Should we still monitor QTc duration in frail older patients on low-dose haloperidol? A prospective observational cohort study

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RESEARCH PAPER

Should we still monitor QTc duration in frail older patients on low-dose haloperidol? A prospective observational cohort study

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Abstract

Background: Haloperidol at high dosage is associated with QTc prolongation and polymorphic ventricular arrhythmia but the effects of low-dose haloperidol remain unknown.
Objective: To evaluate the effects of low-dose haloperidol on QTc-duration in frail hospitalized elderly patients with delirium.
Methods: A prospective observational study including hospitalized patients aged ≥70 years with Groningen Frailty Index-score > 3. We included 150 patients who received haloperidol and 150 age- and frailty-matched control patients. Serial ECG recordings were performed at hospital admission and during hospitalization. QT-interval was corrected according to Framingham (QTc). Patients were grouped according to baseline QTc in normal (nQTc), borderline (bQTc) or abnormal (aQTc). Primary outcome was change in QTc-duration between first and second ECG. Potentially dangerous QTc was defined as QTc >500 ms or an increase of >50 ms.
Results: Patients in the haloperidol group (48% male, mean age 85y, nQT n = 98, bQT n = 31, aQT n = 20) received an average dose of 1.5 mg haloperidol per 24 hours. QTc decreased in patients with borderline (mean − 15 ± 29 ms, $P < 0.05$) or abnormal (−19 ± 27 ms, $P < 0.05$) QTc at baseline, no patients developed dangerous QTc-duration. In the control group (41% male, mean age 84y, nQT n = 99 bQT n = 29, aQT n = 22) QTc decreased to a similar extent (bQT −7 ± 16 ms, aQTc −23 ± 20 ms).
Conclusion: A trend to QTc shortening was seen, especially in patients with borderline or abnormal QTc at baseline, regardless of haloperidol use. These findings suggest that ECG monitoring of frail elderly patients who receive low-dose haloperidol, may not be necessary.

Keywords: haloperidol, corrected QT interval, older people, delirium, frailty

Key points

- ECG monitoring may not be necessary.
- A prospective observational study including frail, older patients (≥70 years) with delirium.
- No frail, older patients with delirium developed a dangerous QTc duration when using low-dose haloperidol.

Introduction

As the older population is increasing, it is estimated that in 2080, 29% of the European population will be 65 or older [1]. Frailty increases disability, dependency, traumatic falls, functional decline, need for long-term medical care and mortality [2]. Up to 37% of hospitalised older people develop delirium [3–7], associated with poor medical outcomes [3–7], increased length of hospital stay and higher health care costs [8]. Efficient diagnosis and treatment of delirium will be one of the major challenges for the future.

Pharmacological therapy may be needed to treat symptoms such as agitation, hallucinations and aggression. The drug of first choice remains haloperidol at the lowest clinically appropriate dose with cautious up-titration according to symptoms [3]. Haloperidol is a typical butyrophenone-type antipsychotic with minimal sedating effects. Although proven effective in clinical practice [9,10], haloperidol has been associated with rate-corrected QT interval (QTc) prolongation on the electrocardiogram (ECG) by its blockade of the cardiac human ether-a-go-go–related gene potassium channels [11–15]. QTc prolongation is a known risk factor for the development of polymorphic ventricular arrhythmias (Torsade de Pointes), which are associated with an increased risk of sudden death [16–18]. Clinicians often monitor QTc duration when treating patients with haloperidol, which could lead to hesitation to initiate treatment [3].

Studies that showed QTc prolongation with haloperidol use were performed in patients with very high doses of oral haloperidol or intravenous haloperidol [19–23]. In the older, frail population, haloperidol is mostly prescribed at low doses and given orally. Studies on QTc prolongation in older patients prescribed low-dose haloperidol are scarce. Recently, Blom *et al*. [24] retrospectively examined the associations between haloperidol use and QTc duration changes in hospitalised older patients with multiple morbidities and co-medications. QTc duration was increased in patients with normal QTc duration prior to haloperidol use and surprisingly, patients with prolonged QTc duration at baseline (male: QTc > 430 ms; female > 450 ms) showed a shortening of QTc duration. The authors concluded that it is unlikely that QTc shortening is due to the effects of haloperidol *per se*. A plausible explanation was that changes in the underlying condition occurred during haloperidol use, and that these changes caused QTc shortening (for example, effects of acute illness and acute phase response).

