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Prospective real-time evaluation of the QTc interval variation after low-dose droperidol among emergency department patients

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ABSTRACT

Objective: To assess the QTc interval variation after low-dose droperidol in a population of undifferentiated, stable, and non-agitated patients receiving droperidol in the emergency department.
Methods: Prospective cohort study of patients aged ≥12 years of age who received low-dose droperidol (≤ 2.5 mg) for indications other than acute behavioral disturbances. QTc intervals were monitored in real-time during prespecified observation periods in the ED. Primary outcome was variation of QTc interval after droperidol administration, defined as the maximum delta (change) of QTc interval. Other outcomes included proportion of patients with a QTc ≥ 500 ms after droperidol, delta ≥ +60 ms, and incidence of clinical adverse events. Patients were monitored up to 30 min after IV bolus and up to 46 min after infusion.
Results: A total of 68 patients were included (mean age 42.1 years, 66.2% females). The median dose of droperidol was 1.875 mg (range 0.625 mg, 2.5 mg) and 94.1% received droperidol for headache management. Most patients received droperidol as a 2-min bolus ($n = 41$, 60.3%). The mean maximum delta of QTc interval after droperidol across all 68 patients was +29.9 ms (SD 15). A total of 12 patients (17.6%) experienced a QTc interval ≥ 500 ms during the observation period after droperidol, and 3 patients (4.4%) had a delta QTc ≥ +60 ms. There were no serious arrhythmias, such as TdP, or deaths among the 68 participants in this study (0/68). However, 13.2% ($n = 9$) had at least one non-serious adverse event including restlessness and/or anxiety.
Conclusion: The QTc interval slightly increased after droperidol administration, but these prolongations were brief, mostly below 500 msec and did not lead to serious arrhythmias. The yield of continuous cardiac monitoring in patients receiving low doses of droperidol is likely low.

1. Introduction

Droperidol is an antipsychotic drug with anti-dopaminergic (D2 receptor antagonist) activity that has been extensively used in emergency departments (EDs) for indications such as acute agitation, headache, nausea, vomiting, and abdominal pain [1]. The United States Food and Drug Administration (FDA), however, has only post-operative nausea and vomiting in their indications for droperidol. In 2001, the FDA issued a black box warning on droperidol due to case reports of QT prolongation and Torsades de Pointes (TdP), a life-threatening arrhythmia [2,3]. Its use decreased significantly following the warning even though many clinicians remained skeptical of the reasons for such restrictions and believed that there were few or no alternative drugs with an improved adverse effect profile [4].

QT prolonging effect of droperidol is presumably dose-dependent [5]. The FDA black box warning was based on case reports and studies using droperidol doses 50 to 100 times higher than those commonly given in EDs in the United States [3,6]. All the reported deaths associated with droperidol were in patients whose dosage exceeds common medical practice, with at least 3 cases with intravenous doses of 600 mg [7]. Several ED-based studies have been published after such warning for a variety of indications and, to date, none have reported high incidence of clinically significant arrhythmias [8-29]. TdP is very rare in patients receiving droperidol in the ED with estimate rates at approximately 6 per 100,000 administrations [8,9]. Given the consistent evidence of safety in the literature, the American Academy of Emergency Medicine

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performed a comprehensive literature review and concluded that "droperidol is a safe medication in the treatment of nausea, headache, and agitation" and that electrocardiogram or telemetry monitoring for doses <2.5 mg were not indicated [30]. Despite the relatively large body of evidence supporting the safety of low-dose droperidol, there are no published studies prospectively evaluating the real-time QTc variation during cardiac monitoring after low-dose droperidol administration in the ED.

In this prospective observational study, we aimed to evaluate in real-time the immediate effect of low-dose droperidol (≤ 2.5 mg) on the QTc interval of non-agitated patients in the ED. Specifically, we sought to assess the QTc variation after low-dose droperidol and to understand its safety by evaluating the incidence of serious arrhythmias in a population of undifferentiated, stable and non-agitated patients receiving droperidol in the ED.

2. Methods

This manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies [31]. Ethical approval was secured through the institutional review board and informed consent was obtained from patients prior to administering droperidol and monitoring of their QTc.

2.1. Study design, setting, and participants

This prospective cohort study was carried out in an academic quaternary ED in Minnesota with approximately 80,000 patient visits per year. Patients aged 12 years of age or older who received low-dose droperidol (≤ 2.5 mg) for indications other than acute behavioral disturbances between June 20, 2019, and July 16, 2021, were included. Eligible indications of droperidol for this study included the treatment of headache, pain other than headache, nausea, and vomiting. Exclusion criteria consisted of critically ill patients, those with an altered level of consciousness or agitation, and pregnant patients. The decision of giving or not droperidol was at the discretion of ED attendings, and we did not restrict the inclusion of patients based on age. The lowest age among patients receiving droperidol during the study period was 12 years and for this reason our sample included patients of that age or older.

Potentially eligible patients for which the ED provider placed an order for droperidol were identified through the electronic health record system. Eligible patients were consented by on-call research coordinators who subsequently monitored patients' QTc intervals in real-time during pre-specified observation periods in the ED.

2.2. QTc interval monitoring

Consented participants were placed in a cardiac monitor (IntelliVue Phillips MX 700) prior to the administration of droperidol and the QTc interval was recorded before (baseline QTc), at the time of droperidol administration, and every 2 min thereafter. The QT interval is an estimation of ventricular repolarization, therefore is dependent of the heart rate. Given the inherent variability of heart rate in different physiological states across time, it is recommended that for a proper interpretation and risk stratification of the QT interval, its length should be corrected by the associated heart rate at the moment of measurement. The corrected interval is denominated "QTc" throughout this manuscript. For the calculation of the QTc interval, the cardiac monitors in our ED used the Bazett correction formula (QTc = interval QT/interval $RR^{1/2}$) by default [32,33]. The decision to use measurements from cardiac monitor was based on feasibility and because the guideline at our facility does not require a 12-lead ECG prior or during droperidol administration for doses ≤2.5 mg.

Patients were administered droperidol as either an IV bolus over 2 min or as an IV infusion over 15 min. The mode of administration of droperidol is IV push by default in our system, as the medication is safe and effective using that route. Nursing staff, however, had the discretion of changing the method as an infusion based on workload as well as preconceptions of the likelihood of adverse effects such as akathisia. This allowed two different methods of administration, and we were able to compare the pharmacological effects of both infusion and bolus, which enriches the quality of the observations in terms of peak effect, duration, and QT prolongation.

