

Anesthesia recommendations for Timothy Syndrome

Disease name: Timothy Syndrome

ICD 10: 145.8

ORPHAcode: 65283

Synonyms: LQT8, Long QT Syndrome type 8, Long QT Syndrome-Syndactyly syndrome

Brief disease summary: Timothy Syndrome (TS) is a rare genetic disorder characterized by a prolonged QT interval, was first described by Timothy et al. in 2004, and has a broad spectrum of cardiac and noncardiac characteristics that include [1,2]:

- Cardiac arrhythmias (prolonged QT interval, bradycardia, 2:1 AV block, T-wave alternans) [1,2,3,4]
- Congenital cardiac defects (PDA, PFO, VSD, tetralogy of Fallot, HOCM) [1,2,3,5]
- Syndactyly (variably the index, middle, ring and little fingers and second and third toes) [1,2,5]
- A tendency to hypoglycemia [2,6,7]
- Epilepsy or tendency to seizures [2,3]
- Craniofacial characteristics, most often a round face, receding hairline and dental caries [1,2,5]
- Immunodeficiency [2]
- Neurodevelopment delay [1,2,3,5]

All cases of TS arise from a mutation of the CACNA1C gene which is located on the short arm of chromosome 12 [1,4,5,8]. This gene encodes the L-type Ca(v)1.2 calcium channel protein [1,4,5,8]. The TS mutation is a missense variant (Gly406Arg) that causes a reduction in the inactivation of the calcium channels during the plateau phase of the cardiac action potential [1,8]. The result is that the calcium channels never close properly allowing excess calcium to flow into the cell which leads to prolongation of the plateau phase and thus the QT interval [1,8]. The clinical implications of this are: an increased risk of spontaneous ventricular tachyarrhythmia, especially torsades de pointes (TdP) and sudden death [1,2,4,8].

Two typical forms of TS are described based on the specific splice variant; originally TS1 described an exon 8a variant that produced prolonged QT interval and syndactyly, whereas TS2 describes the exon 8 variant which does not produce syndactyly (sometimes referred to as 'cardiac-only TS' or 'non-syndromic TS') although evidence has since accumulated that there are more diverse variants and overlap between the clinical manifestations of these two 'types' [1,2,3,8]. Cardiac and non-cardiac features are prevalent across both TS1 and TS2 [2,3,8]. Numerous additional variants in the CACNA1C gene have been identified since Thomas et al first identified the Gly406Arg variant causing TS1 and TS2, and subsequently

individuals with long QT interval and another CACNA1C variant usually receive a diagnosis of Long QT syndrome 8 (also known as 'atypical TS' or 'nsLQT8') [2,8].

Inheritance is autosomal dominant though most cases arise as spontaneous mutations rather than from direct parental inheritance [2]. TS can present in utero with cardiac features, most typically with fetal bradycardia or neonatal tachyarrhythmia [2,6]. Structural cardiac abnormalities can also be detected in utero though are not diagnostic of TS itself [2,6].

Sensitivity to anesthesia is described as 'a serious threat to all TS individuals' in a recent 2024 natural history case series, again by Timothy et al. [2]. There is uncertainty if the tendency to hypoglycemia is significant here, given the standard care of preoperative fasting [2,7]. Patients with TS1 have been described to have fatal intractable hypoglycemia, and although significant life-threatening episodes of hypoglycemia have been reported in those with TS2, there are no deaths attributable solely to hypoglycemia in those with TS2 found in the literature [2,6,7].

Tachyarrhythmia is overwhelmingly the leading cause of death, accounting for over 80% of deaths, followed by infection and complications of intractable hypoglycemia [2,7]. The median life expectancy of a patient with TS was originally described as 2.5 years; however, as diagnosis and management progress there are now several cases described of young adults with TS living up to and into their third decade, and the average life expectancy may be expected to increase [2,6,7].

Diagnosis may be incorrect; if uncertainty exists, the diagnosis should be re-evaluated.

Every patient is unique; individual circumstances must always guide clinical care.

Medicine is in progress; new clinical knowledge may not be yet reflected in this recommendation.