The main purpose of this study was to demonstrate that haloperidol in low dose does not prolong QTc duration. Therefore, we performed a prospective controlled observational cohort study evaluating the effects of low-dose haloperidol on QTc duration in frail hospitalised older patients with delirium.

Methods

Setting and design

Based on power analysis from the study by Blom *et al.* [24], in this prospective observational study we included a total of 300 patients. For calculation of the required group size, a power analysis was performed based on paired differences, with $\alpha = 0.05$ and power $= 0.80$ $(1-\beta)$. We considered a difference in QTc of 20 ms clinically relevant, and based on the results of Blom *et al*. [24], we expected the standard deviation of this difference to be 46 ms. Total of patients that needed to be included was 264. We included 150 patients (50%) in the haloperidol group and 150 (50%) age- and frail-matched patients in the control group admitted to geriatric, surgical, orthopaedic, internal medicine, cardiology, neurology, pulmonology, oncology and urology wards at the Zuyderland Medical Centre, a general hospital in the Netherlands.

Inclusion criteria were: age ≥ 70 years, Groningen Frailty Index (GFI) > 3 and ECG made during the first 24 h of admission (which is common policy for all admitted patients). Exclusion criteria were: haloperidol use in the week before admission, QTc > 500 ms at first ECG, >10% ventricular extra systoles or pacemaker beats or unreliable QTc measurement (due to flat T-waves). The study protocol was approved by the ethics review board at the Zuyderland Medical Centre. The ethics review board waived the need for informed consent and data were de-identified prior to analysis.

To obtain manageable workload alongside clinical duties, the groups were included consecutively and by three investigators (M.S., F.W.K. and E.C.). We first included patients in the haloperidol group in the period between September 2014 and February 2016. We prospectively screened admitted patients for clinical oral haloperidol prescriptions and included the patients who matched inclusion and exclusion criteria. Then we included patients without haloperidol in the control group in the period between January 2016 and October 2017.

Procedures

The ECG's were analysed by one of three study physicians (E.C., M.S. and F.W.K.), trained in clinical cardiology for at least 6 months. While automated QTc interval measurements are accurate and more reproducible than manual measurements, we manually validated each QTc interval, correcting for noise and inclusion of P-waves [25,26].

Considering the pharmacokinetics of haloperidol ($t_{max} = 1$–2 h, $t_{1/2} = 12$–36 h) [27], the second ECG was performed at the estimated maximum blood level, after at least two doses of haloperidol. When haloperidol was prescribed in the morning, an ECG was performed in the morning around noon. When haloperidol was only used in the evening, an ECG was performed early in the morning (mean time an ECG was made after haloperidol dose was 9.5 h).

We used the GFI score to identify frailty. This questionnaire measures the loss of functions and resources in four domains: physical (mobility, vision, hearing, nutrition, comorbidity), cognition, social and psychological (depression or anxiety) [28,29]. The range of the GFI-score is 0–15 and a score > 3 is suggestive for frailty.

QT intervals were corrected for heart rate according to the Framingham Heart Study (QTc = 1000(QT/1000 +

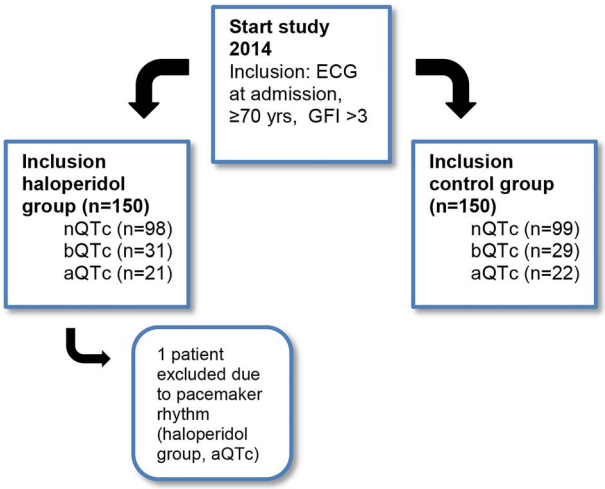

Figure 1. Stratification according to QTc risk categories at baseline. Patients were grouped according to baseline QTc in three subgroups, based on the European Society of Cardiology Guidelines: normal QTc (male ≤ 430 ms, female ≤ 450 ms), borderline QTc (male, 431–450 ms; female, 451–470 ms) and abnormal QTc (male > 450 ms, female > 470 ms). One patient is excluded because of pacemaker rhythm on second ECG.

