Protocolized initiation of clonidine to prevent dexmedetomidine withdrawal: A prospective cohort study

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Protocol Title:	Protocolized initiation of clonidine to prevent dexmedetomidine withdrawal: A prospective cohort study
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Study Coordinator:	n/a
Population:	Patients aged 4 weeks-18 years admitted to the Children's Memorial Hermann Hospital- Texas Medical Center Pediatric Intensive Care Unit and Heart Center Intensive Care Units requiring dexmedetomidine infusion for greater than 72 hours.
Number of Sites:	Single site
Study Duration:	12 months
Subject Duration:	PICU or HCICU admission to hospital discharge

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General Information

- Our study will evaluate the implementation of a clonidine initiation protocol to mitigate dexmedetomidine withdrawal.

Background Information

– The use of dexmedetomidine for PICU sedation has become common place since its introduction to clinical practice in the mid-2000s. Dexmedetomidine is a centrally acting alpha agonist that is about 8 times more potent than clonidine (8). Its use is favored in PICUs due to achievement of adequate sedation without depressing the respiratory drive, this fact allows dexmedetomidine to be used in both intubated and non-intubated patients. As use of dexmedetomidine became more widespread, it has been noted to cause withdrawal symptoms including agitation, tachycardia, hypertension, and insomnia (11, 15). A survey to PICU providers in the United States completed in 2019 found that 88% of responders had concerns about dexmedetomidine withdrawal and 81% managed this concern with a regimented wean and initiation of clonidine (14). The majority of published studies on dexmedetomidine withdrawal note symptoms after 72 hours or more of continuous infusion. The results of these studies are mixed; however, clonidine initiation is consistently not statistically different from a slow dexmedetomidine wean over days and is associated with lower drug costs (2, 3, 7, 8, 9, 10, 12). At our institution it is usual to start clonidine to transition off dexmedetomidine but, at this time we do not have a protocolized way to do this it is rather done at the discretion of the attending physician with assistance from the clinical pharmacy specialists. When the decision to start clonidine is made, generally after about five days on dexmedetomidine therapy, it is most often started at 1 mcg/kg/dose every 6 to 8 hours regardless of the time on or cumulative dose of

dexmedetomidine given. Dexmedetomidine weaning practices are highly variable at this time and are most often not done at regular intervals related to clonidine dosing and it is not unusual for dexmedetomidine weaning to last for two to three days. We currently use dexmedetomidine in all ages admitted to our PICU. Our hypothesis is that with use of a standardized protocol for dexmedetomidine weaning and clonidine initiation we can reduce the burden of dexmedetomidine withdrawal in our PICU.

Objectives

- Our primary objective is to reduce dexmedetomidine withdrawal symptoms with the protocolized use of clonidine. Our secondary objectives include reduction in total number of hours on dexmedetomidine infusion, reduction in PICU length of stay, reduction in costs related to dexmede during hospital admission.
- Our study aims to prospectively assess the use of clonidine to mitigate dexmedetomidine withdrawal using a clonidine initiation protocol. For the purposes of the study, withdrawal is defined as at least one of the following: increase in heart rate, systolic blood pressure or diastolic blood pressure by at least 10% from the 24 hours prior to dexmedetomidine weaning to the 24 hours after dexmedetomidine is discontinued AND at least one of the following: two documented Withdrawal Assessment Tool (WAT-1) scores of ≥ 3 or two study questionnaire scores of ≥ 3 from the time of first dexmedetomidine wean to the time dexmedetomidine is off for 72 hours.

Study Design

- Our study will be a prospective pre and post interventional cohort design with data collection beginning prior to implementation of the study protocol to assess our current practices and rates of dexmedetomidine withdrawal. We plan to collect pre intervention data for 6 months. We will then implement the study protocol in our PICU only and continue to collect data for an additional 6 months to compare outcomes. We plan to introduce/ implement and troubleshoot the protocol over a 2 week period after completion of the preintervention phase. Throughout the entire 12 month study period we will collect the same data in our Heart Center Intensive Care Unit without implementing the study protocol as a control.
- Patients will be recruited from both the Children's Memorial Hermann Pediatric ICU and the Children's Memorial Hermann Heart Center ICU for the entire 12 month duration of the study period.
- We expect to collect data preintervention for 6 months followed by an additional 6 months of data collection with implementing the intervention with goal to enroll 150 patients in both the pre and post intervention data sets.
- Continuation of the implemented protocol beyond the 6 month data collection period will be at the discretion of the PICU medical director.
- Data will be collected from chart review and from discussion with both the bedside nursing team and physician team during dexmedetomidine weaning/ clonidine initiation.
- Primary outcome: Dexmedetomidine withdrawal. Withdrawal is defined as at least one of the following: increase in heart rate, systolic blood pressure or diastolic blood pressure by at least 10% from the 24 hours prior to dexmedetomidine weaning to the 24 hours after dexmedetomidine is discontinued AND at least one of the following: two documented WAT-1 scores of ≥ 3 or two study

