Trends in Anaesthesia and Critical Care 14 (2017) 3–8

Contents lists available at ScienceDirect

Trends in Anaesthesia and Critical Care

journal homepage: www.elsevier.com/locate/tacc

Review

Anesthesia for children with long QT syndrome: Challenges and solutions from pediatric studies

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ARTICLE INFO

Article history:
Received 21 December 2016
Received in revised form
13 April 2017
Accepted 10 May 2017

Keywords:
Prolonged QT interval
Long QT syndrome
Long QT syndrome and anesthesia
Anesthesia and pediatric arrhythmias
Anesthesia and genetic disorders in children

ABSTRACT

Background: The overall prevalence of Long QT syndrome (LQTS) is as high as 1 in every 2534 live births which exceeds few common genetic-bound anesthesia related disorders. Given less attention than even the rarer malignant hyperthermia, LQTS incidence is expected to be much higher during anesthesia and surgery for very reasons that they contribute to acquired LQTS. Thus, confined to original researches on pediatric patients, the aim of this review was to assess challenges and solution of LQTS during pediatric anesthesia.

Methods: and finding: Seventeen studies conducted on pediatric population from Medline and Google scholar search results were finally analyzed. The review protocol was registered in PROSPERO. Assuming that whatever observed in adult researches may not apply for children; we included individual studies carried out just on children. Shortage of purely pediatric researches about LQTS was observed. Widely used in the literature, prolonged QT interval was employed as predictor of LQTS in this review. Narrative approach was used to analyze results. Preoperative anxiety and seizure are risk factors for LQTS. Whereas propofol and halothane shorten QT interval and can be used to treat LQTS; most of inhalational agents and few adjuvant drugs prolong QT interval and predispose children to the syndrome. Beta blockers and magnesium sulphate were effectively used to treat long QT syndrome perioperatively.

Conclusion: LQTS worth emphasis as the prevalence and associated complications exceed some commonly discussed genetic disorders in anesthesia. Preoperative evaluation of pediatric patients directed to identifying perioperative risk factors and preparation for respective management minimizes potentially fatal complications associated with long QT syndrome.

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Contents

1. Introduction

Long QT syndrome has non negligible prevalence yet given less emphasis in the arenas of perioperative care. Different ranges of "educated guess" have been used to estimate the prevalence of LQTS and the figure vary with place and time of the report. The