0.154(1−R-R-interval)) [30]. Patients were grouped according to baseline QTc in three subgroups, based on the European Society of Cardiology Guidelines [31]: normal QTc (male ≤ 430 ms, female ≤ 450 ms), borderline QTc (male 431–450 ms, female 451–470 ms) and abnormal QTc (male > 450 ms, female > 470 ms) (Figure 1). A potentially dangerous QTc was defined as an increase in QTc by >60 ms or to a QTc of >500 ms.

Relevant patient characteristics were retrieved from medical records, which included: age, gender, medical history and medical reason for hospital admission. Furthermore, data on serum C-reactive protein (CRP) levels, leucocyte count and temperature using the measurement closest to the moments of first and second ECG were collected. Signs of inflammation or infection were defined as body temperature > 38.5°C or serum CRP level > 100 mg/l or leucocyte count > 10.0 × 10 × 9/l [24].

Outcomes

The primary outcome of this study was change in QTc duration between first and second ECG. This change in QTc duration was compared between the haloperidol group and control group.

Statistical analysis

Variables are displayed as numbers (percentage) mean ± standard deviation or median (interquartile range), as appropriate. The Kolgomorov test was used to test for normality. Independent sample *t*-tests (or Mann–Whitney *U* test in case of non-normally distributed data) were used to compare mean age, GFI score, days between first and second ECG, heart rate and QRS width between haloperidol and control group. Categorical variables such as gender and presence of diseases in medical history and presence of signs of inflammation were tested for significant differences using a Pearson Chi-square. Differences of included patients according to hospital ward were also tested using a Pearson Chi-square. Comparisons between the haloperidol and control group and the possible interaction of treatment on QTc duration over time was performed by two-way repeated measures analysis of variance (ANOVA). Comparisons between three subgroups (normal, borderline and abnormal) in the haloperidol and control group were performed by one-way ANOVA and post-hoc Bonferroni or Kruskal–Wallis tests. We evaluated associations between QTc duration and age, gender, inflammation, other ECG parameters (heart rate, QRS width) and medical history using a linear regression analysis. All variables with a *P*-value < 0.10 in the univariable model were included in the multivariable model. Statistical significance was accepted at the 95% confidence interval ($P < 0.05$). Statistical analysis was performed using the Statistical Package for the Social Sciences (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA).

Results

Baseline characteristics

A total of 149 patients were included in the haloperidol group (one patient was excluded due to ventricular pacemaker rhythm on the second ECG) and 150 patients in the control group. There were no significant differences in age, gender, GFI score, heart rate and mean QTc at between both groups, reflecting appropriate matching (Table 1). There was no statistically significant difference in the duration between the first and second ECG: in the haloperidol group 4.8 ± 3.3 days versus 4.3 ± 1.1 days in the control group ($P = 0.09$, using an independent sample *t*-test). Average haloperidol dosage was 1.5 mg/day, which was given orally in all patients (range 0.5–3.0 mg/day). Previous delirium ($P < 0.001$) and cognitive disorders ($P = 0.001$) were significantly more present in the haloperidol group compared with controls, using a Pearson Chi-square. QRS duration was significantly longer in control patients (median 103 ms [76–168] compared with patients in the haloperidol group (median 96 ms [66–169], $P = 0.02$). Inclusion by hospital ward is depicted in Supplementary Appendix A1.

QTc-duration change

Examples of QTc duration measurement are shown in Supplementary Appendix A2. The majority of patients had a normal QTc during baseline (with no significant difference between all subgroups, see Table 1, $P = 0.92$) and during the second ECG, as shown in Figure 2. A trend to QTc shortening was seen that did not reach statistical significance; the mean QTc duration decreased −2.9 ± 25 ms in the patients who received haloperidol and −1.8 ± 26 ms in the control group ($P = 0.71$ for comparison between the two

Table 1. Baseline patient characteristics[†]: all, stratified in control and haloperidol group