To evaluate QTc prolongation and variation over time, the QTc interval of patients who received droperidol as a 2-min IV bolus were monitored every 2 min up to 30 min or until other patient care priorities precluded the continuity of monitoring (e.g., patient had to go to radiology for imaging). Similarly, those who received a 15-min infusion had their QTc intervals recorded every 2 min from the start of infusion up to 46 min or until other care priorities precluded the continuity of monitoring. Time zero was defined as the moment in which either the bolus or infusion were started. The 46-min time stamp for those who received the infusion marked approximately 30 min after the end of their infusion.

As for droperidol pharmacokinetics, its onset of action is approximately 3 to 10 min, with peak concentrations reported around 30 to 60 min and a short half-life of 2 h [1]. There is likely a lower, and prolonged peak for an infusion versus a bolus dose [1].

2.3. Baseline characteristics

Baseline characteristics of our cohort were obtained including age, sex, dose of droperidol, indication for which droperidol was given, history of prior long QT interval, use of outpatient medications known to prolong the QT interval, and use of ED medications known to prolong the QT interval. The full list of these drug medications is available in Appendix S1.

Table 1
Description of study cohort and incidence of adverse events.

	Patients Receiving Droperidol in the ED ($N = 68$)
Demographics, medications, prior history of long QT	
Age (years), mean (SD)	42.1 (15.8)
Age < 18 years, n (%)	2 (2.9%)
Age 18–65 years, n (%)	60 (88.2%)
Age > 65 years, n (%)	6 (8.8%)
Female, n (%)	45 (66.2%)
Any home medication known to prolong the QTc interval, n (%)	32 (47.1%)
Any ED medication known to prolong the QTc interval, n (%)	6 (8.8%)
History of Long QT, n (%)	2 (2.9%)
Droperidol details	
Headache*	64 (94.1%)
Abdominal Pain	1 (1.5%)
Nausea/Vomiting	5 (7.4%)
Other	3 (4.4%)
Mean dose (SD)	1.681 mg (0.421)
Median dose (range)	1.875 mg (0.625–2.5)
0.625 mg, n (%)	7 (10.3%)
1.25 mg, n (%)	8 (11.8%)
1.875 mg, n (%)	52 (76.5%)
2.5 mg, n (%)	1 (1.5%)
Bolus, n (%)	41 (60.3%)
Infusion, n (%)	27 (39.7%)
QTc prolongation after droperidol	
QTc interval ≥ 500 ms	12 (17.6%)
Delta of QTc ≥ +60 ms	3 (4.4%)
Adverse events	
Any serious adverse event, n (%)	0 (0.0%)
Serious arrhythmia, n (%)	0 (0.0%)
Death, n (%)	0 (0.0%)
Any non-serious adverse event†, n (%)	9 (13.2%)
Restlessness, n (%)	5 (7.4%)
Anxiety, n (%)	5 (7.4%)

* Patients may have had more than one indication documented.
† One patient reported both restlessness and anxiety.

2.4. Outcome measures

Primary outcome included the variation of QTc interval after droperidol administration, defined as the maximum delta (i.e., change) of QTc interval. This was calculated by subtracting the QTc interval at baseline (before droperidol administration) from the longest/highest value of QTc interval recorded at any time after droperidol for each patient. We also evaluated the differences between the baseline QTc and the QTc interval at 10, 20, 30, 40 (only for infusion group), and 46 min (only for infusion group) after droperidol initiation. Furthermore, we evaluated the proportion of patients who reached a QTc ≥ 500 ms at any time after droperidol administration, and the proportion of patients who had a delta ≥60 ms. The change of ≥ +60 ms in the QTc interval has been reported as concerning by prior literature [34].

Secondary outcomes included clinical adverse events, which were classified as serious or non-serious. Serious adverse events were defined as death or any serious arrhythmias including ventricular dysrhythmias such as TdP, ventricular fibrillation, or ventricular tachycardia. Non-serious adverse events were defined as the presence of akathisia (restlessness), anxiety, dyskinesia, dystonia, or any other extra-pyramidal symptom after the administration of droperidol. Patients were directly asked about adverse events at the end of the monitoring period.

2.5. Data analysis

Statistical analyses were conducted using BlueSky Statistics (Version 7.0.746.34007) GUI for R. For descriptive statistics, continuous features were summarized as means and standard deviations (SD) or median and ranges (minimum, maximum) according to data distribution, while categorical features were summarized as counts and percentages. For the before and after analyses, mean differences (MDs) with 95% confidence intervals were calculated and *p*-values were obtained through a paired *t*-test. When comparing means between independent samples (e.g., comparison of maximum delta of QTc between those who received bolus and those who received infusion), *t*-tests without assuming equal variances were used. When comparing proportions of a certain binary outcome (e.g., proportion of patients with QTc ≥ 500 ms) between independent samples, Fisher exact tests were used. Analyses were stratified by form of droperidol administration (bolus or infusion). All tests were 2-sided, and statistical significance was set at alpha less than 0.05.

3. Results

A total of 68 patients receiving droperidol in the ED for analgesia or as an antiemetic were included in the analysis. Their mean age was 42.1 years (SD 15.8) and 45 (66.2%) were female. Most patients received droperidol as a 2-min bolus ($n = 41$, 60.3%). Overall, the median dose of droperidol was 1.875 mg (range 0.625 mg, 2.5 mg) and 94.1% received droperidol for headache management. Two patients had a history of long QT (2.9%), 32 patients (47.1%) were taking at least one home medication known to prolong the QT interval, and 6 patients (8.8%) received at least one ED medication (other than droperidol) known to prolong the QT interval. (Table 1)

3.1. QTc variation

Among those who received a bolus of droperidol, the mean QTc interval at baseline was 449 ms (SD 28) and the median was 444 ms (range 376, 505). Those who received an infusion had a mean baseline QTc interval of 449 ms (SD 22) and a median of 449 ms (range 400, 493). (Table 2) Fig. 1 illustrates QTc interval changes over time for

Table 2
QTc intervals (ms) stratified by form of droperidol administration.