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http://dx.doi.org/10.1016/j.tacc.2017.05.003
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overall prevalence of LQTS in USA population, for example, is about 1 in 7000 persons out of which 99% is due to Romano-Ward syndrome and only 1% is related to Jervell–Lange-Nielsen syndrome. Accordingly, LQTS accounts for 2000 to 3000 sudden deaths among children and adults in the same nation [1]. According to recent study, about one out of 2534 live births has congenital LQTS [2] and this figure is by no means lower than other frequently discussed gene-bound disorder called malignant hyperthermia (~1:3000) [3]. Although no report has been found so far, the incidence of LQTS in children for surgery is expected to be much higher during anesthesia as a result of different drugs and procedures that predispose apparently health children to acquired long QT syndrome. There are two types of long QT syndrome based on the way how people contracted this fatal condition-congenital and acquired long QT syndrome. Congenital LQTS is well studied than the acquired one, and the former is of great interest in that it is associated with various genetic encoding and mutations. There are about thirteen identified genes associated with distinct congenital QT syndrome subtypes so far, namely KCNQ1(LQT1), KCNH2(LQT2), SCN5A(LQT3), ANKB(LQT4), KCNE1(LQT5), KCNE2(LQT6), KCNJ2(LQT7), CACNA1C(LQT8), CAV3(LQT9), and SCN4B(LQT10), AKAP9(LQT11), SNTA1(LQT12) and KCNJ5(LQT13) [4]. However, about 90% of LQTS are related to the first three sub types: KCNQ1(LQT1), KCNH2(LQT2) and SCN5A(LQT3) [5,6]. Because 5–10% of gene carriers do not exhibit prolonged QT interval [7], genetic screening may not reliably predict congenital long QT syndrome. Various possible etiologies of acquired long QT syndrome-ranging from routine medicines, antiarrhythmic drugs and anesthetics, to some physical factors-have been discussed elsewhere in literature [8]. There are two hypotheses about pathophysiology of long QT syndrome [9]. The first hypothesis suggests that imbalance between left and right cardiac sympathetic activities-increased right and decreased left sympathetic tone causes LQTS. The second pathophysiologic hypothesis, which is more recent and widely accepted one, suggests that cardiac ion channel dysfunction causing repolarization abnormality is responsible for LQTS. Regardless of hypotheses, several drugs and conditions exacerbate both congenital and acquired LQTS while some others attenuate this exacerbation. Prolonged QT interval may be resolved spontaneously but sometime it may be complicated into torsade des pointes (TdP) or other forms of cardiac arrhythmias [10]. QT is an interval on ECG wave which represents ventricular repolarization (Fig. 1) and often corrected to heart rate (QTc) based on Bazett formula, $QTc = QT/\sqrt{RR}$ [11]. Helpful for perioperative prediction, prolonged QTc (Table 1) is single most important risk factor or indicator of long QT syndrome [12] and we rely on the QTc prolongation while discussing findings of perioperative LQTS in this review. The author noted that reviews of LQTS are either less focused-fail to include solely pediatric studies or less generalizable-fail to systematically review empirical data other than case reports. Thus, the aim of this systematic review was to identify challenges and solutions of anesthesia for children with long QT syndrome that underwent or prepared for different non cardiac surgeries and procedures of anesthesia. Persuaded that children are not small adults and a review of pediatrics should employ individual studies pertinent to children, we included existing researches conducted on children. Anesthesia related challenges of patients with LQTS that we sought scientifically recommended solutions begins at preoperative visit, continues intraoperatively and ends in postoperative period. Thus, our analytical discussion follows this logical pattern-firstly, children with LQTS: preoperative challenges and solutions, secondly, children with LQTS: intraoperative challenges and solutions, and thirdly, children with LQTS: postoperative challenges and solutions.

2. Methods

Original researches conducted on pediatric population directly or indirectly related to perioperative management were included in this systematic review with exception of few articles used while discussing the background and rationale of the study. The review protocol had been registered in PROSPERO (ID: CRD42016048259) before start of searching articles [33]. In a period of June 2016 to September 2016 articles were searched using two search engines, namely, Medline and Google scholar. “Causes or treatment of Long QT* during anesthesia AND pediatric* OR children NOT cardiac sympathetic denervation” was the search strategy used. Besides, references of some important articles were used to manually search and include them based on their relevance to the topic. Inclusion criteria were pediatric LQTS or prolonged QT interval articles, articles in English language and original research other than case report, case series and review. Reviews and update were used just as support of finding and respective discussions. Both published and unpublished (gray literature) articles were included (Fig. 2.). Heterogeneity of the study following wider scope of the topic was the reason not to use meta-analysis and we preferred structured systematic narrative approach.

3. Result

Initial search from the two engines (Medlin and google scholar) and manual search resulted in 264 results. After removing 12 articles- 8 duplicated and 2 published in languages other than English, 254 articles were assessed for eligibility. 237 studies that did not fulfill inclusion criteria were excluded and finally 17 studies [13–17,20–31] were qualitatively analyzed. As this review deals only with primary studies on pediatric LQTS, some important non-pediatric patient studies were intentionally excluded. All of the analyzed studies had been conducted on pediatric population. 16 out of 17 studies were quantitative researches. Nine (52.9%) studies assessed the causes of LQTS whereas four (23.5%) studies dealt with its treatments. Each of the remaining four studies was about both cause and treatment; adverse events associated with LQTS; cause, treatment and adverse events; and determinants of life quality of children with LQTS, respectively. Positive family history and unexplained seizure were reported as common predictors of LQTS. Sympathetic stimulation, sevoflurane, isoflurane, desflorane, ondansetron and droperidol were found to prolong QT interval and cause LQTS. Propofol and halothane have neutral or shortening effect on QT interval. Beta blockers and magnesium were reported to prevent and treat LQTS. Any factor that cause or exacerbate LQTS while managing patients is considered as challenge whereas a factor that is known to prevent or treat the condition is considered as solution in this review.