Recommendations are not rules or laws; they provide a framework to support clinical decision-making. Although this recommendation has passed a structured review process, it does not meet the formal criteria of a guideline.

Translations may not always reflect the most recent updates of the English version.



Find more information on the disease, its centers of reference and patient organizations on Orphanet: www.orpha.net

Emergency information

A	AIRWAY / ANESTHETIC TECHNIQUE	No specific airway concerns have been described. Induction of general anesthesia can cause and reveal undiagnosed prolonged QT or other tachyarrhythmia. Prolonged fasting should be avoided due to tendency to intractable and fatal hypoglycemia. Regional and neuraxial techniques have been safely used.
B	BLOOD PRODUCTS (COAGULATION)	Nil specific concerns associated.
C	CIRCULATION	Long QT interval is diagnostic. Bradycardias, 2:1 AV block, T wave alternans common. Implantable devices common. PDA, PFO, VSD, tetralogy of Fallot and HOCM all have been described. Cardiac arrest often refractory to standard treatment.
D	DRUGS	Ketamine, thiopentone, succinylcholine, pancuronium, droperidol, domperidone and ondansetron are contraindicated. Sympathomimetics should be avoided. All volatile agents prolong QT interval, although their use has been successfully described; TIVA is, however, considered the safest. Majority of patients will be on long-term beta-blockade. Detailed information on the general management of long QT syndromes is provided in the relevant OrphanAnesthesia recommendations.
E	EQUIPMENT	Perioperative hypoglycemia monitoring should be performed. Continuous ECG monitoring is recommended postoperatively.

Additional disease information

None.

Typical surgery and procedures

Corrective cardiac surgery; insertion of implantable automated defibrillator or pacemaker; plastic surgery for the correction of syndactyly; dental extractions [1,2,3].

Type of anesthesia

There are reports about the use of volatile anesthetics as well as all intravenous anesthetics without preference [9,10,11,12]. The use of ketamine or thiopentone is not recommended [11,12,13,14]. All types of regional anesthesia have been described [11,15,16]. During surgery, drugs known to increase the QT interval and induce TdP should be avoided [11,12,13,14].

An up-to-date resource listing contraindicated medications and medications to be avoided should be consulted regularly. For further guidance, we refer to the OrphanAnesthesia recommendations applicable to all forms of long QT syndrome.

Necessary additional preoperative testing (beside standard care)

Preoperative planning is of paramount importance and should involve a multidisciplinary team comprising the relevant pediatric surgeon, anesthesiologist and pediatric cardiologist [10,11,12]. Preoperative evaluation must include an ECG [10,11,12]. While the calculation of the resting heart rate, QT interval and recognition of other electrical abnormalities are essential, no recommendations are published regarding the specific cut-offs which may contraindicate surgery [10,11,12]. Ambulatory ECG monitoring can be considered to identify the presence, frequency and duration of paroxysmal arrhythmic episodes [2,10,11]. Any pacemaker or implanted internal defibrillator must be checked preoperatively and surgical teams must consider the effect diathermy may have on the device [10,11,12]. Echocardiography should be performed to identify previously undiagnosed congenital structural cardiac defects and to assess cardiac function [1,2,3]. Serum electrolytes, especially potassium, magnesium and calcium, should be measured and corrected [11,12,13]. Low levels of these electrolytes predispose to delayed ventricular depolarization and therefore prolongation of the QT interval [12,13,14]. Hypoglycemia can be intractable and fatal and prolonged fasting must be avoided with perioperative plans for both serum glucose monitoring and maintenance agreed [2,6,7].

As with any anesthetic candidate, a thorough respiratory history and examination should be performed [11,12]. In addition to assessing for respiratory sequelae of cardiac function abnormalities, signs of intercurrent infection must be looked for as this may influence the preoperative course [2,3,7].

Particular preparation for airway management

No specific recommendations beyond standard care.

Particular preparation for transfusion or administration of blood products

No specific recommendations beyond standard care.