	Bolus			Infusion		
	N	Mean (SD)	Median (Range)	N	Mean (SD)	Median (Range)
Time (minutes) at which QTc intervals were measured						
Before*	41	448.7 (27.9)	444 (376, 505)	27	448.7 (22.4)	449 (400, 493)
0** min	41	452.4 (26.2)	447 (390, 505)	27	447.4 (26.9)	448 (387, 499)
2*** min	41	453.3 (30.9)	450 (383, 522)	25	451.4 (24.2)	452 (403, 508)
4 min	41	457.7 (25.7)	459 (392, 506)	25	444.1 (22.9)	442 (405, 488)
6 min	40	458.9 (28.4)	452 (405, 523)	25	446.3 (28.3)	439 (387, 532)
8 min	39	456.5 (25.8)	455 (398, 511)	25	450.7 (23.1)	447 (420, 496)
10 min	40	457.8 (27.5)	455 (388, 521)	25	450.6 (24.4)	454 (391, 492)
12 min	39	462.3 (26.4)	461 (390, 537)	24	447.0 (23.7)	447 (405, 487)
14 min	39	459.4 (28.0)	458 (379, 519)	23	457.3 (24.6)	465 (402, 496)
16‡ min	39	457.2 (29.3)	458 (395, 529)	24	451.4 (20.2)	452.5 (418, 499)
18 min	36	460.5 (27.2)	456.5 (393, 534)	25	449.8 (23.1)	448 (415, 485)
20 min	34	453.1 (25.6)	456 (400, 499)	23	451.3 (20.5)	453 (405, 483)
22 min	34	455.5 (33.8)	453 (381, 547)	22	449.5 (17.5)	451 (408, 479)
24 min	35	456.3 (29.1)	453 (390, 522)	23	454.6 (21.6)	452 (413, 493)
26 min	34	459.4 (29.8)	457.5 (399, 517)	22	452.9 (23.7)	453 (390, 493)
28 min	35	456.0 (26.7)	455 (395, 524)	21	455.7 (27.1)	455 (413, 529)
30 min	35	454.2 (29.9)	453 (389, 532)	21	457.3 (29.0)	452.5 (416, 526)
32 min	–	–	–	20	454.1 (21.1)	453.5 (421, 495)
34 min	–	–	–	21	455.5 (21.8)	459 (410, 491)
36 min	–	–	–	22	450.4 (20.9)	445 (420, 487)
38 min	–	–	–	21	449.3 (28.3)	449 (386, 505)
40 min	–	–	–	22	453.8 (20.8)	454 (420, 480)
42 min	–	–	–	22	454.9 (23.1)	453 (401, 487)
44 min	–	–	–	22	455.4 (26.0)	463 (413, 505)
46 min	–	–	–	22	454.1 (23.9)	458 (397, 499)
Doses						
Dose (mg)	41	1.630 (0.481)	1.875 (0.625, 2.500)	27	1.875 (0.302)	1.875 (0.625, 1.875)
Longest QTc	41	481.4 (27.3)	481 (419, 547)	27	474.2 (25.4)	474 (432, 532)
Delta† QTc	41	32.7 (12.0)	33 (10, 62)	27	25.5 (18.1)	23 (−12, 62)

* Right before the administration of droperidol (baseline QTc).
** Start of 2-min bolus or 15-min infusion.
*** End of the 2-min bolus.
‡ 1 min after the end of the 15-min infusion.
† Maximum delta of QTc calculated as the maximum QTc interval recorded after droperidol administration minus the QTc interval before administration (baseline).

both bolus and infusion (Fig. 1) Females had longer QTc intervals than males (mean QTc at baseline 456 ms vs 434 ms, $p = 0.001$), and both sexes had similar variation over time. (Fig. 2)

The mean maximum delta of QTc interval after droperidol across all 68 patients was +29.9 ms (SD 15). The smallest delta was -12 ms while the largest was +62 ms. Only 2 patients had a negative delta (i.e., longest value of QTc interval after droperidol was lower than their baseline QTc). The mean longest value of QTc after droperidol was 478.6 ms (SD 26.6). The longest QTc interval after droperidol administration was 547 ms for one patient. The maximum delta of QTc for those who received a 2-min bolus was not statistically different than those who received a 15-min infusion (mean + 32.7 ms with bolus vs +25.5 ms with infusion, $p = 0.075$). Males and females also had similar deltas (mean + 32.9 ms in males vs +28.3 ms in females, $p = 0.266$), along with patients who were taking at least one home medication known to prolong the QT when compared to those not (mean + 30.5 ms vs + 29.3 ms, $p = 0.746$). Those receiving at least one other medication during their ED visit known to prolong the QT also had similar variation compared to those not receiving it (mean + 29.8 ms vs +29.9 ms, $p = 0.996$). Delta QTc's across different droperidol doses were also similar with an average of approximately +30 ms. The one patient who received 2.5 mg had a maximum delta of +43 ms, and the longest measured QTc was 491 ms. (Table 3).

A total of 12 patients (17.6%) experienced a QTc interval ≥ 500 ms during the observation period after droperidol administration, and 3 patients (4.4%) had a delta QTc ≥ +60 ms. (Table 1) Importantly, two patients (2.9%) had a prolonged QTc ≥ 500 ms at baseline, prior to administration of droperidol. Patients who received droperidol as a bolus dose had a higher proportion of QTc ≥ 500 ms after droperidol administration than those who received it as an infusion; this difference was not statistically significant (22.0% vs 11.1%, $p = 0.338$). Similarly, there was no difference in the proportion of patients with delta ≥ +60 ms between groups (4.9% vs 3.7%, $p = 1.0$).

