the present study population, use of low-dose oral haloperidol was not associated with perioperative QTc-interval prolongation. Although in line with our previous results, this contradicts results of other studies, which found that QTc-interval increases upon haloperidol administration. However, most of these studies were carried out with high doses of intravenous haloperidol (14, 28), whereas current guidelines of delirium treatment advise to use haloperidol at the lowest possible dose (29). Previous studies that assessed the influence of oral haloperidol on the QTc-interval have been carried out in healthy volunteers or psychiatric patients, and show contradicting evidence. Desai et al. found that healthy subjects had a significantly greater mean QTc-duration (mean increase of 13 ms) upon administration of a single oral dose of haloperidol (10 mg) than upon placebo (30). Miceli et al. found that QTc-interval in haloperidol-treated patients increased with dose in patients with schizophrenia or schizoaffective disorder (31). However, maximum increase of QTc-interval (7.2 ms) was found at oral doses of 30 mg/day, which is considerably higher than the dose of haloperidol that our study

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subjects received. In none of the study subjects did QTc-duration rise to >450 ms during haloperidol use. Furthermore, although these studies show that QTc-duration increases upon (increasing doses of) oral haloperidol, maximum increase was <15 ms. The clinical implication of this increase is disputable. By contrast, Fulop et al. found that QTc-duration was not influenced by oral haloperidol (maximum dose of 10 mg daily) in forty patients with Tourette's syndrome (32). Interestingly, the differential pattern of perioperative QTc-interval changes stratified according to baseline QTc-subgroup was still visible when patients without haloperidol use were compared with those with haloperidol. Apparently, the influence of haloperidol on QTc-interval (if any at all) is smaller than of other factors that determine the observed pattern.

Potentially dangerous QTc-prolongation

In the present study that addresses an older population, potentially dangerous QTc-prolongation was rare. Also, among those who showed potentially dangerous QTc-prolongation, no TdP episodes were reported. This is a surprising finding, since we previously found surgery before haloperidol use to be a strong risk factor for potentially dangerous QTc-prolongation. Furthermore, we did not find any of the other known risk factors (33) to be associated with a rise in QTc-duration to potentially dangerous levels. Remarkably, neither was the use of haloperidol or other QTc-prolonging medication. Baseline increased QTc-interval is generally regarded as a contra-indication for the administration of QTc-prolonging drugs, such as haloperidol. The results of our studies do not support this recommendation for low dose oral prescriptions of haloperidol.

Strengths and limitations

The present study has several strengths. Our study population was a representative sample of prospectively included older hip-fracture patients with several co-morbidities. This allowed for a realistic assessment of risk of QTc-prolongation in this frail population, in a situation where haloperidol is often prescribed. Patient inclusion was part of a clinical trial, which allowed for comprehensive and reliable ascertainment of clinical information. A broad spectrum of clinical parameters was analyzed along with medication use. All QTc-intervals were measured manually by two independent researchers who were blinded for pre/post surgery and haloperidol status, which ensured reliable outcome measurements.

Some limitations must be mentioned, however. The observational design of our study limits the interpretation of our results. As clinicians are currently discouraged to prescribe QTc-prolonging drugs to patients with a prolonged QTc-interval at baseline, a possible inclusion bias may have occurred. However, we observed no baseline differences in QTc duration between patients who were or were not prescribed haloperidol. Also, our patient group consisted of older persons in need of a traumatic hip-surgery, and our results may not be representative for other (older) patient

groups. Lastly, we included 38 patients of whom the post-operative ECGs were made on indication instead of for research purposes, which may have influenced our results. However, these patients were not different in any of the studied variables, and source population did not affect results in our logistic regression and mixed model analyses.

Conclusions and recommendations

In this old-age in-hospital population, perioperative QTc-durations changed differentially, increasing in patients with normal, but decreasing in patients with abnormal baseline QTc-duration. Changes in perioperative QTc-duration were not influenced by low-dose haloperidol use. In conclusion, low-dose haloperidol use does not appear to pose a risk for QTc-prolongation in this population. Nonetheless, these assuring results need confirmation in other populations before a firm recommendation can be made to omit pre-haloperidol ECG recording as a standard measure in hospital care. We recommend studying patient files for possible risk factors for QTc-prolongation when prescribing haloperidol.

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Author contributions: all authors were involved in study concept and design, analysis and interpretation of data and preparation of manuscript. SJ and MB were involved in acquisition of data.

Sponsor's role: none

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Supplemental table 1
Patient characteristics at baseline, use vs. non-use of haloperidol post surgery

	Use of haloperidol (n=24)	No use of haloperidol (n=52)	p-value
Male, n (%)	5 (20.8)	13 (25.0)	0.691
Age, years, mean (SD)	88.1 (5.7)	81.1 (16.3)	0.046
QTc-duration, ms, mean (SD)	442.8 (34.9)	446.2 (33.4)	0.683
Baseline QTc-interval subgroup, n (%)			0.881
Normal	12 (50.0)	23 (44.2)	
Borderline	5 (20.8)	13 (25.0)	
Abnormal	7 (29.2)	16 (30.8)	
Heart rate, beats per minute, mean (SD)	74.3 (12.7)	77.6 (12.8)	0.304
QRS width, ms, mean (SD)	90.0 (15.4)	94.4 (20.4)	0.356
Atrial fibrillation, n (%)	3 (12.5)	6 (11.5)	1.000
Bundle branch blocks, n (%)	2 (8.3)	7 (13.5)	0.711
Other QT-prolonging drugs prescribed, n (%)	0 (0.0)	4 (7.7)	0.301
Charlson comorbidity index score, median (IQR)	1 (0, 2)	1 (1, 2)	0.971
Delirium during study period, n (%)	17 (70.8)	10 (19.2)	<0.001
Signs of inflammation, n (%)	8 (33.3)	23 (44.2)	0.369
Serum sodium level, mmol/l, mean (SD)	139.3 (4.2)	138.8 (5.0)	0.689
Serum potassium level, mmol/l, mean (SD)	4.0 (0.6)	4.1 (0.6)	0.643

IQR: Inter quartile range, SD: Standard deviation. Other QT-prolonging drugs prescribed: citalopram, sotalol, flecainide and amiodarone; P-values were calculated with Pearson chi-square test or Fischer’s Exact test where appropriate for dichotomous data, and with ANOVA for continuous data. p-value for Charlson Comorbidity Index was calculated with Mann Whitney U test.