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Perioperative Torsade de Pointes: A Systematic Review of Published Case Reports

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Abstract

Background—Torsade de pointes is a rare, but potentially fatal arrhythmia. More than 40 cases of perioperative torsade de pointes have been reported in the literature; however, the current evidence regarding this complication is very limited. To improve our understanding we performed a systematic review and meta-analysis of all published case reports of perioperative torsade de pointes.

Methods—MEDLINE was systematically searched for cases of perioperative torsade de pointes. We included patients of all age groups, and cases that occurred from the immediate preoperative period to the third postoperative day. Patient and case characteristics as well as QT interval data were extracted.

Results—Forty-six cases of perioperative torsade de pointes were identified; 29 occurred in women (67%) and two episodes were fatal (case fatality rate: 4%). Craniotomies and cardiac surgery accounted for 40% of all cases. Preceding events identified by the authors were

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See Disclosures at end of article for Author Conflicts of Interest.

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hypokalemia (12/46, 26%; 99%CI 9% – 43%) and bradycardia (7/46, 15%; 99%CI 2% – 28%). Drugs were implicated in approximately one-third of the events (14/46, 30%; 99% CI 13% – 48%). The mean QTc at baseline was 457 ± 67ms (min. 320ms; max. 647ms; data available in 27/46 patients). At the time of the event, the mean QTc increased to 575 ± 77ms (min. 413ms; max. 766ms; data available in 33/46 patients). On average, QTc increased by +118ms (99% CI 70 – 166 ms; $p < 0.001$) between baseline and after the torsade de pointes event. All patients, except for two, had a substantial prolongation of their QTc interval at the time of the event.

Conclusions—This systematic review identified several common risk factors for perioperative torsade de pointes. Given the nearly uniform presence of a substantial QTc interval prolongation at the time of a torsade de pointes episode, increased vigilance for perioperative QTc interval prolongation may be warranted.

Introduction

Torsade de pointes is a rare, but potentially fatal polymorphic ventricular tachycardia.[1] This arrhythmia characterized by a typical twisting of the QRS complex morphology[2] has several unique features among ventricular tachyarrhythmias.[3] First, the ventricular rate in torsade de pointes is often less than 200 beats per minute and it frequently terminates spontaneously, although it can degenerate into ventricular fibrillation and cardiac arrest. Second, torsade de pointes most frequently occurs when the heart rate-corrected QT (QTc) interval is prolonged >500ms and the electrocardiogram shows a characteristic QT-U wave deformity. Furthermore, torsade de pointes occurs nearly always in patients with an abnormal QT interval which is commonly referred to as long QT syndrome, a condition of abnormal cardiac repolarization.[2,4] The long QT syndrome can be congenital or acquired, or a combination thereof. Acquired long QT syndrome is commonly the result of QT interval-prolonging drugs.[5,6] There is a strong correlation between QTc prolongation and the risk for torsade de pointes, but there is no absolute QTc threshold above which torsade de pointes routinely occurs. Several drugs that are routinely administered in the perioperative setting, such as antibiotics, sevoflurane,[7–10] or ondansetron[11–13] have been shown to cause QTc interval prolongation. Furthermore, in a recent study we found that the 80% of patients undergoing noncardiac surgery under general anesthesia developed postoperative QTc prolongation with a median increase of 23ms.[14]

Since the 1970s more than 40 case reports of torsade de pointes occurring in the perioperative setting have been published. However, there has been no systematic review of this subject on the clinical features, precipitating events, and treatments of the potentially fatal arrhythmia occurring in the perioperative setting. The aim of this study was to perform a systematic review and analysis of all published case reports of perioperative torsade de pointes.

Methods

Search Strategy

The MOOSE (Meta-analysis Of Observational Studies in Epidemiology)[15] and PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses)[16] guidelines were followed in our systematic review. In December 2011, we performed a systematic search on MEDLINE for the following search terms: “Surgery AND Torsades de pointes,” “Surgery AND Torsade de pointes,” “Anesthesia AND Torsades de pointes,” “Anesthesia AND Torsade de pointes,” “Perioperative AND Torsades de pointes,” “Perioperative AND Torsade de pointes,” “Intraoperative AND Torsades de pointes,” “Intraoperative AND Torsade de pointes,” “Postoperative AND Torsades de pointes,” “Postoperative AND Torsade de pointes.” This search resulted in 289 hits (Figure 1).