	All ($n = 299$)	Control ($n = 150$)	Haloperidol use ($n = 149$)	P-value[‡]
Age at onset, years	84 [5.8]	84 [5.6]	84 [6.0]	0.85
Sex, male	133 (45%)	62 (41%)	71 (48%)	0.27
GFI score	6.07 [3.0]	5.92 [3.2]	6.24 [2.7]	0.37
Days between first and second ECG	4.5 [2.5]	4.3 [1.1]	4.8 [3.3]	0.09
QTc at baseline (corrected according to the Framingham Heart Study)				
Normal (male ≤430 ms, female ≤450 ms)	196 (66%)	99 (66%)	98 (66%)	0.92
Borderline (male 431–450 ms, female 451–470 ms)	60 (20%)	29 (19%)	31 (21%)	
Abnormal (male >450 ms, female >470 ms)	42 (14%)	22 (15%)	20 (13%)	
Other information ECG at baseline				
Heart rate, bpm	86 [20]	85 [20]	86 [20]	0.47
QRS width, ms	98 [66–169]	103 [76–168]	96 [66–169]	0.02
QT corrected according to Sagie, ms	431 [27]	433 [29]	429 [26]	0.30
Normal	417 [19]	418 [19]	416 [18]	0.48
Borderline	448 [11]	448 [11]	449 [11]	0.74
Abnormal	473 [16]	482 [17]	463 [9]	<0.001
QT corrected according to Bazett, ms	458 [30]	460 [33]	457 [27]	0.50
Medical history				
Diabetes	79 (26%)	42 (28%)	37 (25%)	0.53
Hypertension	153 (51%)	69 (46%)	84 (56%)	0.09
Delirium	107 (36%)	32 (21%)	75 (50%)	<0.001
Cognitive disorders (dementia, mild cognitive impairment)	122 (40%)	47 (31%)	75 (50%)	0.001
Mobility disorders and frequent falls[§]	62 (21%)	31 (21%)	31 (21%)	0.97
Arrhythmia	125 (42%)	68 (45%)	57 (38%)	0.21
Signs of inflammation				
Inflammation (CRP >100, and/or L > 10), body temperature > 38.5°C n (%)	163 (54%)	78 (52%)	85 (57%)	0.40

[†]Data are represented as mean [SD] or median (in case continuous variables were not normally distributed) [range] or n (%).
[‡]Comparison between control and haloperidol group, based on independent samples t-tests or Mann–Whitney U tests for continuous variables and Pearson Chi-square tests for categorical variables.
[§]Not defined, information from medical history file.

groups, 2-way repeated measures ANOVA). We analysed subgroups stratified by baseline QTc duration (normal, borderline and abnormal). The patients with normal QTc duration during baseline showed a slight prolongation in QTc: haloperidol: +4, 4 ± 24 ms, $P = 0.04$ compared with baseline and control: +4, 5 ± 26 ms, $P = 0.09$. QTc duration in patients who had borderline and abnormal QTc at baseline decreased (Figures 3 and 4). In the patients who received haloperidol during admission, the mean QTc decrease was −15 ± 29 ms ($P \leq 0.001$) in patients with borderline baseline QTc and −19 ± 27 ms ($P = 0.004$) in patients with abnormal baseline QTc. In the control group, the decrease in QTc was −7 ± 16 ms ($P = 0.02$) in the patients with borderline baseline QTc and −23 ± 20 ms ($P < 0.001$) in patients with abnormal baseline QTc (Supplementary Appendix A3). For the three subgroups stratified by baseline QTc there was no significant difference in delta QTc between the haloperidol and control group, using a one-way ANOVA. One control patient developed a QTc classified as potentially dangerous but probably explained due to major change in heart rate (ECG 1: QTc 401 ms with atrial fibrillation at 129 beats per minute (bpm), ECG 2: QTc 505 ms with sinus rhythm at 62 bpm). There is a significant difference ($P = 0.01$ using an independent sample t-test) in mean delta QTc between men (1.7 ± 27 ms) and woman (−5.6 ± 25 ms).

Fifty-four percent of patients had signs of inflammation, 85 haloperidol patients (57%) versus 78 control patients (52%, $P = 0.40$). A small but significant difference was shown in mean change of QTc in patients with inflammation versus those without inflammation (+1.0 ± 26 ms versus −6.5 ± 25 ms, respectively, $P = 0.011$). In the multivariable regression model with age, gender, inflammation and heart failure only inflammation and gender remained independently associated with change in QTc duration ($P = 0.015$ and 0.20, respectively) This effect was not significant different between haloperidol and control group.

