Use of Dexmedetomidine in Acute Stroke and Cerebral Vasospasm Interventions

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Dex in Acute Stroke Intervention
PI Blackham

STUDY TITLE

A Randomized, Controlled Trial on Dexmedetomidine for Providing Adequate Sedation and Preserved Neurologic Examination for Endovascular Treatment of Acute Ischemic Stroke or Cerebral Vasospasm.

1.0 Protocol Overview

1.1 Objective
The purpose of this study is to evaluate the efficacy of Dexmedetomidine (Precedex) during acute endovascular ischemic stroke or subarachnoid hemorrhage induced cerebral vasospasm treatment for achieving a desired level of conscious sedation and its correlation with preserved neurological function.

1.2 Study Design
Prospective, randomized trial with patient and patient assessor blindness, consisting of one arm receiving Precedex for conscious sedation and the other arm receiving usual standard of care, which is either no sedation or, if necessary and as per clinician discretion, conventional conscious sedation with opioids and anxiolytics.

1.3 Eligibility
Subjects over the age of 18 with an ischemic stroke or cerebral vasospasm requiring endovascular intervention.

1.4 Required sample size
16 patients in each arm; total 32 patients.

2.0 Abstract

Precedex is a unique FDA-approved intravenous medication for conscious sedation in that it allows for “arousable” sedation, which is particularly appealing for use in patients with compromised neurologic function. While Precedex has been shown to be equivalent, if not superior to, conventional sedation in the procedural setting, it has not yet been evaluated in the setting of endovascular treatment of acute stroke and cerebral vasospasm. This setting is particularly ripe for evaluation, as there is currently controversy over the best method for management of patient sedation in light of the auxiliary need to preserve neurologic function. In order to evaluate the benefit of Precedex in this setting, it must be compared to the usual standard of care. Through our double blinded randomized trial, we will obtain information on the comparison between two arms, one receiving Precedex and the other the usual standard of care at our institution, for achieving and maintaining a pre-defined level of conscious sedation, while preserving baseline neurologic status. This assessment will optimistically serve as the basis for future large-scale studies and ultimately to the establishment of Precedex as a first-line sedative in the management of acute stroke patients undergoing endovascular intervention.

3.0 Background and Significance

Randomized trials have shown that endovascular therapy in the setting of a severe acute stroke has proven effective for large vessel occlusion (1). Several clinical studies demonstrate that multimodal endovascular therapy (pharmacologic agents and the use of various thrombectomy devices) leads to successful recanalization in patients with an acute ischemic stroke (2-5).

Patients with SAH commonly present with change in mental status such as drowsiness or confusion and can have neurologic deficits, which are graded according to severity by the Hunt and Hess scale (below). Similarly to stroke patients, these deficits can be exacerbated from sedation with anxiolytics and pain medication.

HUNT and HESS SUBARACHNOID HEMORRHAGE SCALE of SEVERITY, 1968

Grade	Signs and symptoms	Survival
1	Asymptomatic or minimal headache and slight neck stiffness	70%
2	Moderate to severe headache; neck stiffness; no neurologic deficit except cranial nerve palsy	60%
3	Drowsy; minimal neurologic deficit	50%
4	Stuporous; moderate to severe hemiparesis; possibly early decerebrate rigidity and vegetative disturbances	20%
5	Deep coma; decerebrate rigidity; moribund	10%

Patients with SAH have high risk for developing complications such as vasospasm. Cerebral vasospasm consists in vessel constriction that reduces blood flow and can lead to brain ischemia and stroke, if untreated. All SAH patients are monitored closely in the neuroscience ICU for at least 14 days following the rupture of their aneurysm, which is the time frame for which they are a greatest risk for cerebral vasospasm. Patients are suspected of having cerebral vasospasm if velocities are elevated on daily screening transcranial Doppler (TCD) studies or if there is a change in neurologic status. Prompt imaging evaluation of the intracranial vascular tree is necessary in order for accurate diagnosis and management. Cerebral angiography is preferable as it allows for simultaneous diagnosis and treatment.