4. Discussion

Problems related to anesthesia for children with long QT syndrome might occur either preoperatively, intraoperatively or postoperatively. Based on findings, the pattern of perioperative challenges and recommended solutions are discussed below.

1. Children with LQTS: preoperative challenges and solutions

The magnitude and characteristics of preoperative presentations-familial or personal history, physical examination and diagnostic study findings of children with congenital LQTS was addressed in an international study by Garson et al. Accordingly, 85% of patients with congenial LQTS are symptomatic of who more than half were with serious symptoms such as syncope (26%),

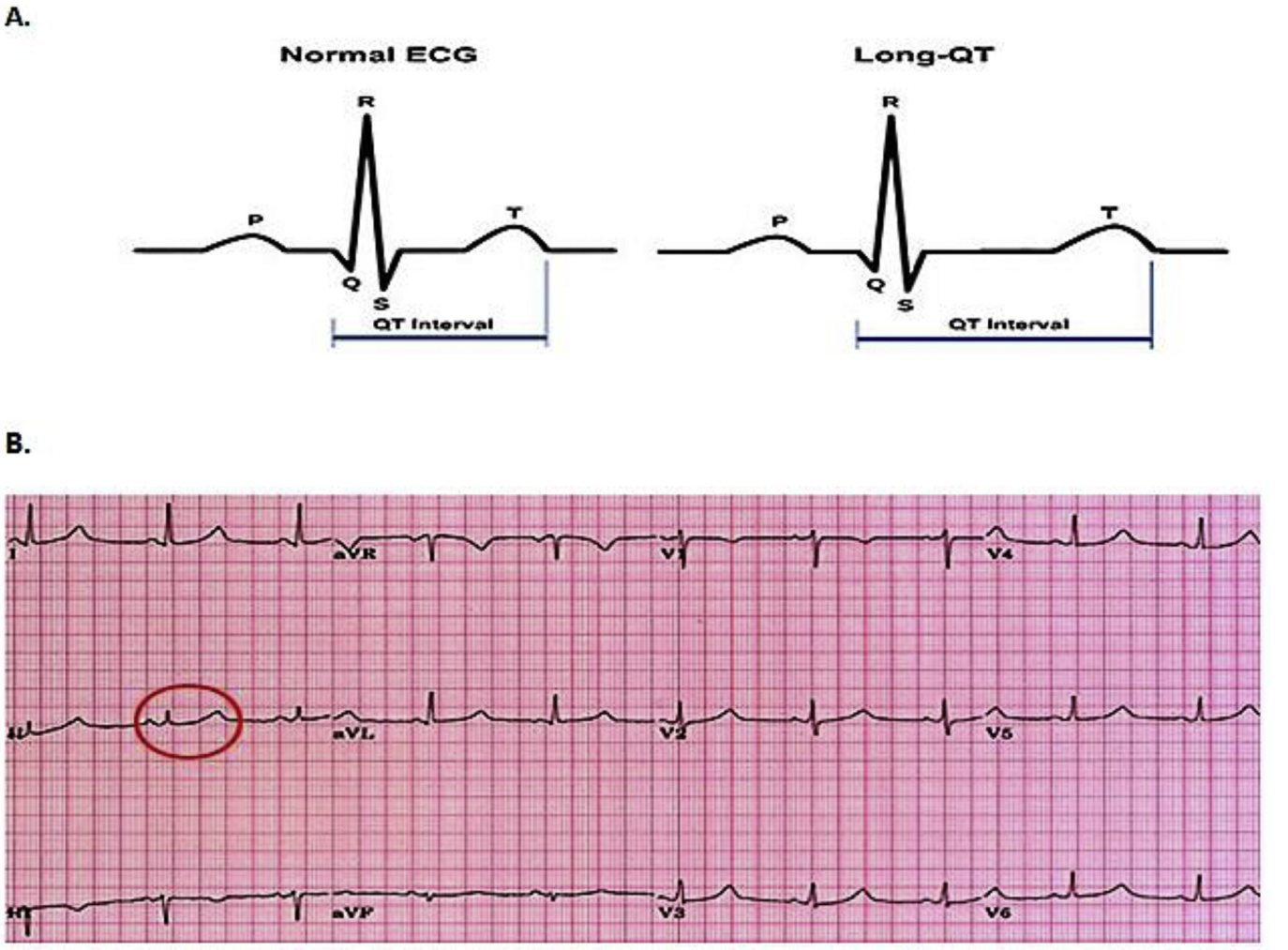

Fig. 1. A. Normal and prolonged QT interval **B**. prolonged QT on sample ECG.