3.2. QTc changes at different times

At 10 min, the QTc interval of patients who received droperidol as a bolus was significantly higher compared to their baseline (mean difference + 10.5 ms, 95% CI +5.2 ms to +15.9 ms). At 20 and 30 min, point estimates were also positive but the differences were not statistically significant. For those who were administered droperidol as an infusion, mean differences ranged from +3.0 ms (at 10 min) to +10.3 ms (at 30 min), but only the difference between the 30-min mark and baseline was statistically significant. (Table 4)

3.3. Clinical adverse events

There were no serious arrhythmias, such as TdP, or deaths among the 68 participants in this study. However, 13.2% ($n = 9$) had at least one non-serious adverse event including restlessness and/or anxiety. (Table 1) Among the bolus group, 6 of 41 (14.6%) patients experienced a non-serious adverse event, while 3 of 27 (11.1%) experienced non-serious adverse events when receiving a droperidol infusion. Patients who had a non-serious adverse event had higher maximum delta of

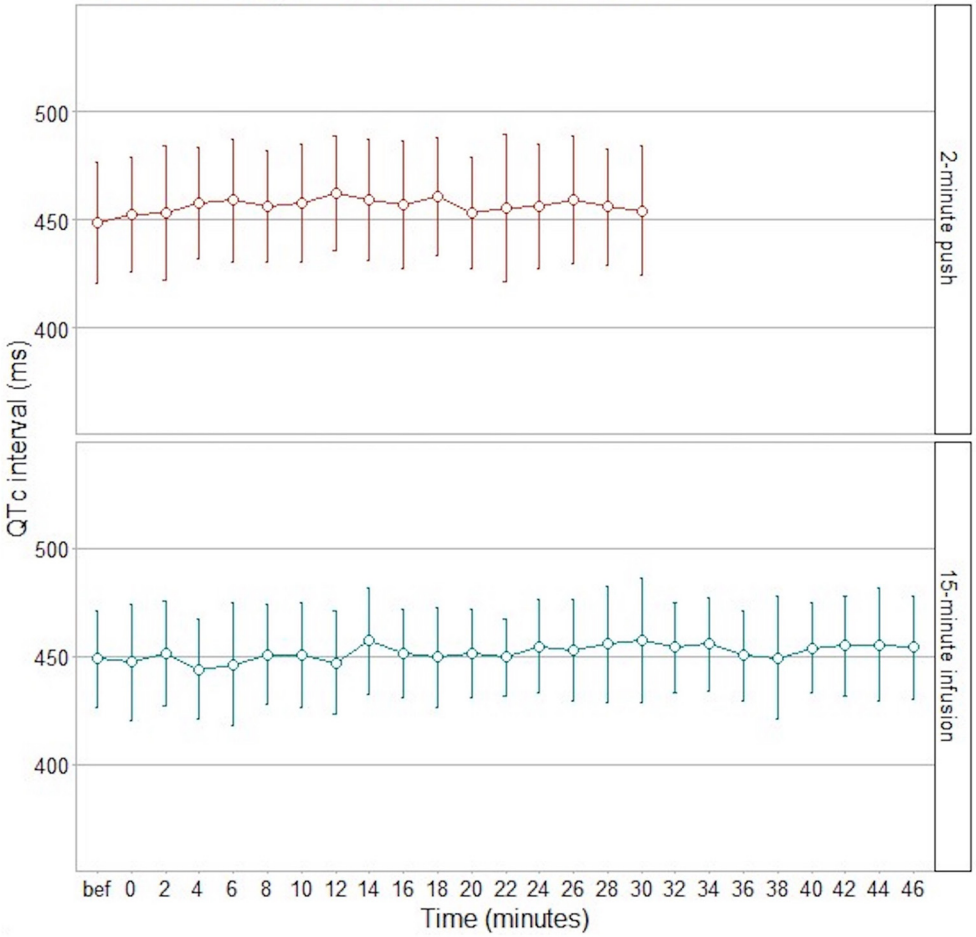

Fig. 1. Mean QTc interval (ms) at baseline (before) and every 2 min after droperidol stratified by the form of administration (bolus or infusion). The circle represents the mean QTc interval, and the lines represent 1 standard deviation above and below the mean.

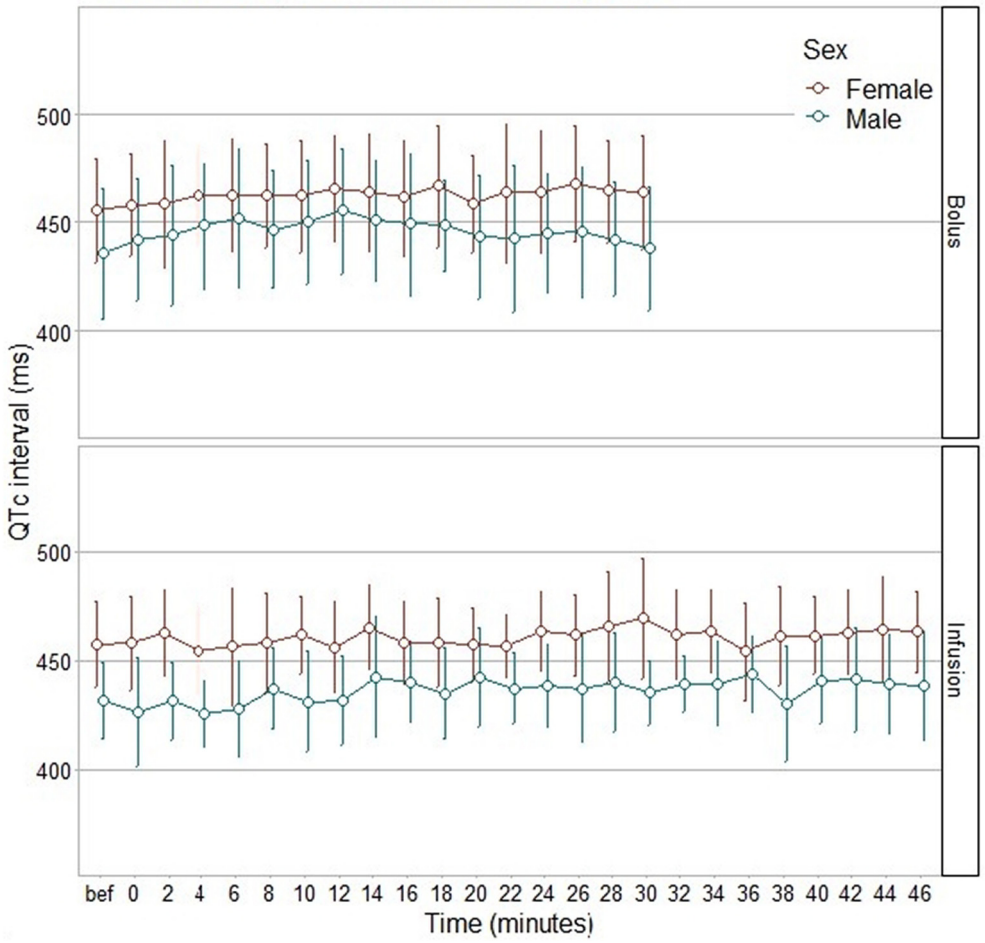

Fig. 2. Mean QTc interval (ms) at baseline (before) and every 2 min after droperidol stratified by the form of administration (bolus or infusion) and sex (female or male). The circle represents the mean QTc interval, and the lines represent 1 standard deviation above and below the mean.