Case report selection

Case reports were eligible for inclusion when they reported episodes of torsade de pointes occurring in close temporal relationship to a surgical procedure either under general or regional anesthesia or sedation in human patients. The torsade de pointes event must have occurred between the immediate preoperative phase and the third postoperative day. We did not exclude any age group. Cases were considered from all languages and a particular emphasis was put on including reports from non-English sources. If the publication could not be accessed electronically or in print, we attempted to contact authors by email. The search and case report selection was primarily conducted by one author (JJ) with the help of a second (SP) under supervision by PN. Selection of cases was typically straightforward and any initial disagreement resolved by consensus.

Data Extraction

If available, the following variables were extracted from the case reports: patient characteristics (e.g., age, sex), timing of the torsade de pointes event, heart rates at baseline and at the event, electrolytes, administered drugs, pre- and postevent QT interval duration administered treatments such as defibrillation and magnesium, and outcome (fatal/nonfatal).

Statistical Analysis

Correction for heart rate of the QT interval (QTc) is reported using Bazett's formula ($QTcB = QT/\sqrt{RR}$). Pooled categorical and nominal variables are summarized by frequencies and percentages in a fixed-effects meta-analysis. We compared QTc interval duration before the torsade de pointes event with QTc during or after the event using an unpaired two-sided t-test. The D'Agostino and Pearson omnibus normality test was used to determine if QTc measurements were normally distributed before hypothesis testing (QTc values at baseline: $p= 0.0606$; QTc values at or after torsade de pointes: $p= 0.5064$). GraphPad 6.01 was used for graphing and statistical analysis (GraphPad Software Inc., LaJolla, CA).

Results

The comprehensive search strategy identified 46 case reports of perioperative torsade de pointes.[17–60] These reports were published between 1978 and 2011. Of the 46 cases, 29 occurred in female patients (67%), 14 in male patients (33%) and 2 were of unknown sex. Five patients had a diagnosis of congenital long QT syndrome. The median age among patients with congenital long QT syndrome who developed torsade de pointes was 11 years (range: 8 to 32 years); among patients without congenital long QT syndrome the median age was 56 years (range: 6 weeks to 80 years).

The mean duration of the baseline QTc interval (available in 27 of 46 cases) was 457 ± 67ms (min. 320ms; max. 647ms). At the time of the event, or shortly thereafter, the mean QTc increased to 575 ± 77ms (min. 413ms; max. 766ms; data available for 33 of 46 patients) as shown in Figure 2. At the time of the event, the median heart rate was 62/min (minimum 40 – maximum 105/min; data available for 15 of 46 patients). In 24 patients, QTc interval duration was available before and after the event. These results showed that the QTc increased by +118ms (99% CI 70 – 166 ms; $p< 0.001$; Figure 2). Two patients had only a minor change in their respective QTc (less than ± 10ms); all others had a substantial prolongation of the QTc interval at the time of the event. Before the torsade de pointes episode, 14 of 27 patients (52%; 99% CI 27% – 77%) had a QTc >440ms and 6 of 27 >500ms (22%); after the event, 32 of 33 (97%; 99% CI 89% – 100%) had a QTc >440ms and 26/33 (79%; 99% CI 61% – 97%) >500ms.

The systematic review and meta-analysis identified several characteristics associated with perioperative torsade de pointes (summarized in tables): Table 1 reports the time point and Table 2 lists all surgical procedures during which torsade de pointes events occurred. Preceding events identified by the authors of the individual case reports are shown in Table 3. In nine cases (20%), the combination of several factors such as hypokalemia or congenital long QT syndrome and QT interval-prolonging drug was identified as trigger for the torsade de pointes event. Table 4 lists all implicated drugs. Two episodes of perioperative torsade de pointes were fatal (case fatality rate: 4%); 40% were treated with magnesium and more than one in four patients required defibrillation. Table 5 lists all commonly used treatment strategies.