Table 1
QT interval reference values for children.

QTc rating	Values[a]
Normal	<440 ms
Border line	440-460 ms
Prolonged	>460 ms

[a] Commonly for age 1–5 years.

seizure (10%) and cardiac arrest (9%). Anesthesia accounts for 2% of the etiology of symptomatic patients. On routine ECG, both symptomatic and non-symptomatic patients had ventricular arrhythmia with incidence of 16% and prolonged QTc, but these signs were significantly more ($p < 0.01$ and $p < 0.001$) in symptomatic patients. TdP accounts for 6% of ventricular arrhythmias. Hearing loss and congenital heart problem were common concomitant problems of children with LQTS consisting of 4.5% and 12% of all patents, respectively. These patients had positive family history of the same illness (60%), sudden death (31%), syncope (6%) and seizure (2%). Some 6% of patients with diagnosed congenital LQTs had normal QT interval (QTc<0.44sec), but those patients with QTc greater than 0.55sec had associated serious symptoms at presentation. Bradyarrhythmia was observed in 20% of patients before treatment. Patients were presented with various treatments: propranolol (51%), other beta blockers (27%), phenytoin (5%), mexiletine (3%), left sellectomy (2%), pacemaker implantation (15%) and defibrillator implantation (1%) [13]. During preoperative evaluation and preparation of children with LQTS, the provider should understand the lived experience of patients yet the failure may create the vicious cycle- LQTS needs preoperative treatment and treatment *per se* may aggravates LQTS if it causes anxiety and stress. Moreover, in a qualitative study by McElwaine, children with LQTS experience symptoms of anxiety and it was attributed to potential increment in sympathetic outflow and probably worsens LQTS. In this regard, in the same study it was also hypothesized that children with LQTS do not enjoy going for treatment and sometimes it may cause anxiety [14]. Fear and anxiety were not seemed to be the only findings reported, but other factors found less relevant to this subject. The report has both the pros and cons of qualitative study-in depth understanding of the problem and non-generalizability of the finding, respectively. The finding of this qualitative study may not be generalized to all children with LQTS, yet it is possible to draw conclusion for similar group of children participated in that study, and most importantly it is possible to draw testable hypothesis that "going to hospital and getting treatment causes anxiety among children with LQTS which by itself worsens the syndrome". So, to be on the safer side, we should assume that our pediatric patients with LQTS may have anxiety which predisposes to exacerbation of LQTS unless cautiously premedicated during preoperative visit. On the other hand, according to Sadmie et al., patients with history of