Discussion

No patients receiving low-dose haloperidol developed dangerous QTc duration. In fact, a trend to QTc shortening was seen in patients receiving haloperidol. Patients with normal baseline QTc showed minor QTc prolongation in both groups. Most of the patients had a normal QTc at baseline and during admission and only one patient in the control group (0.3%) developed a QTc > 500 ms. Interestingly, a decrease in QTc duration was observed in patients who had borderline and abnormal QTc at baseline. Our results are in line with the study from Blom *et al.* [24], which

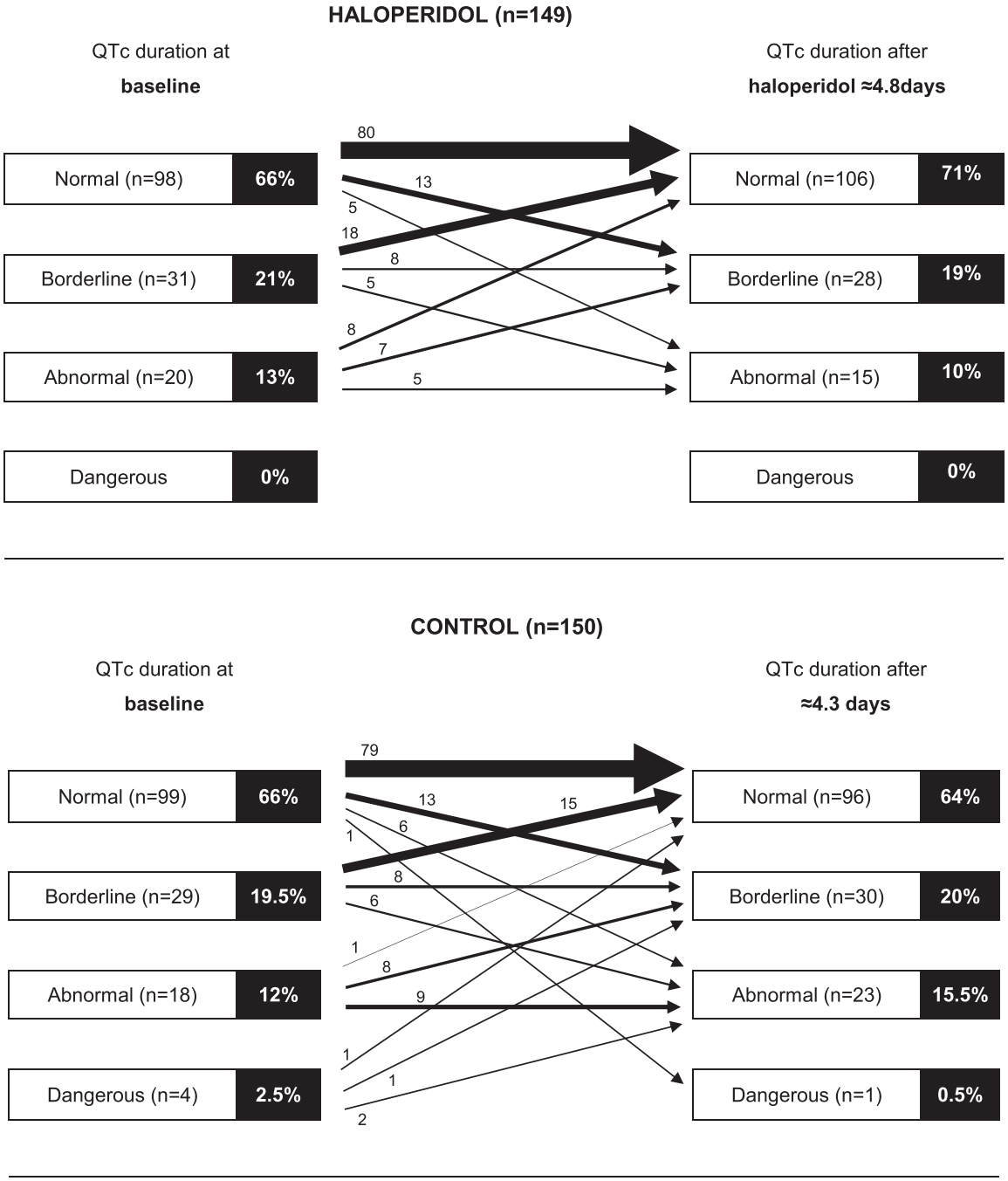

Figure 2. Box plot showing changes in QTc risk categories. Split in control and haloperidol group; this figure shows the change in QTc risk categories (normal, borderline, abnormal and dangerous).

was a retrospective study with fewer patients ($n = 97$) and without planned ECGs. The mean dose of haloperidol in our study was lower in comparison with the study of Blom *et al.* [24] (1.5 versus 2.6 mg). In their study, haloperidol was given orally in 75% of patients and intravenously in 25% of patients. In our study, there are no patients with intravenous haloperidol because in clinical practice intravenous haloperidol is almost never used in this older, frail population.