Discussion

In what we believe is the first systematic analysis of perioperative torsade de pointes, we were able to identify 46 case reports. There are several pertinent findings resulting from the pooling of the available evidence from these case reports. First, nearly all episodes of perioperative torsade de pointes occurred when the QTc interval was substantially prolonged. Our data show an increase of > 100ms at the time of the event compared to baseline in the majority of patients while only two patients had no significant increase in QTc. It therefore appears that QTc interval prolongation is nearly always required to develop perioperative torsade de pointes, but in itself is not sufficient to trigger actual episodes. As in other settings, perioperative torsade de pointes appears to be triggered by a simultaneous occurrence of several factors in the presence of QTc prolongation, such as hypokalemia, bradycardia, or drug-drug interactions. In a recent prospective study we found that among 469 patients undergoing noncardiac surgery under general anesthesia, more than 80% developed postoperative QTc prolongation and one patient developed torsade de pointes (incidence rate of 0.4%).[14] As in this report, many of these patients received several drugs within a short period of time that likely contributed to QTc prolongation. Consistent with previous evidence, perioperative torsade de pointes appears to be more prevalent in women than men.[61,62] Patients with diagnosed congenital long QT syndrome had episodes of perioperative torsade de pointes at a much earlier age (median age 11 years)[63] compared to patients without this diagnosis (median age 56 years).

It is noteworthy that several drugs were implicated in the case reports of perioperative torsade de pointes, but not droperidol for which the Food and Drug Administration issued a “black box” warning regarding the QTc prolongation risk.[12,13,64] Many other perioperatively administered drugs such as ondansetron[65] and metoclopramide[66] also prolong the QTc interval.

Among the 46 identified cases of perioperative torsade de pointes, procedures and conditions, such as cerebral aneurysm rupture, cardiac surgery, and pheochromocytoma, appear to be over-represented. We do not have a clear explanation for this observation and it may represent random chance, but perhaps it is related to elevated catecholamine levels. Catecholamine release and stress have been previously shown to trigger episodes of torsade de pointes[67,68] so these surgical procedures and conditions may be associated with a higher risk for perioperative torsade de pointes. It is noteworthy that only 4% of perioperative torsade de pointes cases were fatal. However one in four patients required defibrillation but the majority of events responded to magnesium, lidocaine or were self-terminated.[5]

Evidence regarding even the most basic facts about perioperative torsade de pointes is largely missing. Since most episodes are unreported, there is little evidence regarding the precise incidence or prevalence of this condition. Nonsurgical hospitalized patients are at higher risk for torsade de pointes[3] and the perioperative period may also be a period of

increased risk due to the potential exposure to multiple drugs that can affect myocardial repolarization.[14] Forty-six case reports over 40 years may indicate a very low, negligible prevalence of perioperative torsade de pointes. Reporting bias, the tendency to under-report less desirable findings, was clearly a major limitation of our study. Neither numerator nor denominator are known to accurately estimate the prevalence of torsade de pointes in surgical patients and only large-scale epidemiological studies will be able to provide this evidence. Recently the American Heart Association and the American College of Cardiology Foundation published guidelines on the "Prevention of Torsade de Pointes in Hospital Settings" with the goal to raise awareness about this potentially fatal arrhythmia and its prevention.[3] The authors of this statement argue that hospitalized patients are often at higher risk for torsade de pointes as they have other risk factors for proarrhythmic response and are often exposed to multiple QT-prolonging drugs.

This study had several limitations. First, the quality of any systematic review is dependent on the available studies and published case reports. Case reports of perioperative torsade de pointes did not follow a uniform reporting standard, so missing data were a substantial limitation. Important variables such as medical risk factors, drugs, and level of electrolytes were not uniformly captured. Furthermore, it is to be expected that there are many more cases of perioperative torsade de pointes than represented by the 46 reports we identified. Second, cases that occurred in the 1970s and 1980s may have become less relevant for modern medical practice as several of the drugs implicated in perioperative torsade de pointes or are no longer widely used (e.g., halothane, droperidol, flecainide or sotalol). As mentioned above, reporting bias is without a doubt the most significant limitation of this study. Nevertheless, we believe that even given these severe limitations, our study provides novel and potentially important insights into perioperative torsade de pointes.

In conclusion, this systematic review identified several common characteristics among 46 case reports of perioperative torsade de pointes. Nearly all episodes were preceded by a substantial QTc prolongation that was commonly the result of several QTc-prolonging factors. Given the common exposure to drugs and physiologic stressors with potential effects on myocardial repolarization, increased vigilance for perioperative QTc interval prolongation and the potential for torsade de pointes may be warranted.

