# STUDY PROTOCOL

**Title**
The effects of dexmedetomidine on myocardial repolarization in children

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**Question**
What are the effects of a bolus dose of dexmedetomidine on indices of myocardial repolarization, and on blood glucose and potassium concentrations in healthy children undergoing total intravenous general anesthesia (TIVA)?

**Background**
Dexmedetomidine (Precedex®, Hospira Healthcare) is a potent, centrally acting $\alpha_2$ adrenoreceptor agonist with sympatholytic, sedative, amnestic, anxiolytic and analgesic effects, which properties make it popular for use in both pediatric anesthesia and intensive care (1,2). The reported benefits include reduced post-operative analgesic requirements (3), reduced emergence delirium (4,5),smoother extubation conditions(6), treatment of emergence delirium (7,8) and reduced post-operative shivering (9). Its respiratory sparing effects may also be of value in children with obstructive sleep apnea undergoing adenotonsillectomy, who are at particular risk of opioid- and anesthetic-induced respiratory complications post-operatively (10). Furthermore it has promising future applications in neuroprotection (11,12)

In 2013, dexmedetomidine was added to the "possible risk factor for torsades de pointes (TdP)" drug list (13). Clinicians are currently advised to be vigilant about potential QT prolongation with dexmedetomidine, especially in patients with congenital long QT syndrome (LQTS). However, current evidence for dexmedetomidine-induced prolonged heart-rate corrected QT (QTc) is sparse and somewhat contradictory. One recent case report described profound QTc prolongation with use of dexmedetomidine in a pediatric clinical care setting, and suggested that LQTS Type 2 was "unmasked" by the drug (14). Another study investigating the effects of dexmedetomidine on cardiac electrophysiology in children indicated that the drug significantly increased the length of QTc intervals; however none of the patients actually developed abnormally long QT (>445ms) (15). In contrast, one study in adults showed that dexmedetomidine promoted a faster recovery from a prolonged QTc interval induced by spinal anesthesia, and may in fact be helpful in patients who have a prolonged QTc interval (16).

Another consideration is that drug-induced QTc prolongation is not synonymous with drug torsadogenicity (i.e. risk of causing TdP). A more relevant measure of torsadogenicity is the interval between the peak and the end of the ECG T wave (Tp-e), which is a marker of transmural dispersion of repolarization (TDR) across the myocardial wall. Research supports the concept of exaggerated TDR as a more appropriate substrate for TdP (17,18) However, the effect of dexmedetomidine on the Tp-e interval has not been reported in detail in adults or children.

Another poorly defined pharmacodynamic effect of dexmedetomidine is its effect on blood glucose concentration. The $\alpha_{2A}$ adrenoreceptor has been identified as an important regulator of blood glucose homeostasis. Activation of $\alpha_2$ receptors on pancreatic $\beta$ cells inhibits insulin secretion (19). Administration of dexmedetomidine would therefore be expected to cause hypoinsulinaemia and a

resultant increase in blood glucose levels (hyperglycaemia). Previous studies are in contrast to this however; Mukhtar and colleagues reported that dexmedetomidine decreased cortisol levels leading to reduced blood glucose levels, and suggested that dexmedetomidine may attenuate the neuroendocrine response to stress (20). Furthermore, a case report describing a child who was given a 60-fold increase in the intended dose of dexmedetomidine as a drug error during a cardiac catheterization procedure reported significant hypoglycemia (21). The authors postulated that a large decrease in circulating norepinephrine caused by an overdose of dexmedetomidine, might also inhibit β-adrenergic stimulation, thereby causing hypoglycemia. Considering the popularity of dexmedetomidine use in pediatric anesthesia, pediatric intensive care and its increasing use in the neonatal population, increased knowledge of the effect of dexmedetomidine on blood glucose would be valuable.

Finally, hypokalemia is listed as a treatment-emergent adverse event occurring in >2% of adult patients receiving dexmedetomidine in long-term intensive care unit sedation studies (22). The effect of dexmedetomidine on serum potassium levels in healthy children has yet to be elucidated. Given that hypokalemia increases the risk of TdP, and that there is a possibility that dexmedetomidine may be torsadogenic, this effect is also worthy of investigation.

**Rationale**

The use of dexmedetomidine is associated with many clinical benefits, but its effects on indices of myocardial repolarization, as well as its effects on glucose and potassium metabolism, remain poorly understood and need to be better defined in order to use this drug safely and effectively.

**Specific Aims**

The primary aim of this study is to investigate the effects of three different doses of dexmedetomidine (0.25/0.5/0.75 mcg/kg) on both QTc and Tp-e. This study will also sample venous blood to measure glucose and potassium concentrations before and after dexmedetomidine administration to ascertain if there is any significant effect of a single bolus dose on either of these.