QTc after droperidol than those without an adverse event (mean + 42.4 ms vs +27.9 ms, mean difference + 14.5 ms, 95% CI +4.29 ms to +24.70 ms, $p = 0.009$).

4. Discussion

In this prospective observational study, we found that, on average, the maximum delta of QTc interval was 30 ms longer, with only 4.4% of patients reaching a delta ≥ +60 ms immediately after the administration of low-dose droperidol in the ED. Although 17.6% had a QTc ≥ 500 ms at some point after droperidol, none of them had a serious arrhythmia. Given the lack of a control group, it is uncertain if such changes would similarly occur in the absence of droperidol or with other drugs. Non-serious adverse events including restlessness and anxiety occurred approximately in 1 in 10 patients receiving droperidol, and those who had at least one non-serious adverse event had higher deltas of QTc than those without adverse events.

For those receiving droperidol as a bolus, the QTc interval peaked 10 min after the administration of the 2-min bolus and decreased thereafter. For those receiving an infusion, it peaked at 30 min (i.e., approximately 15 min after the end of the 15-min infusion) and decreased thereafter. A potential corollary of the timing of QTc variation in our data set is that by the time the ED encounter is done, the effects of droperidol on QTc have largely worn off and it is safe to discharge these patients from a cardiac monitoring perspective.

On average, the maximum QTc interval change after droperidol was approximately +30 ms in our study. This is lower than what previous authors have reported as concerning (change ≥ +60 ms) [34]. There were a few patients in our cohort who experienced a delta QTc ≥ +60 ms (4.4%) or a QTc interval ≥ 500 ms at some point after droperidol administration (17.6%) but none of these patients developed serious arrhythmias. These findings reflect prior evidence showing droperidol can transiently increase the QTc interval, but it does not necessarily translate into an increased risk of serious arrhythmias, even at higher doses [28,35]. Given the lack of a control group, it is uncertain how much of the increase seen in our study is due to the independent effect of droperidol on the QTc interval. This might have occurred due to the predominance of females in our cohort (longer baseline QTc intervals) and other factors such as a significant proportion of patients already using medications with potential QT-prolonging effects prior to the ED visit. However, deltas were similar when we stratified by these variables. Prior controlled experiments have challenged the association between low-dose droperidol and QTc prolongation. For example, in a randomized study in the operating room setting, White and colleagues compared the outcome of QTc prolongation between low doses of droperidol (0.625 to 1.25 mg) and saline (placebo), and there were no significant differences [36]. Other operating room-based randomized controlled studies have shown similar QTc prolongations between ondansetron and low-dose droperidol [37,38]. Moreover, one ED-based study (the DORM trial) evaluating a dose of 10 mg of droperidol for acute agitation found similar proportions of abnormal QTc between droperidol and midazolam [12].

No patients receiving low-dose droperidol had a serious adverse event in our study. These findings are largely consistent with prior literature that indicates that droperidol is safe to be used in the ED, especially at low doses (≤ 2.5 mg) [8,9,30,34,39,40]. A recent Cochrane

Table 3
Maximum delta and longest values of QTc interval (ms) after droperidol stratified by different variables of interest.

	Maximum Delta† of QTc interval (ms)	Longest Value* of QTc interval (ms)
All ($n = 68$)		
Mean (SD)	+29.9 (15.0)	478.6 (26.6)
Median (range)	+31.5 (−12, +62)	476.5 (419, 547)
2-min bolus ($n = 41$)		
Mean (SD)	+32.7 (12.0)	481.4 (27.3)
Median (range)	+33 (+10, +62)	481 (419, 547)
15-min infusion ($n = 27$)		
Mean (SD)	+25.5 (18.1)	474.2 (25.4)
Median (range)	+23 (−12, +62)	474 (432, 532)
Female ($n = 45$)		
Mean (SD)	+28.3 (14.0)	484.6 (25.1)
Median (range)	+29 (−5, +62)	483 (440, 547)
Male ($n = 23$)		
Mean (SD)	+32.9 (16.8)	466.8 (26.1)
Median (range)	+33 (−12, +62)	467 (419, 523)
History of Long QT ($n = 2$)		
Mean (SD)	+31.5 (12.0)	485 (1.4)
Median (range)	+31.5 (+23, +40)	485 (484, 486)
Without History of Long QT ($n = 66$)		
Mean (SD)	+29.8 (15.2)	478.4 (27.0)
Median (range)	+31.5 (−12, +62)	476 (419, 547)
Any other ED medication known to prolong QT ($n = 6$)		
Mean (SD)	+29.8 (18.0)	482.3 (34.5)
Median (range)	+25 (+13, +62)	485.5 (441, 532)
Without other ED medications known to prolong QT ($n = 62$)		
Mean (SD)	+29.9 (14.9)	478.2 (26.1)
Median (range)	+32.5 (−12, +62)	476 (419, 547)
Any home medication known to prolong QT ($n = 32$)		
Mean (SD)	+30.5 (15.1)	482.6 (28.1)
Median (range)	+33 (−12, +62)	480.5 (432, 547)
No home medications known to prolong QT ($n = 36$)		
Mean (SD)	+29.3 (15.1)	475.0 (25.2)
Median (range)	+30.5 (−5, +62)	474.5 (419, 532)
0.625 mg ($n = 7$)		
Mean (SD)	+31.6 (11.1)	474.7 (39.3)
Median (range)	+31 (+13, +44)	462 (440, 547)
1.25 mg ($n = 8$)		
Mean (SD)	+28.3 (9.5)	479.0 (28.2)
Median (range)	+31 (+13, +40)	473 (443, 526)
1.875 mg ($n = 52$)		
Mean (SD)	+29.6 (16.3)	478.8 (25.2)
Median (range)	+31 (−12, +62)	476.5 (419, 534)
2.5 mg ($n = 1$)		
Mean (SD)	+43 (NA)	491 (NA)
Median (range)	+43 (NA)	491 (NA)
Any adverse events ($n = 9$)		
Mean (SD)	+42.4 (12.7)	471.2 (28.1)
Median (range)	+37 (+29, +62)	467 (436, 526)
Without adverse events ($n = 59$)		
Mean (SD)	+27.9 (14.5)	479.7 (26.5)
Median (range)	+29 (−12, +62)	478 (419, 547)