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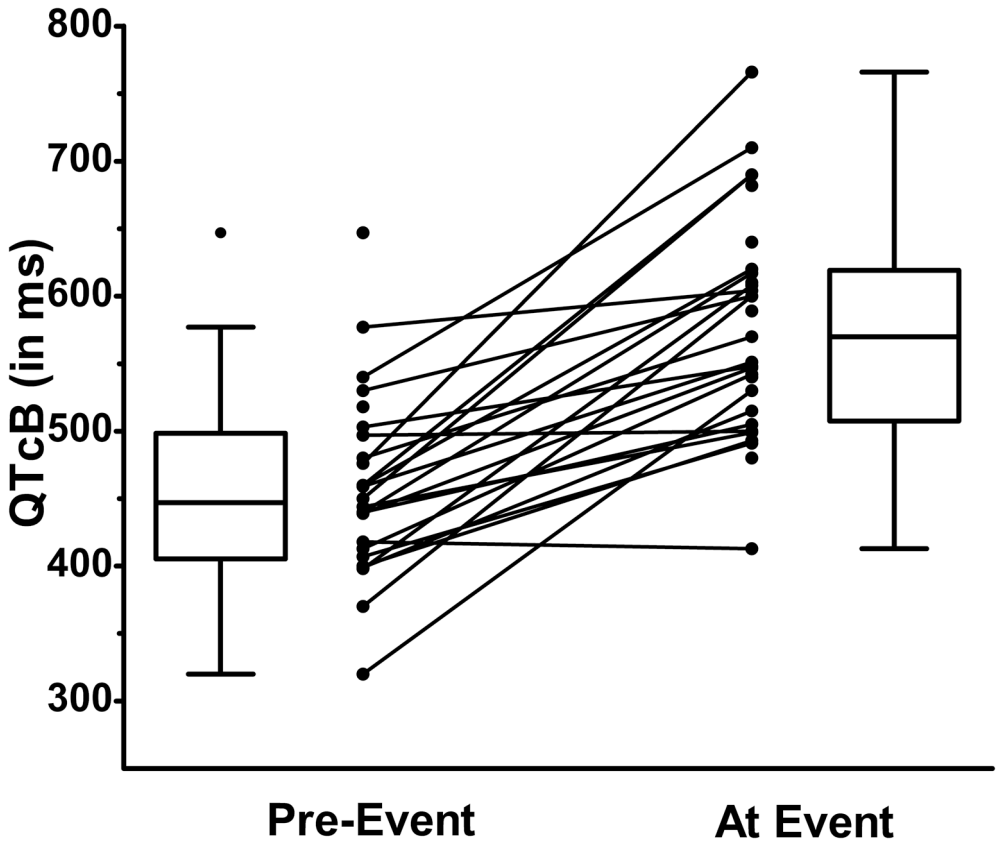

Figure 1.
Study selection process.