As with any patient, sedation is commonly employed during angiography for SAH patients, however, adequate sedation is particularly important in this situation for two reasons: first, these patients are more frequently agitated and combative and second, they are likely to undergo treatment (medication infusion) which puts them at higher risk for angiographic complications. As with stroke patients, it is preferable that the level of sedation allows them to be aroused easily enough to have their neurological status assessed during the procedure.

Across North America and Europe, interventional neuroradiology practices are highly variable with regard to the use of sedation or anesthesia in vascular and interventional procedures (6). The reason for this high variability is that there are clearly illustrated benefits to both practices. The benefits of no sedation or moderate conventional sedation include the preservation of the neurologic examination, reduced time delay for commencement of the procedure and lower rates of hemodynamic changes (7).

Neurologic testing during the procedure is important because it can reveal symptom resolution or progression which will affect how the procedure is continued (7). Disadvantages of no sedation include an increased level of consciousness in the patient which inevitably leads to increased patient movement, in general, and also as a response to pain, which can increase the technical difficulty of the case and lead to operator error. Disadvantages of moderate conventional sedation include the increased risk of hypoxemia and hypercapnia and an increased risk of aspiration due to an unprotected airway as well as a compromised neurologic exam (8-9). Proponents of anesthesia argue that an immobile patient allows for better image quality and better intra-procedural blood pressure control, as well as reduction in iatrogenic vessel injury (9-10). Disadvantages of anesthesia are an inability to monitor neurologic status, increased time delay for commencement of the procedure, and the risks associated with endotracheal intubation and extubation, which include increased intracranial pressure and hypotension (8-9).

Dexmedetomidine hydrochloride (trade name Precedex) is a potent and highly selective central alpha 2-adrenoreceptor agonist that is used therapeutically as a sedative. It was approved by the U.S. Food and Drug Administration in 1999 as an intensive care unit (ICU) sedative. The downstream action of the drug is decreased sympathetic activity due to diminished release of catecholamines in the locus coeruleus of the brainstem (11). Animal models have shown it to induce a dose-dependent decrease in activity, increase in sedation, and dose-dependent increase in time of being free from pain (12). Approved for use in the ICU, this drug is enjoying immense popularity in the critical care setting (13). It is used as a short term sedative in patients who are intubated and mechanically ventilated, particularly for imaging studies and for weaning patients off the ventilator. It offers a low risk of respiratory depression and increased hemodynamic stability during this period as compared to other sedatives (14). It is also unique as a sedative because it allows for arousable sedation (11). It has been especially efficacious in the neurologic ICU as studies have shown that it can improve long-term brain function in patients who are critically ill. The neuroprotective properties conferred by the drug include its ability to preserve sleep architecture and ventilatory drive (15). Studies also show that it does not compromise cognition or impair intellectual function, thus accurate patient neurologic status can continuously be obtained while on this drug (16). The risks associated with using Precedex are low, but there is a recognizable risk of hypotension and bradycardia, especially in patients with a history of hypotension. Because of its dual role as an analgesic and a sedative with low risks of respiratory depression, much interest has been generated in extending the use of this drug outside of the ICU setting and studies have shown it to be as efficacious at sedation as propofol and Midazolam, while still maintaining a much lower risk of respiratory depression. (17-19).

4.0 Study Objectives

The primary objective of this study is to compare the efficacy of Precedex versus usual standard of care in the setting of endovascular treatment of acute stroke or cerebral vasospasm by assessment of the following outcome measure:

1. Comparison of number of “events” (as defined by any movement by subject during the procedure that delays or adversely affects the performance of the procedure in a safe and timely manner; See Appendix 13.3 for definition) in the Precedex arm versus the control arm. This will be measured as the proportion of one-minute intervals during the procedure in which an event occurred.

The secondary objectives of this study include the preservation of the neurological exam and ability to stay within a specified sedation target in the Precedex group. These objectives will be evaluated with the following outcome measures:

1. Measurement of the modified National Institutes of Health Stroke Scale (mNIHSS) score (See Appendix 13.2 for definition) at baseline and five times after the start of the procedure.

2. Measurement of the Richmond Agitation-Sedation Scale (RASS) score (See Appendix 13.1 for definition) at baseline and every 20 minutes after the start of the procedure and at every time a NIH stroke score is obtained.