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questionnaire scores of ≥ 3. WAT and questionnaire scores will be collected every 12 hours starting with the first dexmedetomidine wean until 72 hours after dexmedetomidine is discontinued.

- Secondary outcomes: We also aim to reduce the total number of dexmedetomidine infusion hours, PICU length of stay and dexmedetomidine/clonidine costs during hospitalization. We will compare the average of these data points from the pre and post intervention data sets to assess for reduction.
- Efficacy and safety of both dexmedetomidine and clonidine are well established.

Study Population

- Patients aged 4 weeks to 18 years admitted to our PICU or HCICU and placed on dexmedetomidine for sedation.
- Inclusion criteria:
    - Age 4 weeks to 18 years
    - Dexmedetomidine infusion for >/= 72 hours
- Exclusion criteria:
    - Admission for head trauma
    - Psychiatric history
    - Use of alpha-2 agonist medications at home
    - Death while on dexmedetomidine
- We will use a cut off of 72 hours or more of continuous dexmedetomidine infusion as the majority of published studies on dexmedetomidine withdrawal noted symptoms after this amount of time or started weaning with or without clonidine administration at this time. We exclude patients with head trauma or psychiatric history as one of the main symptoms of dexmedetomidine is agitation it may be difficult to differentiate this being due to withdrawal versus related to disease process. We also exclude patients who are prescribed alpha-2 agonists as home medications as they will be placed back onto these mediations regardless of time of dexmedetomidine therapy.
- We will assess all patients during the study period admitted to our PICU/HCICU for dexmedetomidine use and duration of use prior to enrollment into our cohort.

Study Procedures

- We will obtain information from chart review during and after patient discharges. Specifically, MRN, age, gender, primary admission diagnosis, number of hours on dexmedetomidine infusion, total cumulative dose of dexmedetomidine, average hourly dose of dexmedetomidine, SBS scores minimum every 12 hours starting 24 hours prior to dexmedetomidine wean and ending when dexmedetomidine is off for 24 hours, WAT-1 and CAPD scores at least every 12 hours starting with first dexmedetomidine wean until dexmedetomidine is off for 72 hours, descriptions of agitation or insomnia in daily physician progress notes, agitation/insomnia questionnaires, need for rescue doses of clonidine or resumption of dexmedetomidine, highest documented heart rate and blood pressure 24 hours prior to dexmedetomidine wean and 24 hours after dexmedetomidine discontinuation, dexmedetomidine weaning schedule, length of ICU and hospital stay, other sedation medications used with timing and enteral sedation wean, cost associated with dexmedetomidine and clonidine. In the pre-intervention phase, we will also collect data related to clonidine initiation, ie after how many hours on dexmedetomidine, at what dose and frequency, and clonidine tapering schedule.