NA, not applicable.
* Defined as the longest QTc interval recorded for each patient after the initiation of droperidol.
† Defined as the longest value of QTc interval at any time after droperidol minus the QTc interval at baseline (before droperidol administration).

systematic review supports the findings of very low incidence of life-threatening cardiac events related to droperidol administration [41], with benefits probably outweighing the risks. Weibel and colleagues evaluated 95 randomized trials that assessed droperidol as an agent for postoperative nausea and vomiting in adults undergoing general anesthesia and there were zero studies reporting a serious adverse event secondary to droperidol administration (doses of droperidol in these studies ranged from 0.25 mg to 7.5 mg) [41]. When the authors evaluated studies reporting the incidence of any arrhythmia between droperidol and placebo, they found a lower incidence of arrhythmias with droperidol as compared to placebo across 7 studies (2/336 [0.6%] vs 3/323 [0.9%]) [41]. Most recently, Cole and colleagues estimated the incidence of TdP in patients receiving droperidol in the ED to be 1/16,546 (0.006%, or 6 per 100,000) [9]. Average doses of droperidol in this study, however, were mostly greater than 2.5 mg. Other factors to consider to completely understand the occurrence of TdP are the association of droperidol and other QTc prolonging drugs, the use of cumulative doses, presence of structural heart disease and most importantly acute electrolyte abnormalities around the administration of the drug.

Lastly, approximately 13% of our cohort had non-serious adverse events such as anxiety and restlessness after receiving droperidol. The proportion of patients reporting restlessness (i.e., akathisia) was similar to other prospective studies including a randomized blinded ED-based study in which patients received 2.5 mg of droperidol for acute migraine headaches, and akathisia was reported in 13.3% of patients [19]. As previously mentioned, given the lack of a control group in our study, we cannot evaluate causality between droperidol administration and subsequent extrapyramidal symptoms. Nevertheless, the Cochrane systematic review by Weibel and colleagues found 23 randomized controlled trials comparing the incidence of extrapyramidal symptoms between droperidol and placebo in the context of postoperative nausea and vomiting prevention, and they found that those receiving droperidol had a higher incidence of these symptoms (60/1726 [3.5%]) than those receiving placebo (23/1544 [1.5%]), but the pooled effect estimate yielded a wide confidence interval (pooled risk ratio 1.43, 95% CI 0.87 to 2.35) [41]. Most importantly in our cohort, patients who had at least one non-serious adverse event had greater delta QTc's compared to those without adverse events (mean + 42.4 ms vs +27.9 ms). This data suggests that non-serious adverse events after low-dose droperidol might assist on the identification of patients at higher risk of having greater QTc changes.

5. Limitations

There are several limitations requiring acknowledgment. First, this was a single-center study at an academic institution with a relatively small sample of patients enrolled. However, the QTc interval was measured before and at several time points after droperidol administration which provided us more than 2000 QTc intervals recorded. Second, we used measurements of Bazett-corrected QT interval automatically calculated from a portable cardiac monitor. Although widely used in the droperidol literature, there is overcorrection at high heart rates and under correction at lower heart rates with the Bazett's QT correction [42]. Third, there is likely selection bias in our sample because this was a convenience sample at the times when a research coordinator was available, and we had to pause the enrollment for several months due to COVID-19. Moreover, as droperidol was given at the discretion of ED providers, there is certainly some additional selection bias that could be present due to providers avoiding droperidol in patients at higher risk of having cardiac arrhythmias (e.g., those with electrolyte disturbances or underlying cardiac disease). Fourth, some data points were missing due to interruptions in the context of usual ED care (e.g., patient needed to go to radiology for CT imaging). However, none of the patients who had at least one QTc interval missing at some point ($n = 21$) experienced a serious adverse event during the ED visit. Fifth, one possible factor to consider for the QTc variation in our population is the relation between QTc prolongation and electrolyte abnormalities. Our study population includes a portion of patients who had nausea and vomiting, and therefore changes in serum potassium are possible, affecting QTc intervals prior to the administration of droperidol [43]. Lastly, the incidence of non-serious adverse events may be overestimated. Because of unblinding, prospective data collection, and the Hawthorne effect [44], patients may have overreported their symptoms after the administration of droperidol. Also, because there was no control group in this study, it is not possible to claim that droperidol was independently responsible for the QTc prolongation or the non-serious adverse events.

Table 4
Mean differences between the QTc interval (ms) before (baseline) and after the start of droperidol at different time marks.

	Bolus			Infusion		
	N	Mean (SD)	Mean difference (95% CI) *p* value*	N	Mean (SD)	Mean difference (95% CI) *p* value*
10 min						
Before	40	447.3 (26.7)	+10.5 ms	25	447.6 (22.5)	+3.0 ms
10 min	40	457.8 (27.5)	(+5.2 to +15.9)	25	450.6 (24.4)	(−4.5 to +10.6)
			$p = 0.003$			$p = 0.4155$
20 min						
Before	34	449.1 (28.0)	+4 ms	23	447.4 (21.2)	+3.9 ms
20 min	34	453.1 (25.6)	(−2.2 to +10.2)	23	451.3 (20.5)	(−3.9 to +11.7)
			$p = 0.1969$			$p = 0.3083$
30 min						
Before	35	446.3 (28.0)	+8.0 ms	20	447.1 (22.9)	+10.3 ms
30 min	35	454.2 (29.9)	(+1.8 to +14.1)	20	457.3 (29.0)	(+2.8 to +17.7)
			$p = 0.0128$			$p = 0.0094$
40 min						
Before	–	–	–	22	449.0 (22.8)	+4.8 ms
40 min	–	–		22	453.8 (20.8)	(−3.9 to +13.4)
						$p = 0.2629$
46 min						
Before	–	–	–	22	449.0 (22.8)	+5.1 ms
46 min	–	–		22	454.1 (23.9)	(−3.2 to 13.3)
						$p = 0.2172$

* *P* values were obtained through paired t-test with alpha set at 0.05.