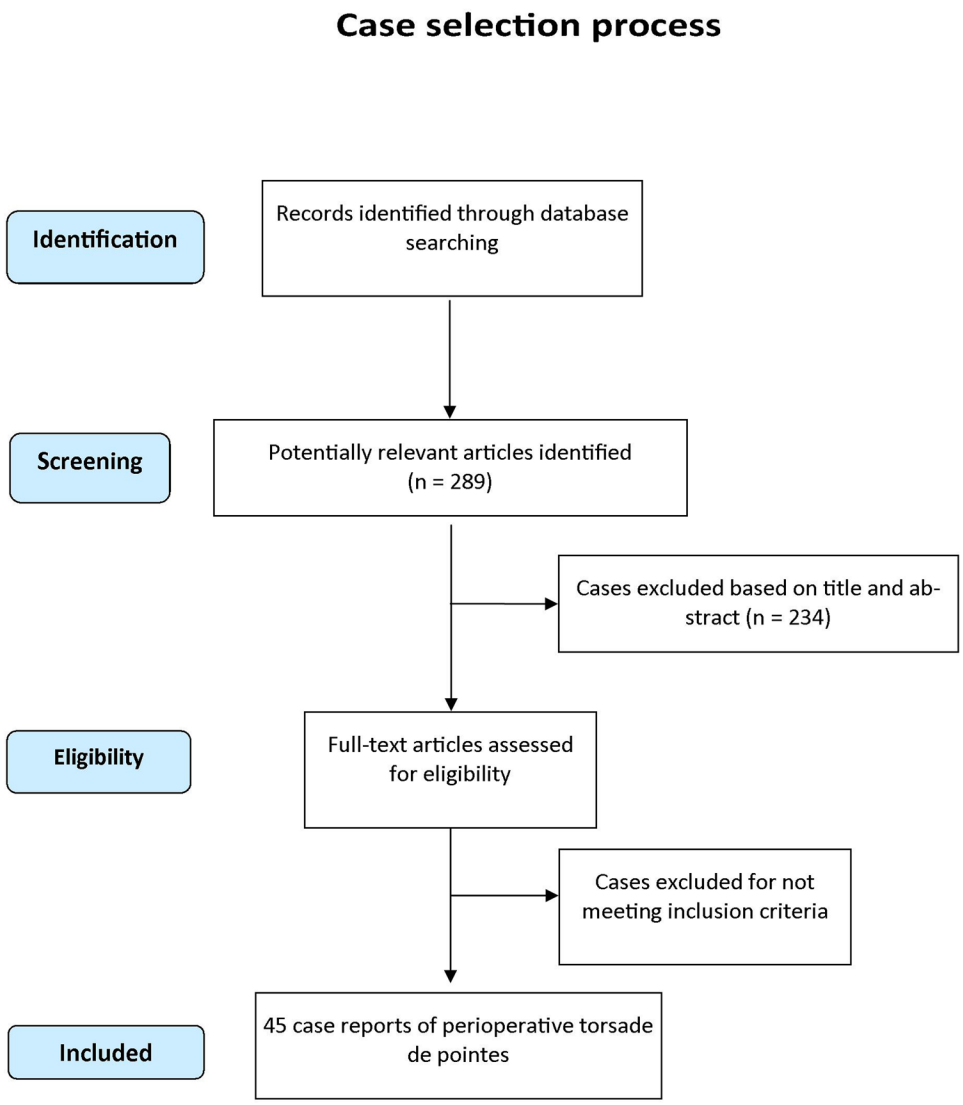

Figure 2.

Dispersion of QTc interval duration before, during, or after the perioperative torsade de pointes event (n=45). QTcB = heart-rate corrected QT interval using Bazett's formula. Box plots indicate the 25th and 75th percentile; the whiskers reflects the median and the error bars indicate the Tukey's distance (1.5 times the interquartile distance).

Table 1

Time Point of Torsade de Pointes Episode

Time Point of Torsade de Pointes Event	Frequency n (%)
Preoperative	2 (4)
Induction	3 (7)
Maintenance	22 (49)
Emergence	1 (2)
Postoperative	19 (42)

Some events occurred more than once. Percentages do not add to 100%.

Table 2

Procedures where Torsade de Pointes Episodes Occurred

Procedures	Frequency n (%)
Cardiac	12 (27)
CABG	3 (7)
Cardiac surgery, non-CABG	3 (7)
Radiofrequency Ablation	4 (9)
AICD	2 (4)
Craniotomy	6 (13)
Cerebral Aneurysm Clipping	4 (9)
Meningioma Resection	2 (4)
Liver Transplant	3 (7)
Adrenalectomy	3 (7)
Colon Resection	2 (4)
Others (all 1 case only)	19 (42)
Total	*46 (100)*

CABG – coronary artery bypass graft; AICD – automated implantable cardioverter-defibrillator

Table 3

Preceeding Events for Torsade de Pointes Episodes Identified by the Authors of the Case Reports

Preceeding Events	Frequency n (%)
Hypokalemia	12 (28)
Hypomagnesemia	4 (9)
Hypocalcemia	2 (5)
Bradycardia	7 (16)
Drugs	13 (30)
Congenital Long QT Syndrome	5 (12)

More than one factor could be present in an episode of torsade de pointes.

Table 4

Drugs Implicated in Torsade de Pointes Episodes.

Drugs
Procainamide
Mannitol and subsequent hypokalemia
Sevoflurane, Disopyramide, Lidocaine
Cyclobenzaprine
Haloperidol
Halothane
Sevoflurane
Dolasetron
Flecainide
Sotalol
Erythromycin, Amiodarone, Ciprofloxacin
Tacrolimus
Papaverine

Drugs are listed as reported in the published case reports. Several episodes of torsade de pointes occurred as a result of drug-drug interactions.

Table 5

Treatment used for Torsade de Pointes Events

Treatment	Frequency n (%)
Magnesium	18 (40)
Lidocaine	14 (31)
Defibrillation	12 (28)
Potassium	5 (11)
Overdrive pacing	5 (11)
Isoproterenol	3 (7)
Amiodarone	1 (2)

More than one treatment may have been necessary to treat the torsade de pointes event