Particular preparation for anticoagulation

There are no prerequisites for anticoagulation for the syndrome itself, and no coagulopathies have been described [1,2,3]. However, there may be indications for anticoagulation specific to congenital cardiac abnormalities and their subsequent correction [1,2,3].

Particular precautions for positioning, transportation and mobilization

No specific recommendations beyond standard care.

Interactions of chronic disease and anesthesia medications

Bradycardia related to adequate beta-blockade is common; however, the use of chronotropic drugs may increase the QT interval and therefore should be used with caution [2,11,12,13]. Again, reference is made to the OrphanAnesthesia recommendations applicable to all forms of long QT syndrome [17].

Anesthetic procedure

Precautions should begin during the immediate preoperative period and should focus on minimizing the stress associated with the impending surgery [11,12,13]. The patient should be kept in a warm, quiet and supportive environment. Prolonged fasting should be avoided due to the risk of poorly tolerated and intractable hypoglycemia [2,6,7]. The application of topical local anesthetic creams to potential venipuncture sites is advised [11,12]. There is also a suggestion that sedation prior to venipuncture and cannulation should be considered as the act of venipuncture has been documented to induce arrhythmias [10,11].

Adequate sedation and analgesia reduce catecholamine release [12,13]. Midazolam is considered an appropriate drug for providing sedation as it has no effect on the QT interval in healthy adults [12,13,14]. Midazolam reduces sympathetic activity in unstimulated patients; however, it does not blunt the hemodynamic response to oral or nasal intubation [14]. Fentanyl and morphine are commonly used analgesics and, while the effects of fentanyl on the QT interval are conflicting, fentanyl and morphine have been used in patients with congenital long QT syndrome without any adverse effects [11,12,13,14].

Some literature has advocated the administration of magnesium sulfate prophylactically, even in the presence of normal serum magnesium levels [10,17].

Positive pressure ventilation strategies should ensure that sustained high intrathoracic pressures are avoided as this mimics a Valsalva maneuver, which can lengthen QT intervals in patients who are not fully beta-blocked [12,13].

The use of central and regional neuroblockade has been described and, if successful, provides excellent analgesia and sympatholysis [11,15,16]. However, should any block fail, additional analgesia would be required [11,12]. Epidural anesthesia with the gradual establishment of the sympathetic block is preferred to single dose spinal anesthesia due to the associated lower risk of hypotension with the need for vasopressors [15,16]. Due to the young age of the average patient, caudal epidurals or epidural catheters are placed following the induction of general anesthesia [11,16].

Induction of anesthesia can be performed using either halogenated volatile anesthetics or with intravenous agents [11,12,13,14]. Many anesthetic drugs are known to prolong the QT interval; nevertheless, all anesthetic agents have been successfully used [9,10,11,12]. Halothane, enflurane, isoflurane, desflurane and sevoflurane all prolong the QT interval, even if the data available for some of these agents is controversial [12,13,14]. Propofol infusion is an alternative to inhaled anesthetic gases for the maintenance of anesthesia and is a drug with which most anesthesiologists are very familiar [11,12,13].

Ketamine should be avoided as its sympathomimetic properties may precipitate the onset of TdP [11,12,13,14]. Thiopentone is known to prolong the QT interval and should also be avoided [12,13,14].

Succinylcholine and pancuronium are known to prolong the QT interval [12,13,14]. Rocuronium, vecuronium, atracurium and cisatracurium do not prolong the QT interval and are considered safe for use in patients with TS [12,13,14].

Case reports describing the use of remifentanyl infusions have suggested that it is an excellent sympatholytic intraoperatively, and also during the induction of anesthesia [10,11].

The use of vasopressors in the management of hypotension is a balance of risk [12,13]. Epinephrine, norepinephrine, ephedrine and phenylephrine are known to increase the QT interval; however, case reports of their successful use are published [11,12,13]. The authors would recommend optimization of fluid balance together with the use of metaraminol as this is not known to prolong the QT interval [12,13]. Atropine and glycopyrrolate are thought to be safe [12,13].