Because we also included a control group, we could exclude the use of haloperidol as the explanation of this finding since a similar decrease was seen in patients without haloperidol use. We could not clearly identify why QTc shortening occurred in patients with a prolonged QTc interval at baseline. Lack of inflammation and the female gender were associated with slightly higher decrease. Prior research showed a relation between elevated CRP and prolonged QTc interval, independent of confounding factors [32].

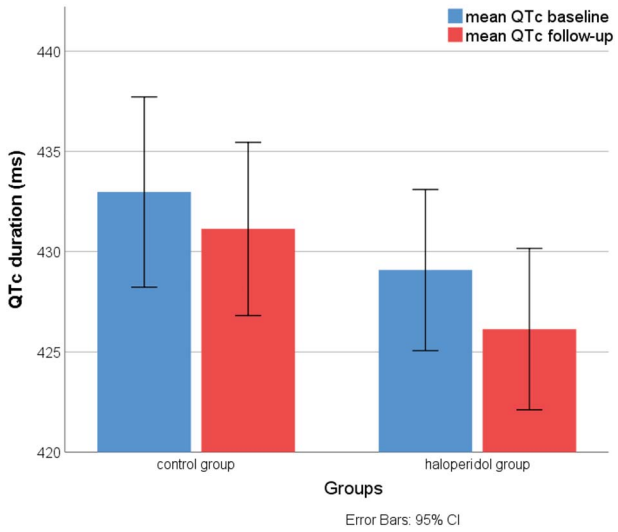

Figure 3. Change in QTc duration. Bars with error bars showing the mean QTc at baseline and follow-up in the control and in the haloperidol group.

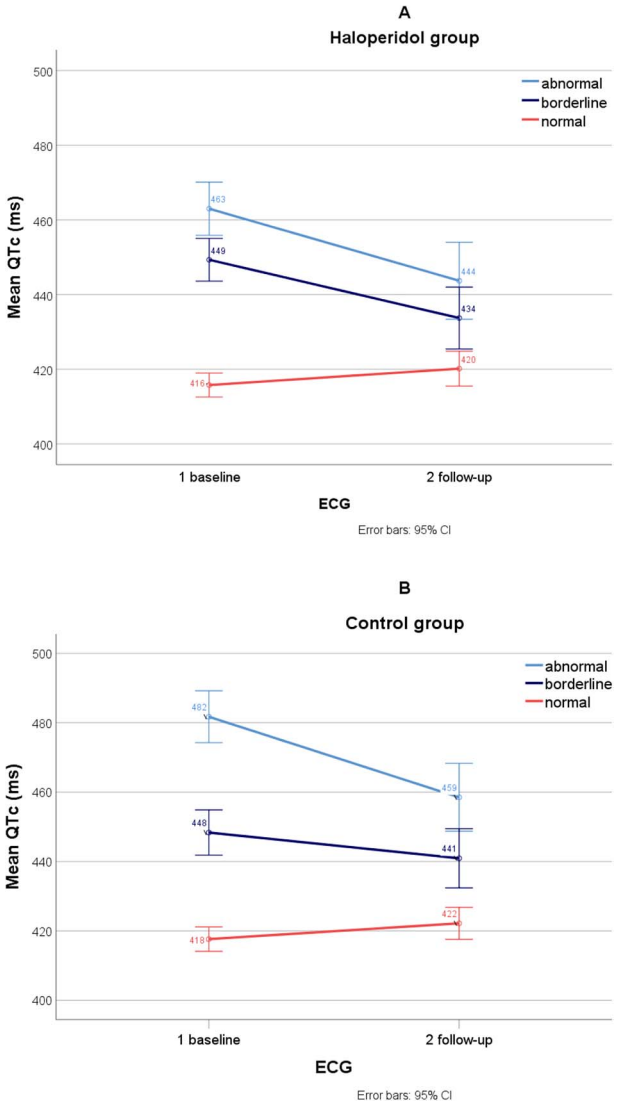

Figure 4. Repeated measurement QTc duration. (A) Shows mean QTc at baseline (first ECG) and after haloperidol use (second ECG) stratified in QTc risk categories normal, borderline and abnormal. (B) Shows mean QTc at baseline and at second ECG in control group stratified in QTc risk categories normal, borderline and abnormal.