**Method**

*Research design*

We propose a randomized, single blinded, 4-group comparative study to characterize the effects of different doses of dexmedetomidine on myocardial repolarization and blood glucose and potassium levels. The study-specific interventions will include a bolus of dexmedetomidine (or saline) following induction, recording two 12-lead ECGs (one before and one after dexmedetomidine administration), and taking three 1mL venous blood samples (one before and two after dexmedetomidine administration; total blood sampling volume 3mL/patient).

*Inclusion Criteria*

- ASA I-II
- Age ≥ 3 to ≤ 10 years
- Elective surgical procedure requiring general anesthesia
- Use of dexmedetomidine deemed clinically appropriate by the staff anesthesiologist
- No pre-operative analgesic or anxiolytic medications given

*Exclusion criteria*

- Previous diagnosis of Long QT Syndrome (LQTS)
- Previous diagnosis of cardiac disease or rhythm abnormalities
- Family history of LQTS or abnormal cardiac conduction
- Currently taking medications known to prolong QT
- Currently taking medications known to predispose to hypokalemia
- Known hypersensitivity to dexmedetomidine or other study medication

- Weight < 5th centile or > 95th centile for age
- Previously diagnosed hypokalemia
- Impaired renal or liver function
- Pre-operative anxiety requiring sedatives or opioids
- Refusal to participate

*Consent/Assent*
The parent or legal guardian(s) of participants meeting inclusion criteria will be approached by a staff nurse with a Letter of Initial Contact in the Surgical Day Care Unit (SDCU) of BC Children's Hospital (BCCH). If the parent or legal guardian(s) wishes for more information they can request an introduction to a member of the Pediatric Anesthesia Research Team (PART), who will then provide them with details of the study and invite them to participate. Written informed consent will be obtained from the parents or guardians of eligible participants. In addition, assent will be obtained from children over 7 years of age.

All participants will be aware of the study rationale, as well as any potential risks. For example, there is a small risk of unexpectedly discovering a baseline ECG abnormality. Families will be advised that all traces will be analyzed by a pediatric cardiologist, and should an abnormality be detected, they will be notified if further management is required.

**Treatments and Procedures**
*Preoperative*
All potential participants will have fasted according to the BCCH Pre-Anesthesia and Procedural Sedation Fasting Guidelines (minimum 2hrs for clear liquids, minimum 6hrs for light meal), as per standard practice. Once a participant has consented to be in the study, the attending anesthetist will ensure that they are not given oral pre-medication (eg. acetaminophen) in SDCU. Rather, simple analgesics, if indicated, will be given non-orally intraoperatively instead, after the second ECG has been obtained. Thus, analgesics will not be withheld.

Basic demographics including gender, height and weight will be recorded on the data collection form. Topical local anesthetic cream will be applied to potential cannulation sites approximately 45mins before the procedure is scheduled to begin, as per standard SDCU procedures. A baseline 12-lead ECG will then be obtained in SDCU. This initial ECG will be screened by the attending anesthetist to ensure that the QTc interval is within normal range. If the QTc interval is greater than 450msec in males, or 460msec in females, the patient will be excluded from the study and referred to a pediatric cardiologist for further investigation. Eligible participants will then be randomized into one of four treatment groups:

- Group 1 will receive a dose of 0.25mcg/kg dexmedetomidine
- Group 2 will receive a dose of 0.50mcg/kg dexmedetomidine
- Group 3 will receive a dose of 0.75mcg/kg dexmedetomidine
- Group 4 will receive a small volume (10mL) of normal saline solution

The anesthetist will know the dose of dexmedetomidine being administered, but the subject and cardiologist will be blinded to this information.

*Intra-operative*
All participants will receive standard monitoring of vital signs (heart rate, blood pressure, SpO2) throughout the entire procedure. These data will be captured electronically from the patient monitor every second and recorded on a study laptop.
Intravenous (IV) access will be established and anesthesia induced as per standard BCCH practice, with a bolus of lidocaine (0.5mg/kg) followed by a bolus of propofol (5mg/kg). In an attempt to

minimise sympathetic stimulation, laryngoscopy will not be permitted during the study period and the airway will be maintained by facemask. Immediately after induction, maintenance of anesthesia will be initiated with propofol 200mcg/kg/min and remifentanil 0.1mcg/kg/min administered via an automated infusion pump. This default infusion rate may be adjusted by the anesthetist at any time.