The secondary objectives of this study also include collection of the following data and comparison across arms (see Appendix 13.3 for definitions):

1. Estimation of the proportion of patients with preserved neurologic exam in the Precedex arm versus the control arm.
2. Mortality and symptomatic hemorrhage rates.
3. Peri-procedural complications.
4. Recanalization time.
5. Use of additional sedatives.

We will also explore associations between motion related events and status of preserved neurologic exam with these outcomes.

5.0 Research Design and Methods

5.1 Study Design

This is a prospective, randomized trial with patient and patient assessor blindness, investigating the ability of Precedex during acute endovascular ischemic stroke or cerebral vasospasm treatment to provide adequate conscious sedation with preserved neurological function. 32 subjects with diagnosis of acute ischemic stroke or cerebral vasospasm will be included in this study. 16 subjects will be randomized to the Precedex arm and 16 subjects will be randomized to the control arm. Eligible subjects will be those over 18 with acute ischemic stroke or cerebral vasospasm requiring endovascular intervention. The treating physicians and nurses will not be blinded to the treatment arm. However, the research nurse/patient assessor will be blinded to the study in its entirety except for the measures he/she is instructed to obtain.

Drug Administration

Dexmedetomidine arm: Precedex will be started after randomization and prior to arterial intervention and will be stopped at the end of the procedure. The Precedex will be used for an average of 90 minutes; minimum duration of procedure is 30 minutes and maximum duration 4 hours. The Precedex will be used as a continuous intravenous infusion started at 0.3 mcg/kg/hour. If the heart rate is greater than 80 beats per minute and blood pressure greater than 120/70, a full loading dose (1.0 mcg/kg/hour) will be administered over 10 minutes. If heart rate is between 60 and 80 or systolic pressure between 90 and 120, or the patient is greater than 65 years of age, a reduced loading dose of 0.5 mcg/kg will be given over 10 minutes. If there is no evidence of volume overload by physical examination, 500mL of colloid (hespan or albumin) will be bolused with 0.2mg of glycopyrrolate, in the absence of contraindications to glycopyrrolate, such as a history of glaucoma. Every 10 minutes, Precedex will be titrated by 0.1 mcg/kg/hour with the goal of achieving and maintaining RASS of 0 to -1. Additional Fentanyl and Midazolam intravenous bolus doses may be used, as per clinician discretion. Every 20 minutes, a full RASS score will be assessed and, also, if at any time point during the procedure it is noticed that patient is at a level of moderate or deep sedation (RASS of -2 to -4) that cannot to be attributed to stroke or cerebral vasospasm in evolution itself or to procedure related complication, then Precedex will be titrated to a lower dose.

Control arm: Our usual standard of care is to attempt the intervention without sedation. As per attending physician discretion, Fentanyl (50mcg) and/or Midazolam (0.5 mg) intravenous boluses will be used to control aggressive patient movement that adversely affects the technical capacity of the procedure. The boluses will be repeated at interval of 10 minutes, as necessary. Control arm patients will receive a normal saline placebo drip for the purposes of ensuring patient assessor blindness.

For the purposes of ensuring blindness of the research nurse/patient assessor, the treating physicians and nurses will be instructed to communicate in terms of administering or adjusting "the sedative medication", and the actual details of any medication adjustment will be discussed out of hearing range of the research nurse/patient assessor.

All subjects will be closely monitored by the radiology nurse during the procedure for hypotension, bradycardia and oxygenation saturation.

Primary Outcome – Number of 'Events' (see Appendix 13.3 for definition)
Continuous monitoring by the research nurse/patient assessor will be done to evaluate for patient movements by the subject that delay or adversely affect the performance of the procedure in a safe and timely manner (an 'event'). If the subject has such a movement, then it will be considered an event. One minute interval between patient event assessments will be given to prevent subjective bias. After every one minute, it will be determined if an event has occurred. Over the length of the procedure, the total number of one-minute intervals with an event occurrence will be summed. In turn, this summed value will be divided by the total number of minutes in the procedure, so that we obtain a standardized value as the primary outcome measure. This ratio is the proportion of oneminute intervals with events during the procedure, which allow for direct comparison of values across procedures of varying length. This outcome measure employs short observation intervals for counting events to encourage more precise measurement. At the same time, this approach will be more systematic and more easily replicable than counting events directly, which requires interpretation as to when a movement event begins and ends, which can be difficult and more subjective.