Droperidol, domperidone and the 5-HT₃ antagonists (e.g., ondansetron) prolong the QT interval and should be avoided [11,12,13,14]. Metoclopramide is not contraindicated [12,13]. However, dexamethasone is considered to represent the safest, most effective option [12,13].

Particular or additional monitoring

Anesthesiologists should have a low threshold for invasive monitoring, especially an arterial line, considering the risk of tachyarrhythmia with associated cardiac instability [10,11,12]. Arterial access would also allow regular serum glucose monitoring [2,6,7]. Volume status must be carefully monitored as beta-blocked patients tolerate hypovolemia poorly [12,13].

Possible complications

There are several case descriptions of induction or maintenance of general anesthesia being the precipitating factor of a first tachyarrhythmia or even cardiac arrest in patients later diagnosed with TS [9,10,18]. The anesthesiologist must be prepared to deal with malignant arrhythmias, particularly TdP, and be aware that the treatment is still empiric without hard evidence [10,11,12,13]. Electrolyte abnormalities, particularly hypokalemia, should be corrected [11,12,13].

Fatal intractable hypoglycemia is of particular concern in TS1, though is a risk for all TS patients, and has been described as a cause of perioperative death [2,6,7].

Magnesium is the drug therapy of choice both for the prevention of repeated and treatment of established TdP [10,11,12,17]. An initial bolus of 30 mg/kg should be administered over 2-3

minutes followed by an infusion of 2-4 mg/kg/hr [10,17]. For resistant TdP a further bolus may be given after 15 minutes [17]. Plasma magnesium levels should be monitored to avoid toxicity [17]. Magnesium acts as a calcium channel blocker and also promotes membrane stability by the activation of sodium-potassium ATPase [17].

Intravenous lidocaine is also advocated at a dose of 1-2 mg/kg [10,11,12]. This may be administered either before or with magnesium and may prevent degeneration of the arrhythmia [10,11].

Should magnesium prove ineffective, temporary overdrive pacing may be necessary [10,11,17]. In one case, calcium channel blockers and ranolazine were found to be effective [19].

The most serious sequela of TdP is the progression to ventricular fibrillation [10,11]. The anesthesiologist must be familiar with advanced pediatric life support algorithms and prepared to deliver asynchronous defibrillation and chest compressions [10,11,12]. It should be noted that several case reports of perioperative cardiac arrest are refractory to standard treatment despite correction of reversible causes, suggesting multifactorial decompensation and highlighting the multisystemic nature of TS in particular as a congenital long QT syndrome [9,7,10,18].

Postoperative care

In the postoperative period, continuous ECG monitoring in a high dependency environment is advised [10,11,12,13]. The environment should be kept quiet, calm and warm in order to reduce sympathetic stimulation [11,12,13]. It is important to rapidly recognize and treat postoperative pain, nausea and vomiting, thus reducing the associated sympathetic stimulation [11,12,13,14]. Senior recovery staff is recommended to care for this cohort of patients [10,11]. There should be easy access to emergency resuscitation equipment and drugs [10,11,12]. ECG monitoring may be required for up to 24 hours post-surgery [10,11,12].

Serum glucose level monitoring should continue until feeding is re-established postoperatively [2,6,7].

Hypothermia prolongs the QTc, so core temperature should be checked regularly and normothermia maintained [12,13,14]. Hypothermia can also increase the risk of postoperative infection [13].

Disease-related acute problems and effect on anesthesia and recovery

No specific recommendations beyond standard care.

Ambulatory anesthesia

Cases of ambulatory anesthesia are not reported, most likely due to the nature of the syndrome and the likely surgical procedures [2,3,7].

However, the advantages of early mobilization of patients postoperatively should not be overlooked [13].

Obstetrical anesthesia

There are currently no case reports or descriptions of obstetric anesthetic procedures for patients with TS [2,7]. This is most likely attributable to the high infant mortality rate [2,7]. However, multiple case reports on obstetric anesthesia in patients with other congenital long QT syndromes are available, and further guidance is provided in the OrphanAnesthesia recommendations applicable to all forms of long QT syndrome [15].

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Date last modified: **October 2026**

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