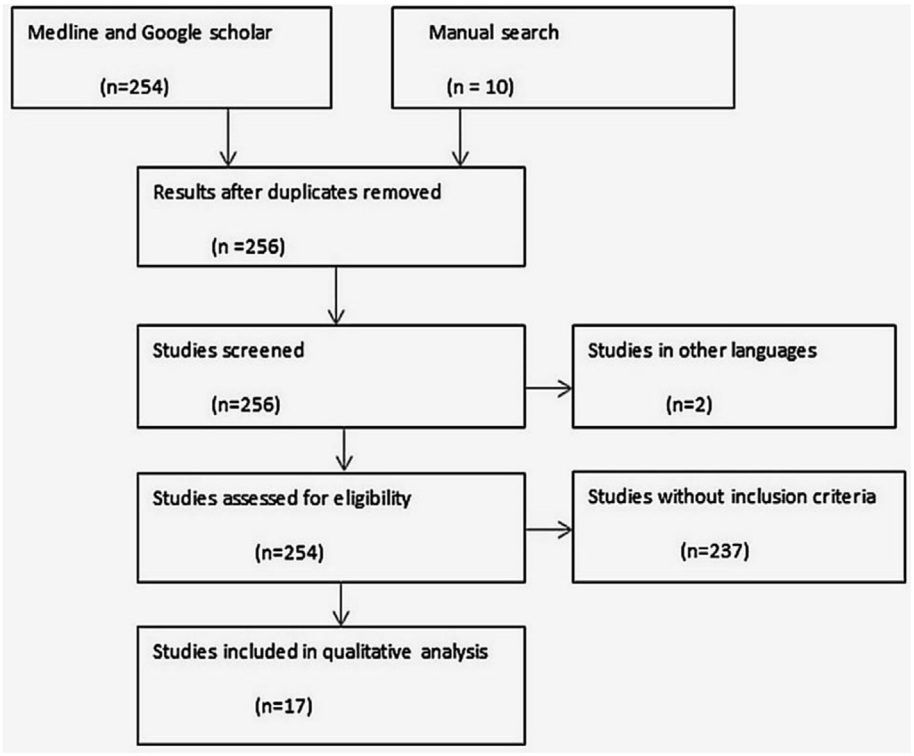

Fig. 2. Flow diagram of search records.

seizure of unknown origin have higher risk of developing prolonged QT interval which predisposes them to long QT syndrome. History of seizure is routinely assessed as "past medical history" during preoperative evaluation of surgical patients, and we should suspect perioperative LQTS for children with positive history unless ruled out [15]. Symptomatic children during presentation may have different outcome compared to nonsymptomatic patients. Relevant to preoperative evaluation, as reported in recent study by Villian et al., majority of symptomatic patients had syncope (72.1%) followed by cardiac arrest (11.5%), sinus bradycardia (9.8%) and 2:1 atrioventricular block (6.5%). During diagnosis symptomatic group had longer QTc mean (SD) compared to asymptomatic counterpart, 510 (62)ms verses 469 (31)ms ($p = 0.009$). During treatment 90.2% of group diagnosed with symptoms and 98.4% of group diagnosed with familial screening (initially asymptomatic) remained free of symptoms with beta blocker as sole treatment [16]. Thus, this finding may logically implies standard dose beta blocker therapy during anesthesia for pediatric patients with LQTS improves cardiac events and the effectiveness of the treatment is mainly related to preoperative presentation of patients. On the other hand, if screened preoperatively, low serum ionized calcium level may indicate long QTc in children with seizure. Compared to children with one episode of seizure and those without any, children with frequent seizure have significantly prolonged QTc and low ionized calcium level [17]. This association might help care providers in two ways-firstly, predict presence of long QTS in convulsing patients and secondly, probability of prolonged QTc in patients with low serum ionized calcium level. An important thing which routinely sought during preoperative visit is history of medication where beta blockers being one of treatments children with LQTS might be on. Beta-blockers were introduced for treatment of LQTS as early as 1970s and ever since it has been used as mainstay of pharmacologic treatment of the condition because it blocks the sympathetic stimulation that triggers life threatening arrhythmias [18,19]. Nevertheless, all beta blockers are not equally effective in preventing and treating QTc prolongation [20]. Accordingly the prototype beta blocker, propranolol reduces QTc more than metoprolol ($p < 0.003$) and nadolol ($p < 0.004$). The QTc shortening by propranolol is more effective when QTc is initially prolonged (>0.48sec) than normal or border line. In the same study it was suggested that propranolol is effective treatment for symptomatic congenital LQTS particularly LQT1 and LQT2.