- The agitation/insomnia questionnaires will be given to the bedside nurse by a member of the study group once every 24 hours starting the day dexmedetomidine is first weaned until dexmedetomidine has been off for 72 hours. It will be collected for research purposes only and will not become part of the medical record. The purpose of this questionnaire is to assess insomnia and agitation in a standardized manner as it is common for these symptoms to not be documented in the nursing or physician notes.
- During the intervention phase we will use a tiered approach to treat dexmedetomidine withdrawal.
    - We will observe patients without initiating clonidine with dexmedetomidine infusion time of 72-119 hours. To wean off dexmedetomidine we will decrease the infusion by 25% of the starting dose every 6 hours.
    - We will begin clonidine at 1 mcg/kg enterally every 6 hours for patients with dexmedetomidine infusion time of 120-144 hours. We will decrease the dexmedetomidine infusion by 25% of the starting dose 1 hour after each dose of clonidine until off (wean every 6 hours).
    - We will begin clonidine at 1.5 mcg/kg enterally every 6 hours for patients with dexmedetomidine infusion time of 145-167 hours. We will decrease the dexmedetomidine infusion by 25% of the starting dose 1 hour after each dose of clonidine until off (wean every 6 hours).
    - We will begin clonidine at 2 mcg/kg enterally every 6 hours for patients with dexmedetomidine infusion time of >/= 168 hours or with infusion time of 120-167 hours at doses >/= 1.1 mcg/kg/min. We will decrease the dexmedetomidine infusion by 25% of the starting dose 1 hour after each dose of clonidine until off (wean every 6 hours).
- To implement this clonidine dosing and dexmedetomidine weaning schedule we will create a Care4 MPP versus using a paper order set given to the primary resident and fellow taking care of the enrolled patients. Administration of clonidine and weaning of dexmedetomidine will be carried out by bedside nursing staff per physician orders.
- As patients are being weaned from dexmedetomidine we will monitor WAT-1 scores at least every 12 hours to assess for withdrawal. A WAT-1 score of >/= 3 will indicate presence of withdrawal symptoms. With scores between 3 and 5 we will continue to monitor without change in clonidine dosing. If scores are >/= 6 we will step up the dose by 0.5 mcg/kg/dose up to a maximum dose of 3 mcg/kg/dose.
- Once dexmedetomidine is off and patient is stable (ie no withdrawal symptoms) for 48 hours we will begin weaning clonidine by 20% every day until the medication is off. If patients are on other enteral sedation (ie methadone and/or lorazepam) their weaning schedule will include 20% reductions in those medications on alternating days. For example, a patient on clonidine, methadone, and lorazepam will have clonidine weaned on day 1, then methadone on day 2, then lorazepam on day 3, and so on. This is our standard weaning practice at this time and will not change with protocol initiation.
- Clonidine tablets are compounded to an oral suspension in the Children's Memorial Hermann Inpatient Pediatric Pharmacy for patients who are unable to swallow tablets due to age, development or condition. The pharmacy compounds a 20 microgram/milliliter oral suspension for inpatient use. Only one concentration of clonidine oral suspension is utilized at this institution to prevent possible errors from having multiple concentrations available. The recipe is as follows:

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- Ten 0.1 mg clonidine tablets are crushed in a glass mortar and pestle with 1-2 milliliters of simple syrup to serve as a levigating agent. Once all tablet particles are crushed homogenously, the contents are transferred into a calibrated amber bottle and more simple syrup is added to achieve a total quantity of 50 milliliters. The final compounded clonidine concentration is 0.02 milligrams/milliliter or 20 micrograms/milliliter. Once the oral suspension is compounded, it is kept in the pharmacy, refrigerated at 4° C and given a stability of 28 days from date of compounding. The Children's Memorial Hermann Inpatient Pediatric Pharmacy, located on the 10th floor of Hermann Pavilion, is responsible for compounding, storing, maintaining, and dispensing the clonidine oral suspension. Prior to being dispensed, the oral solution is shaken to disperse the clonidine oral suspension and each patient-specific dose is drawn into an oral syringe to be checked by a pharmacist. One checked for accuracy, the clonidine syringe is delivered to the floor and kept in the unit refrigerator in a patient-specific medication bin until ready to for administration.

Data and Safety Monitoring

- Potential adverse effects of our treatment protocol include withdrawal from dexmedetomidine despite initiation of clonidine and hypotension, bradycardia, or over sedation associated with the clonidine taper. We will identify withdrawal as defined above and side effects of clonidine by continuous cardiac monitoring and nursing assessments.
    - If a patient experiences decrease in blood pressure or heart rate with clonidine dosing, we will give a fluid bolus or atropine based on age standard norms. In general, the minimum tolerated blood pressure before treatment will be the 5th percentile for age and minimum tolerated heart rate before treatment will be < 50 with or without associated hypotension.
        - In addition to acute treatment of vital sign instability we will decrease the clonidine dose by 0.5 mcg/kg/dose to start with the next dose.
    - If a patient experiences oversedation, defined as excessive sleepiness and monitored with neurologic checks by bedside nursing, we will decrease the clonidine dose by 0.5 mcg/kg/dose starting with the next dose.
    - All patients admitted to the PICU or HCICU are placed on continuous cardiac monitoring with telemetry to measure heart rate, blood pressure, respiratory rate and pulse oximetry. Vitals are recorded into the EMR based on cardiac monitoring approximately every 1 hour during ICU admission.
- We will report any hemodynamic instability requiring intervention or over sedation requiring increased respiratory support to the IRB.
- We will assess for adverse events daily while patients are on clonidine therapy. Adverse events will be documented with our results.
- We will intermittently monitor for protocol deviations and follow up with the primary physician team for reasoning.
- We as a research team will monitor data continuously for completion and correctness.