6. Conclusion

The QTc intervals slightly increased 10 to 30 min after droperidol administration, but these prolongations were brief, mostly below 500 msec and did not lead to arrhythmias. These data suggest that low-dose droperidol (≤ 2.5 mg) is safe from the cardiac perspective for the use in non-agitated ED patients, and that the yield of continuous cardiac monitoring in this patient population is probably low.

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Presentations

Preliminary analysis of this work was presented in an internal conference at the Mayo Clinic.

Author contributions

FB, DC, and LOJS conceived and designed the study. LHR, DV, and AEG conducted the acquisition of the data. LOJS analyzed the data. LHR, FB, DC, and LOJS interpreted the data. LHR and LOJS drafted the manuscript and all authors contributed substantially to its revision with critical revision of the manuscript for important intellectual content.

Conflicts of interest

The authors disclosed no conflicts of interest related to this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2021.12.039.

References

[1] Richards JR, Schneir AB. Droperidol in the emergency department: is it safe? J Emerg Med. 2003;24(4):441–7. https://doi.org/10.1016/S0736-4679(03)00044-1.
[2] Horowitz BZ, Bizovi K, Moreno R. Droperidol—behind the black box warning. Acad Emerg Med. 2002;9(6):615–8. https://doi.org/10.1197/AEMJ.9.6.615.
[3] Jackson CW, Sheehan AH, Reddan JG. Evidence-based review of the black-box warning for droperidol. Am J Heal Pharm. 2007;64(11):1174–86. https://doi.org/10.2146/AJHP060505.
[4] Richards JR, Weiss SJ, Bretz SW, Schneir AB, Rinetti D, Derlet RW. The effects of the FDA warning on the use of droperidol by U.S. emergency physicians. Calif J Emerg Med. 2003;4(1):3 /pmc/articles/PMC2906954/?report=abstract. Accessed August 31, 2021.
[5] Lischke V, Behne M, Doelken P, Schledt U, Probst S, Vettermann J. Droperidol causes a dose-dependent prolongation of the QT interval. Anesth Analg. 1994;79(5):983–6. https://doi.org/10.1213/00000539-199411000-00028.
[6] Mullins M, Van Zwieten K, Blunt JR. Unexpected cardiovascular deaths are rare with therapeutic doses of droperidol. Am J Emerg Med. 2004;22(1):27–8. https://doi.org/10.1016/J.AJEM.2003.09.003.
[7] Mattson A, Friend K, Brown CS, Cabrera D. Reintegrating droperidol into emergency medicine practice. Am J Heal Pharm. 2020;77(22):1838–45. https://doi.org/10.1093/AJHP/ZXAA271.
[8] Gaw CM, Cabrera D, Bellolio F, Mattson AE, Lohse CM, Jeffery MM. Effectiveness and safety of droperidol in a United States emergency department. Am J Emerg Med. 2020;38(7):1310–4. https://doi.org/10.1016/J.AJEM.2019.09.007.
[9] Cole JB, Lee SC, Martel ML, Smith SW, Biros MH, Miner JR. The incidence of QT prolongation and torsades des pointes in patients receiving droperidol in an urban emergency department. West J Emerg Med. 2020;21(4):728. https://doi.org/10.5811/WESTJEM.2020.4.47036.
[10] Faine B, Hogrefe C, Van Heukelom J, Smelser J. Treating primary headaches in the ED: can droperidol regain its role? Am J Emerg Med. 2012;30(7):1255–62. https://doi.org/10.1016/J.AJEM.2011.08.010.
[11] Szwak K, Sacchetti A. Droperidol use in pediatric emergency department patients. Pediatr Emerg Care. 2010;26(4):248–50. https://doi.org/10.1097/PEC.0B013E3181D6D9F2.
[12] Isbister GK, Calver LA, Page CB, Stokes B, Bryant JL, Downes MA. Randomized controlled trial of intramuscular droperidol versus midazolam for violence and acute behavioral disturbance: the DORM study. Ann Emerg Med. 2010;56(4):392–401.e1. https://doi.org/10.1016/J.ANNEMERGMED.2010.05.037.
[13] Hill CH, Miner JR, Martel ML. Olanzapine versus droperidol for the treatment of primary headache in the emergency department. Acad Emerg Med. 2008;15(9):806–11. https://doi.org/10.1111/J.1553-2712.2008.00197.X.
[14] Knott JC, Taylor DMD, Castle DJ. Randomized clinical trial comparing intravenous midazolam and droperidol for sedation of the acutely agitated patient in the emergency department. Ann Emerg Med. 2006;47(1):61–7. https://doi.org/10.1016/J.ANNEMERGMED.2005.07.003.
[15] Braude D, Soliz T, Crandall C, Hendey G, Andrews J, Weichenthal L. Antiemetics in the ED: a randomized controlled trial comparing 3 common agents. Am J Emerg Med. 2006;24(2):177–82. https://doi.org/10.1016/J.AJEM.2005.08.017.
[16] Martel M, Sterzinger A, Miner J, Clinton J, Biros M. Management of acute undifferentiated agitation in the emergency department: a randomized double-blind trial of droperidol, ziprasidone, and midazolam. Acad Emerg Med. 2005;12(12):1167–72. https://doi.org/10.1197/J.AEM.2005.07.017.