2. Children with LQTS: intraoperative challenges and solutions

Intraoperative etiologies are attributed to either induction drugs, maintenance agents or any procedures carried out intraoperatively. Propofol at different doses or target effect site concentrations that known to produce surgical anesthesia (3, 4.5, or 6 μg/mL) has no effect on the two predictors of torsade des pointes- QTc and Tp-e even if used as sole induction anesthetic [21]. Therefore absence of associated clinical or statistical prolongation of QTc and Tp-e favors use of propofol for children with long QT syndrome. But, when used as inhalational induction or maintenance agent sevoflurane increases QT interval in children compared to propofol-more than 30 ms versus 8 ms from baseline after 15th minute, respectively ($p < 0.05$) [22]. Thus, it can be concluded that Sevoflurane may cause LQTS in otherwise healthy children perioperatively but it doesn't necessarily mean sevoflorane anesthesia causes TdP. Does the effect of sevoflurane depend on dosage? No. Sevoflorene prolongs QTc without dose-response association in children. According to Whyte et al., at age adjusted MAC of 1, 1.25 and 1.5; all children exposed to different doses of sevoflurane showed significant QTc prolongation compared to pre-exposure intervals, but there were no statistically significant variation among the three groups [23]. This finding, with sound design, confirms exposure of children to sevoflurane prolongs the QTc, but the prolongation is not dose

dependent. Sevoflurane has taken over the position of halothane as pediatric inhalational induction agent for its relatively rapid onset. However sevoflorane prolongs QTc and causes LQTS in otherwise healthy infants compared to halothane. In a study compared three point interval ECG recordings-before induction, 15th minute during anesthesia and an hour after emergence-sevoflurane abnormally prolonged QTc (greater than 440 ms) intraoperatively but the QTc was less than 440 ms in all groups an hour after emergence from anesthesia [24]. Therefore, although sevoflorane has good profile for mask induction; it predisposes pediatric patients to LQTS compared to halothane. Can halothan shorten QTc, then? Yes. Halothane anesthesia shortens QT interval in children whereas isoflurane anesthesia prolongs it. In a study where several confounders were controlled, Isoflurane significantly ($p < 0.001$) prolonged QTc whereas halothane shortened it ($p < 0.001$) [25]. The report may suggest use of halothane in case of both acquired and congenital LQTS intraoperatively so that it shortens QT interval. Premedication with potent benzodiazepines such as midazolam and induction with propofol may not blunt "clinical" prolongation of QTc and subsequent arrhythmias if desflorane is used at pediatric standard MAC [26]. Regardless of clarity in design regarding consistency of laryngoscopy manipulation among groups and effect of very small and varying sample size in the report, desflorane showed significant QTc prolonging effect than sevoflorane for 30 min after induction of anesthesia. Beside beta blockers and halothane, dexmedetomidine is suggested as an option for shortening QTc and managing intraoperative LQTS in bolus administration [27]. However, a report from adult cardiac electrophysiological study resulted in doubt about the perceived benefit of dexmedetomidine as it caused slight QTc prolongation [28]. The effect of dexmedetomidine should be further investigated using stronger study design in the future to test the contradicting hypothesis. Similar to beta blockers, magnesium is widely recommended in literature for treatment of LQTS. Magnesium sulfate (MgSO4) therapy effectively reverses torsade de pointes secondary to either congenital or acquired long QT syndrome. Accordingly, Hoshino et al. studied effect of MgSO4 with IV bolus dosage of 2.3–12 mg/kg in six children and the same bolus plus two more boluses every 5–12 min (total 30 mg/kg) for a neonate and found that the therapy effectively reversed TdP without shortening QTc interval [29]. Intravenous infusion used for prevention of recurrence with a rate of 0.3–1.0 mg/kg/h and entire plasma concentration of magnesium after magnesium therapy was within normal physiologic range. However the change in QTc was not statistically significant after treatment. Before starting successful intervention with IV MgSO4, TdP treatment in one patient was attempted with multiple therapies such as lidocaine, phenytoine, atropine, isoprenaline, ventricular pacing and counter shock that finally failed. Though the study employed small sample and only male patients, it is of great importance for a management of either acquired or congenital LQTS with complication of TdP during pediatric anesthesia and surgery (see Tables 2 and 3).