Statistics

- We will use a variety of statistical methods due to the number of discrete and non-discrete variables we plan to obtain in our data collection including student t-test for parametric continuous variables,

Mann Whitney U-test for non-parametric continuous variables, fisher exact test; chi-squared test, and multi-variable logistic regression.

- We plan to enroll 300 patients (150 in both the pre and post intervention cohorts) based on 35% incidence of dexmedetomidine withdrawal noted in a retrospective cohort study completed by Nguyen et al at our center completed in 2019. (12) From this incidence, we used a conservative estimate of a 50% reduction in rate of withdrawal in our calculations to obtain a power of 80%.
- Level of significance will be set to a p value of <0.05.
- All eligible subjects will be included in our analysis.

Ethics

- We will not obtain written consent from individual patient's families as we are not deviating from standard of care and there is minimal harm associated with empiric use of clonidine for dexmedetomidine withdrawal. A member of the study team will provide families (and patients >/= 7) with information regarding the study and obtain their verbal consent/assent for data collection and study participation.
- To protect patient privacy all data will be deidentified prior to data analysis.

Data handling and record keeping

- Any protected health information (PHI) identifiers, medical record number, extracted or obtained from medical chart records or received from medical providers will be kept strictly confidential and will not be shared with anyone not directly associated with the study. Any data collected in log format will be kept under lock and key, and access will only be permitted by the primary investigators and the research staff. Data transferred to an electronic database will be maintained on a computer that is encrypted and password protected with access only by the research staff.

- Records will be kept until the end of the study and then any PHI that has not been de-identified will be destroyed. Any codes or links relating back to individually identifiable PHI will also be destroyed. Electronic records will be deleted, and paper records or logs will be shredded.

Publication Plan

- We plan for publication in a peer reviewed journal at the conclusion of our study.
- Results will not be returned to research subjects.

WAT-1 scoring

Table 4

WITHDRAWAL ASSESSMENT TOOL VERSION 1 (WAT - 1) and Instructions

Patient Identifier	
	Date:
	Time:
Information from patient record, previous 12 hours	
Any loose /watery stools	No = 0 Yes = 1
Any vomiting/wretching/gagging	No = 0 Yes = 1
Temperature > 37.8°C	No = 0 Yes = 1
2 minute pre-stimulus observation	
State	$SBS^{I} \leq 0$ or asleep/awake/calm = 0 $SBS^{I} > +1$ or awake/distressed = 1
Tremor	None/mild = 0 Moderate/severe = 1
Any sweating	No = 0 Yes = 1
Uncoordinated/repetitive movement	None/mild = 0 Moderate/severe = 1
Yawning or sneezing	None or 1 = 0 >2 = 1
1 minute stimulus observation	
Startle to touch	None/mild = 0 Moderate/severe = 1
Muscle tone	Normal = 0 Increased = 1
Post-stimulus recovery	
Time to gain calm state ($SBS^{I} \leq 0$)	< 2min = 0 2 - 5min = 1 > 5 min = 2
Total Score (0-12)	

WITHDRAWAL ASSESSMENT TOOL (WAT - 1) INSTRUCTIONS

• Start WAT-1 scoring from the **first day of weaning** in patients who have received opioids +/or benzodiazepines by infusion or regular dosing for prolonged periods (e.g., > 5 days). Continue twice daily scoring until 72 hours after the last dose.

• The Withdrawal Assessment Tool (WAT-1) should be completed along with the SBS^{I} at least once per 12 hour shift (e.g., at 08:00 and 20:00 ± 2 hours). The progressive stimulus used in the SBS^{I} assessment provides a standard stimulus for observing signs of withdrawal.

Obtain information from patient record (this can be done before or after the stimulus):

✓ **Loose/watery stools**: Score 1 if any loose or watery stools were documented in the past 12 hours; score 0 if none were noted.

✓ **Vomiting/wretching/gagging** : Score 1 if any vomiting or spontaneous wretching or gagging were documented in the past 12 hours; score 0 if none were noted

✓ **Temperature > 37.8°C**: Score 1 if the modal (most frequently occurring) temperature documented was greater than 37.8 °C in the past 12 hours; score 0 if this was not the case.