In the study by *Blom et al.* [24], surgery before haloperidol use was associated with increased risk of potentially dangerous QTc prolongations ($P = 0.009$), as was male gender ($P = 0.06$). We were not able to analyse the effect of surgery on QTc duration, as surgery was uncommonly performed in this frail older population. In our study, there was a significant difference in delta QTc between men and women ($P = 0.01$), but we considered this as not clinically relevant as it was only 7 ms.

The explanation for QTc shortening in patients with prior borderline or abnormal QTc in both the haloperidol group and in the control group remains unclear. A possible explanation could be a relation between autonomous tone and QTc duration. Our study consisted of frail older patients admitted through the emergency department and since the second ECG was taken a few days later, changes in autonomous tone were likely to occur. Indeed during baseline, at the emergency department, the heart rate (bpm) was significantly higher than during second ECG. But we adequately corrected for this difference in heart rate using the Framingham Heart Study correction. The commonly used Bazett formula (used by ECG machines) is suboptimal as it was validated in a limited population and it is associated with overcorrection of the QTc interval at heart rates > 80 bpm. We used an improved correction method; The Framingham correction (also known as Sagie's formula) based on the Framingham Heart Study in which long-term cohort data are available from a large and representative population of over 5,000 subjects [30,34]. At baseline there were indeed more patients with borderline and abnormal QTc duration when using Bazett formula (91 patients had borderline and 131 patients had abnormal QTc duration). Nevertheless QTc is still decreasing in patients with borderline (-7 ± 22 ms) and abnormal (-15 ± 31 ms) QTc at baseline, regardless of haloperidol use, which is comparable to our results when using the Framingham Heart Study correction. So changes in heart rate could not explain the decrease in QTc duration but Cuomo *et al*. [33] suggest that autonomic tone is a significant determinant of ventricular repolarisation duration with both rate-dependent and independent effects.

It is also known that mental stress elicits various cardiovascular reactions, such as QTc prolongation [35]. Admission through the emergency department is associated with mental stress, which may pose a possible explanation for QTc shortening during the course of admission.

Prolongation of the QT interval may also be caused by an adverse drug reaction of, amongst others: antibiotics, certain antiarrhythmic drugs, antipsychotic drugs and

antidepressants [27]. Polypharmacy is very common in this older population. Our study was not designed to examine the effect of additional drugs on QTc interval. It would be worthwhile to examine the possible effects of drugs in this frail older hospitalised population in a larger study focussing on patients with borderline or increased QTc interval. Electrolyte disturbances, like hypocalcaemia and hypocalcaemia, and thyroid disorders could also affect QTc interval [36]. Advancing age is not only associated with increases in QTc duration but also with a higher variability within QTc durations. Together with the previously mentioned suspicion of autonomic effects on ventricular depolarisation, we raise the idea that, especially in older people, hospital admissions may exacerbate changes in ventricular depolarisation more than in a younger population [37]. It will be difficult to associate changes in QTc duration directly to the effect of one of mentioned factors.

Strengths and limitations

The main strengths of this study were the prospective design of the study and the real-life clinical setting. To our knowledge, our study is the first prospective study to examine the effect of low-dose haloperidol on QTc duration in frail older hospitalised patients. This study also has some limitations. The investigators were not blinded for haloperidol use. Since QTc duration was measured automatically (a few corrections did occur due to obvious over sensing of P-wave or intermittent noise), the influence of this bias is negligible. Because it is not ethically justified to administer haloperidol to patients without delirium because of possible side effects and its prior association with higher incidence of sudden cardiac death, we performed an observational study in which the groups were not randomised. The effects of polypharmacy and other QTc-prolonging drugs were not investigated in this study as it would a larger study sample. Also, the effect of electrolyte derangement was not investigated as these were not systematically repeated during the second ECG. Acute ECG abnormalities (e.g. ischaemia) could have confounded results as they can be a risk factor for prolonged QTc.

Conclusion and recommendations

The findings of our prospective observational study suggest that ECG monitoring of frail, older patients who receive low-dose haloperidol may not be necessary. A trend to QTc shortening was seen, especially in patients with borderline or abnormal QTc at baseline, regardless of haloperidol use.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Declaration of Conflicts of Interest: None.

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