[17] Weaver CS, Jones JB, Chisholm CD, et al. Droperidol vs. prochlorperazine for the treatment of acute headache. J Emerg Med. 2004;26(2):145–50. https://doi.org/10.1016/J.JEMERMED.2003.05.005.
[18] Silberstein SD, Young WB, Mendizabal JE, Rothrock JF, Alam AS. Acute migraine treatment with droperidol. Neurology. 2003;60(2):315–21. https://doi.org/10.1212/01.WNL.0000042477.63516.B2.
[19] Richman PB, Allegra J, Eskin B, et al. A randomized clinical trial to assess the efficacy of intramuscular droperidol for the treatment of acute migraine headache. Am J Emerg Med. 2002;20(1):39–42. https://doi.org/10.1053/AJEM.2002.30007.
[20] Meek R, Mee MJ, Egerton-Warburton D, et al. Randomized placebo-controlled trial of droperidol and ondansetron for adult emergency department patients with nausea. Acad Emerg Med. 2019;26(8):867–77. https://doi.org/10.1111/ACEM.13650.
[21] Chase PB, Biros MH. A retrospective review of the use and safety of droperidol in a large, high-risk, inner-city emergency department patient population. Acad Emerg Med. 2002;9(12):1402–10. https://doi.org/10.1197/AEMJ.9.12.1402.
[22] Irving C, Richman P, Kaiafas C, Eskin B, Allegra J. Intramuscular droperidol versus intramuscular dimenhydrinate for the treatment of acute peripheral Vertigo in the emergency department: a randomized clinical trial. Acad Emerg Med. 2002;9(6):650–3. https://doi.org/10.1197/AEMJ.9.6.650.
[23] Klein LR, Driver BE, Horton G, Scharber S, Martel ML, Cole JB. Rescue sedation when treating acute agitation in the emergency department with intramuscular antipsychotics. J Emerg Med. 2019;56(5):484–90. https://doi.org/10.1016/J.JEMERMED.2018.12.036.
[24] Yap CYL, Taylor DM, Knott JC, et al. Intravenous midazolam–droperidol combination, droperidol or olanzapine monotherapy for methamphetamine-related acute agitation: subgroup analysis of a randomized controlled trial. Addiction. 2017;112(7):1262–9. https://doi.org/10.1111/ADD.13780.
[25] Taylor DMD, Yap CYL, Knott JC, et al. Midazolam-droperidol, droperidol, or olanzapine for acute agitation: a randomized clinical trial. Ann Emerg Med. 2017;69(3):318–26 e1. https://doi.org/10.1016/J.ANNEMERGMED.2016.07.033.
[26] Calver L, Page CB, Downes MA, et al. The safety and effectiveness of droperidol for sedation of acute behavioral disturbance in the emergency department. Ann Emerg Med. 2015;66(3):230–238.e1. https://doi.org/10.1016/J.ANNEMERGMED.2015.03.016.
[27] Calver L, Drinkwater V, Gupta R, Page CB, Isbister GK. Droperidol v. haloperidol for sedation of aggressive behaviour in acute mental health: randomised controlled trial. Br J Psychiatry. 2015;206(3):223–8. https://doi.org/10.1192/BJP.BP.114.150227.
[28] Calver L, Isbister GK. High dose droperidol and QT prolongation: analysis of continuous 12-lead recordings. Br J Clin Pharmacol. 2014;77(5):880–6. https://doi.org/10.1111/BCP.12272.
[29] Calver L, Isbister GK. Parenteral sedation of elderly patients with acute behavioral disturbance in the ED. Am J Emerg Med. 2013;31(6):970–3. https://doi.org/10.1016/J.AJEM.2013.03.026.
[30] Perkins J, Ho JD, Vilke GM, Demers G. American academy of emergency medicine position statement: safety of droperidol use in the emergency department. J Emerg Med. 2015;49(1):91–7. https://doi.org/10.1016/J.JEMERMED.2014.12.024.
[31] Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007;147(8):573–7. https://doi.org/10.7326/0003-4819-147-8-200710160-00010.
[32] Bazett H. An analysis of the time-relations of electrocardiograms. Heart. 1920;7:353–70. https://doi.org/10.1111/J.1542-474X.1997.TB00325.X.
[33] Bazett formula. LITFL • Medical Eponym Library. https://litfl.com/bazett-formula/. Accessed August 31, 2021.
[34] Kao LW, Kirk MA, Evers SJ, Rosenfeld SH. Droperidol, QT prolongation, and sudden death: what is the evidence? Ann Emerg Med. 2003;41(4):546–58. https://doi.org/10.1067/MEM.2003.110.
[35] Yimcharoen P, Fogel EL, Kovacs RJ, et al. Droperidol, when used for sedation during ERCP, may prolong the QT interval. Gastrointest Endosc. 2006;63(7):979–85. https://doi.org/10.1016/J.GIE.2006.01.052.
[36] White PF, Song D, Abrao J, Klein KW, Navarette B. Effect of low-dose droperidol on the QT interval during and after general anesthesiaa placebo-controlled study. Anesthesiology. 2005;102(6):1101–5. https://doi.org/10.1097/00000542-200506000-00007.
[37] Tracz K, Owczuk R. Small doses of droperidol do not present relevant torsadogenic actions: a double-blind, ondansetron-controlled study. Br J Clin Pharmacol. 2015;79(4):669–76. https://doi.org/10.1111/BCP.12527.
[38] Charbit B, Albaladejo P, Funck-Brentano C, Legrand M, Samain E, Marty J. Prolongation of QTc interval after postoperative nausea and vomiting treatment by droperidol or ondansetron. Anesthesiology. 2005;102(6):1094–100. https://doi.org/10.1097/00000542-200506000-00006.
[39] Nuttall GA, Eckerman KM, Jacob KA, et al. Does low-dose droperidol administration increase the risk of drug-induced QT prolongation and torsade de pointes in the general surgical population? Anesthesiology. 2007;107(4):531–6. https://doi.org/10.1097/01.ANES.0000281893.39781.64.
[40] Nuttall GA, Malone AM, Michels CA, et al. Does low-dose droperidol increase the risk of polymorphic ventricular tachycardia or death in the surgical patient? Anesthesiology. 2013;118(2):382–6. https://doi.org/10.1097/ALN.0B013E31827DDE8D.
[41] Weibel S, Rücker G, Eberhart LH, et al. Drugs for preventing postoperative nausea and vomiting in adults after general anaesthesia: a network meta-analysis. Cochrane Database Syst Rev. 2020.;19(10). https://doi.org/10.1002/14651858.CD012859.pub2 CD012859.
[42] Vandenberk B, Vandael E, Robyns T, et al. Which QT correction formulae to use for QT monitoring? J Am Hear Assoc Cardiovasc Cerebrovasc Dis. 2016.;5(6). https://doi.org/10.1161/JAHA.116.003264.
[43] Chen Y, Guo X, Sun G, Li Z, Zheng L, Sun Y. Effect of serum electrolytes within normal ranges on QTc prolongation: a cross-sectional study in a Chinese rural general population. BMC Cardiovasc Disord 2018 181. 2018;18(1):1–8. https://doi.org/10.1186/S12872-018-0906-1.
[44] Hawthorne effect. Wikipedia. https://en.wikipedia.org/wiki/Hawthorne_effect. Accessed August 31, 2021.