2 minute pre-stimulus observation:

✓ **State**: Score 1 if awake and distress (SBS^{I}: ≥ +1) observed during the 2 minutes prior to the stimulus; score 0 if asleep or awake and calm/cooperative ($SBS^{I} \leq 0$).

✓ **Tremor**: Score 1 if moderate to severe tremor observed during the 2 minutes prior to the stimulus; score 0 if no tremor (or only minor, intermittent tremor).

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SBS Scoring

Table 3

State Behavioral Scale (SBS)

Score as patient's response to voice then gentle touch then noxious stimuli (planned endotracheal suctioning or <5 seconds of nail bed pressure)

Score	Description	Definition
−3	Unresponsive	No spontaneous respiratory effort No cough or coughs only with suctioning No response to noxious stimuli Unable to pay attention to care provider Does not distress with any procedure (including noxious) Does not move
−2	Responsive to noxious stimuli	Spontaneous yet supported breathing Coughs with suctioning/repositioning Responds to noxious stimuli Unable to pay attention to care provider Will distress with a noxious procedure Does not move/occasional movement of extremities or shifting of position
−1	Responsive to gentle touch or voice	Spontaneous but ineffective nonsupported breaths Coughs with suctioning/repositioning Responds to touch/voice Able to pay attention but drifts off after stimulation Distresses with procedures Able to calm with comforting touch or voice when stimulus removed Occasional movement of extremities or shifting of position
0	Awake and able to calm	Spontaneous and effective breathing Coughs when repositioned/Occasional spontaneous cough Responds to voice/No external stimulus is required to elicit response Spontaneously pays attention to care provider Distresses with procedures Able to calm with comforting touch or voice when stimulus removed Occasional movement of extremities or shifting of position/increased movement (restless, squirming)
+1	Restless and difficult to calm	Spontaneous effective breathing/Having difficulty breathing with ventilator Occasional spontaneous cough Responds to voice/No external stimulus is required to elicit response Drifts off/Spontaneously pays attention to care provider Intermittently unsafe Does not consistently calm despite 5 minute attempt/unable to console Increased movement (restless, squirming)
+2	Agitated	May have difficulty breathing with ventilator Coughing spontaneously No external stimulus required to elicit response Spontaneously pays attention to care provider Unsafe (biting ETT, pulling at lines, cannot be left alone) Unable to console Increased movement (restless, squirming or thrashing side-to-side, kicking legs)

CAPD Scoring

RASS Score ____ (if -4 or -5 do not proceed) Please answer the following questions based on your interactions with the patient over the course of your shift:						
	Never 4	Rarely 3	Sometimes 2	Often 1	Always 0	Score
1. Does the child make eye contact with the caregiver?						
2. Are the child's actions purposeful?						
3. Is the child aware of his/her surroundings?						
4. Does the child communicate needs and wants?						
	Never 0	Rarely 1	Sometimes 2	Often 3	Always 4	
5. Is the child restless?						
6. Is the child inconsolable?						
7. Is the child underactive—very little movement while awake?						
8. Does it take the child a long time to respond to interactions?						
					TOTAL	

Figure 1.
Cornell Assessment of Pediatric Delirium revised. RASS = Richmond Agitation and Sedation Scale.

Refrigerated: 30 days

Childrens - Clonidine 20 microgram/ml oral suspension

RECIPE ID
126 v013

TYPE
Batch

INGREDIENTS
Clonidine Hydrochloride 0.1mg Oral tablet
Simple Syrup

INSTRUCTIONS

Clonidine 20 microgram/ml oral suspension

Ingredients	Quantity to make 50 ml	Quantity to make 100 ml
Clonidine 0.1mg tablet	10 tablets	20 tablets
Simple syrup	qs ad 50 ml	qs ad 100 ml

Directions:

1) Crush Clonidine tablets with 1-2 ml of simple syrup as a levigating agent with mortar and pestle.

2) QS to total volume with simple syrup and mix well.

References:

Ann Pharmacother. 2016; 50(3):243-4

HS-create
KL - mod

WORKFLOW
1. Gather Components
2. Print Batch Labels
3. RPH Approve
4. Print Post Verification Label

Clonidine will be compounded into a liquid formulation, maintained, stored, and dispensed by the Children's Memorial Hermann inpatient pharmacy located on the 10th floor of the Hermann pavilion.

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