3. Children with LQTS: Postoperative challenges and solutions

Intraoperative etiologies of LQTS may contribute for postoperative LQTS, and hence perioperative prevention or treatments discussed in the context of preoperative and intraoperative periods may also be used postoperatively. However, there are reports about postoperative LQTS and its management. Normally emesis is common during emergence and recovery from anesthesia. Unfortunately, drugs often used for treatment of emesis such as ondansetron and droperidol increases QTc in pediatric patients. In this regard, Mehta D et al. studied effect of ondansetron, droperidol, combination of ondansetron and droperidol, and normal saline while other potential causes were controlled and found that QTc was significantly prolonged in all groups compared to pretreatment values [30]. But, there was no difference within the group and abnormal prolongation resulting in absolute QTc greater than 450 ms was not observed in any of four groups. Though the observed effect of saline injection needs further researches, ondansetron and droperidol may cause or worsen LQTS perioperatively. On the other hand in pediatric patients who underwent general anesthesia for noncardiac surgery or procedure, adverse events such as torsade des pointes, ventricular tachycardia, bigeminy and sinus tachycardia were reported in three cases out of seventy six retrospective cohort of children with congenital LQTS [31]. The timing of these adverse events in all three cases was during emergence from anesthesia. The child who had TdP had coincidentally been exposed to sodium pentothal, propofol, isoflorane, pancronium, ondastrone, anticholinesterase and anticholinergic drug. The TdP was successfully treated with Propranolol bolus 3 mg IV, lidocaine bolus 30 mg IV, followed by 30mic/kg/min lidocaine infusion. The occurrence of the adverse events during anesthesia emergence implies that sympathetic stimulation worsens the cardiac events in children with long QT syndrome (see Table 4).

Table 2
Safe drugs to be used during anesthesia management of children with LQTS.

1	Propofol
2	Halothane
3	Dexmedetomidine

Table 3
Drugs to be avoided during anesthesia management of children with LQTS.

1	Sevoflurane
2	Isoflurane
3	Desflorane
4	Ondansetron
5	Droperidol

5. Conclusion

Long QT syndrome worth emphasis as the incidence is by far higher than several commonly discussed comorbidities in anesthesia. Prolonged QT interval is the better indicator of long QT syndrome. Drugs and procedures during anesthesia may cause LQTS in apparently healthy children or trigger life threatening complications such as cardiac arrhythmias in children with congenital LQTS. Patients with LQTS may exhibit fear and anxiety that can even worsen the scenario preoperatively. Preoperatively, risk factors for LQTS such as idiopathic seizure or seizure secondary to hypocalcemia should be assessed in children. Because of very reason that most of children with long QT syndrome have episodes of syncope, in any pediatric patient with the history of unexplained

Table 4
Prevention and treatment of LQTS for children under anesthesia.

1	Beta blockers: - Propranolol (2.5 mg/kg/day) - Nadolol (2.5 mg/kg/day) - Metoprolol (1.4 mg/kg)
2	Magnesium Sulphate (2.3–12 mg/kg)
3	Prevent and correct electrolyte imbalance (K, Ca, Mg)

syncope or seizure LQTS should be ruled out preoperatively. On the other hand, the risk of complication among symptomatic patient is higher compared to asymptomatic patients. Most of patients with LQTS may be on beta blockers to prevent the occurrence of sudden critical incidence which is proven effective. But, it's of great interest for perioperative care provider to consider potential interaction between beta blockers and any drugs to be administered. In pediatric patients; sevoflurane, desflurane, isoflurane and droperidol are known to prolong QT interval and cause acquired LQTS. There is a controversial reports regarding effect of dexmedetomidine-shortening and slight prolonging. Fortunately, propofol and halothan have no QT prolonging effect if not shortening. Beta blockers and magnesium are recommended drugs to treat LQTS in pediatric patients with both acquired and congenital LQTS. Although they didn't meet the inclusion criteria of this review, there are plenty of literature including updates suggesting several causes of LQTS and possible management options. For instance, IV lidocaine effectively prevents QT prolongation following laryngoscopy and intubation in adults [32]. But, sometimes it is a routine practice in medicine to use evidences generated from adult subjects to pediatrics and, hence it is up to the expert of the arena to appropriately use these evidences available elsewhere. With increasing prevalence, risk factors and complications; LQTS during pediatric anesthesia should not be undermined and must be treated accordingly.

Disclosure

Author has no conflict of interest to disclose.

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