A baseline venous blood sample (1mL) will be obtained from the IV 1 minute post induction (defined as the end time of propofol bolus administration). Three minutes post induction, the randomized bolus dose of dexmedetomidine or saline will be administered. All dexmedetomidine doses will be diluted with normal saline to a standard 10mL volume, and will be delivered over 60 seconds using an automated infusion pump through the IV. While the product monograph suggests delivering dexmedetomidine as a loading dose over 10-20 minutes, administration as a rapid bolus has been shown to be safe in children (Dawes et al., 2014), and 60 seconds represents a typical timeframe over which dexmedetomidine is currently being administered in clinical practice at BCCH. Nevertheless, the anesthetist will vigilantly monitor the patient's vital signs for instances of clinically-relevant dexmedetomidine-induced bradycardia or hypertension requiring intervention.

A second 12-lead ECG will be obtained 60 seconds after the end time of dexmedetomidine bolus administration. This ECG will also be screened by the anesthetist. If the anesthetist observes significant QT prolongation on the second ECG, they will discuss their observations with cardiology, and the participant will be referred to a pediatric cardiologist if deemed appropriate. Blood pressure will be assessed every minute until the second ECG is complete. Thereafter, maintenance of anesthesia will continue at the anesthetist's discretion, and simple analgesics will be administered to compensate for the absence of pre-medication if appropriate. Venous blood will be sampled again at 15 and 30 minutes post induction. Each sample will volume will be 1mL. All venous blood samples will be sent for analysis (using the GEM4000 blood gas analyzer located in the pediatric intensive care unit) immediately after acquisition. No dextrose-containing fluids will be given during the study period, to avoid altering blood glucose levels. Other fluids (eg. normal saline; Ringers Lactate) may be administered at the anesthetist's discretion.

If the anesthetist would like to administer dexmedetomidine to a participant in the control group as part of their normal practice, they can do so after the study period is over (after the final blood sample has been taken).

**Outcome Measures**

*Primary*

The primary outcome measure is placebo-adjusted change from baseline in myocardial repolarization (QTc and TP-e intervals) at 1 minute post dexmedetomidine.

*Secondary*

The secondary outcome measures are placebo-adjusted change in serum glucose and potassium concentrations at 15 and 30 minutes post dexmedetomidine.

**Rescue Medication and Risk Management**

According to the Canadian Product Monograph for dexmedetomidine, the most common treatment-emergent adverse reactions, occurring in greater than 2% of adult patients in both Intensive Care Unit and conscious sedation studies include hypotension, bradycardia and dry mouth. Product literature suggests glycopyrrolate, atropine or ephedrine for drug-induced bradycardia or hypotension in adults. There are no recommendations for treatment options in children.

For the purpose of the current study, our recommendation for hemodynamic rescue will be as follows: to treat significant bradycardia associated with *hypo*tension, a bolus of glycopyrrolate 10mcg/kg or atropine 20mcg/kg should be given, followed by reassessment after 1 minute. This

may be repeated as necessary, to a maximum dose of glycopyrrolate 400mcg and atropine 600mcg. Further interventions will be according to the clinician's preference and the clinical situation, including altering or stopping the propofol and remifentanil infusion rate, raising the legs, further intravenous fluid boluses and/or a dose of ephedrine 0.1 mg/kg. If significant bradycardia associated with *hyper*tension is observed, the subject should be observed for 1 minute followed by reassessment. This baroreceptor-mediated response is usually transient and has rarely required treatment in previous studies. In fact, an exaggerated hypertensive response has been observed when glycopyrrolate 5 mcg/kg was used to treat bradycardia without associated hypotension in a recent case report series. The mechanism for this remains unclear. Other interventions to treat bradycardia associated with dexmedetomidine have not been investigated. Ultimately, all rescue procedures will be at the anesthetist's discretion.

**Discontinuation Criteria**
The study will be stopped at the request of the participant and/or the participant's parents/guardians, without prejudice to future treatment by the physician. However, due to the nature of the study, once the participant is in the operating room, the participant and the participant's parents/guardians will no longer be able to make this request. If induction or maintenance of anesthesia becomes complicated by adverse events, such that the patient's cardiorespiratory stability is compromised before or during the study period, the study will be terminated at the anesthesiologist's discretion. Additionally, on receiving new information about a participant's health or their response to the anesthetic medications given, the attending anesthetist may consider it to be in the participant's best interests to withdraw them from the study without their consent if they judge that it would be better for their health. For example, if the anesthetist detects a prolonged QTc interval on the patient's baseline ECG, that subject will be excluded from the study, and referred to a pediatric cardiologist. Should this occur, the parent or legal guardian(s) will be informed after the surgery is complete.

In the instance of any serious adverse drug reaction (SADR), the study will immediately be stopped and the case will be reviewed in detail by the BCCH Data Safety Monitoring Board (DSMB) to determine whether the study may be continued.

Study defined serious adverse drug reactions (SADR) include:

- Hypo- or hypertension post-dexmedetomidine bolus requiring rescue intervention
- Bradycardia, AV block or sinus arrest requiring cardiopulmonary resuscitation
- Anaphylactic reaction requiring intervention

Documentation, and any necessary treatment of SADRs, will occur both immediately after the intravenous administration of the study medication and immediately prior to discharge from PACU. SADRs occurring in hospital after the study period will be reported to the Department of Anesthesia and treated appropriately. All SADRs will be reported to the UBC Clinical Research Ethics Board, the DSMB within 72 hours of the event. A report of the SADR will also be submitted to Health Canada within 7 days, or within 15 days if the event was neither fatal nor life-threatening.

**Data Collection**
All demographic data and measured variables are shown on the data collection form.

**Interim Analysis**
Meetings with the study team and the DSMB will be scheduled:

- After 5 participants have been recruited, or 6 months after study initiation (whichever comes first), to discuss safety outcomes and study progress
- After 30 participants have been recruited, to investigate preliminary results of outcome measures

- After the occurence any SADR, to discuss safety outcomes and decide whether the study may continue

**Data Analysis**

*ECG Analysis Methods*

All ECG traces will be analyzed independently at a later date by a pediatric cardiology co-investigator (Dr. Sherwin) who will be blinded to the participant, group assignment, and the timing of the ECG recording (pre or intra-operative), and who will not be involved in the recruitment or randomization of participants, or in the conduct of anesthesia or acquisition of ECG recordings. If an abnormality is noted in any ECG by the pediatric cardiologist, the principal investigator will be contacted, and will be responsible for re-identifying the participant and contacting their family in order to refer them to a cardiologist.

The QT interval, RR interval and Tp-e interval will be measured in leads II and V5 at each time point. The QT interval will be measured for 3 complete P-QRS-T cycles from the start of the QRS complex to the end of the T-wave, defined as the point of return to the T-P baseline. If U waves are present, the end of the T wave will be taken as the nadir of the curve between the T and U waves. QT intervals will be corrected according to the formula of Bazett where $QTc = QT/\sqrt{RR}$.

The Tp-e interval will be measured for 3 complete P-QRS-T cycles from the peak of the T-wave to the end of the T-wave. Monophasic T wave peaks can be identified visually and for more complex T-wave morphologies, the peak will be identified according to the criteria of Emori and Antzelevitch (23).

*Statistical Analysis*

Within-group and between-group comparisons of pre- and intra-operative ECG indices of myocardial repolarization and blood glucose and potassium concentrations will be performed using two-way factorial analysis of variance. Any identified differences will be further examined using Bonferroni-corrected paired t-tests within groups, and unpaired t -tests between groups.

Sample size calculations are based on ECG results from previously published studies in healthy children. These data showed a mean/SD Tp-e of 66/12 msec in 135 pre-operative ECG traces from healthy children (24). Thus, we have determined that 12 patients are required per group in order to detect a clinically relevant difference of 25msec in Tp-e between the intra-operative means of the 4 groups with a power of 99% and the criterion for significance set at 0.01. In order to provide a buffer for unplanned exclusions, 60 patients will be recruited, 15 patients in each of the 4 groups. An additional 9 patients will be recruited to offset unanticipated technical problems arising from the electronic capture and transmission of ECG data.

**Strengths**

This is the first study to formally investigate the effects of dexmedetomidine on myocardial repolarization and blood glucose and potassium levels in healthy children undergoing TIVA.

Overall, the benefits of this work will be a better understanding of the safety profile of dexmedetomidine. Regarding the influence of dexmedetomidine on myocardial repolarization, if we do find that it is torsadogenic at any of the doses tested, we will conclude that it should be used with caution in susceptible patients and possibly in procedures more risky of arrhythmias such as cardiac ablation/catheterization, as well as in patients with known prolonged QT. Similarly, if we find that dexmedetomidine has a significant impact on blood glucose or potassium homeostasis at any of the doses tested, this will inform future clinical use in all patients, especially in neonates who are more susceptible to blood glucose dysregulation and/or in patients with liver/kidney dysfunction who are more prone to hypokalemia.

**Limitations**

Our study will recruit healthy children and will specifically exclude those with or who are at risk of long QT syndromes. Therefore, the current results will not be directly applicable to these susceptible populations. They will, however, potentially help anesthetists to decide whether dexmedetomidine may add to pre-existing risk in such patients.

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