Secondary Outcome -- Preserved Neurologic Exam
Dexmedetomidine arm: Neurologic status using the modified NIHSS scale (mNIHSS, see Appendix 13.2) will be assessed five times: 1) in the emergency room, 2) prior to the start of the procedure, 3) one time at a convenient moment during the procedure (usually after some revascularization has occurred), 4) at the conclusion of the procedure, 5) 1-2 hours after the conclusion of the procedure. RASS score will also be concomitantly assessed with each preserved neurologic exam assessment. The observed proportion of times out of the 5 trials after the start of the procedure that neurologic exam is preserved during a procedure will be a secondary outcome of this study.

If clinical worsening of subject of mNIHSS >4 at any time point during the procedure is noticed with the level of sedation of RASS score of 0 to -1 that cannot to be attributed to stroke in evolution itself or to procedure related complication, then administration of Precedex will be stopped and patient will be reexamined at 15 minute intervals until patient returns to baseline mNIHSS or change in mNIHSS can be attributed to stroke or cerebral vasospasm in evolution or procedure related complication, or any other physiologic compromise.

Control arm: Neurologic status using the mNIHSS scale will be assessed five times for this arm as well: 1) in the emergency room, 2) prior to the start of the procedure, 3) one time at a convenient moment

during the procedure (usually after some revascularization has occurred), 4) at the conclusion of the procedure and 5) 1-2 hours after the conclusion of the procedure. If clinical worsening of subject of NIH >4 at any time point during the procedure is noticed that cannot to be attributed to stroke in evolution itself or to procedure related complication then subject will not receive any additional Midazolam or Fentanyl and patient will be reexamined at 15 minute intervals until the patient comes back to baseline mNIHSS or change in NIHSS can be attributed to stroke or cerebral vasospasm in evolution or procedure related complication, or any other physiologic compromise.

Secondary Outcome – Maintaining Sedation Target

Dexmedetomidine arm: RASS score will be determined at baseline and then every 20 minutes by the patient assessor. The clinical judgment of the treating physician will determine if Precedex will be titrated by 0.1 mcg/kg/hour with the goal of achieving and maintaining RASS of 0 to -1. Control arm: RASS score will be determined at baseline and then every 20 minutes. There will be no medication given or adjusted based on the RASS score. Medications will be administered at clinician discretion. The number of events and mNIHSS will be scored and recorded by a clinical research nurse/patient assessor who will be blinded to the study protocol in its entirety with the exception of the data to be acquired as noted above, and with the exception of the 3 hour post-procedure mNIHSS, which will be obtained by the NSICU nurse as per standard of care. The research nurse will be from a pool of nurses who are trained in the use of the RASS and mNIHSS. The research nurse will be on call and contacted by the interventional fellow or attending as soon as he/she becomes aware of the possibility of the interventional management of an acute stroke. Clinical judgment by the treating physician and nurses will be used to determine the level of sedation (RASS score) in order to make titration decisions in the Dexmedetomidine arm. Data entry will be done performed by the research assistant on the day following the procedure. Subsequent to the patient discharge, data extraction from follow-up clinical and imaging data regarding mortality, symptomatic hemorrhage rates and peri-procedural complications will be collected by the research assistant. 5.2 Reference Standard The reference standard or control group will receive the usual standard of care at our institution. For the majority of patients, this means no sedation at all. In the case of a patient in the range of agitation which corresponds to a +3 or higher on the RASS, it is likely that the patient will receive the minimum combination of Midazolam and Fentanyl, as per attending physician discretion.

5.3 Investigator and Institutional Requirements

All investigators participating in this clinical trial are qualified and certified to conduct clinical trials involving humans according to our institutional regulations. UniversityHospitals of Cleveland, Department of Radiology, has access to a research coordinator, statistical support (as listed above), a medical writer, an IRB committee, a pharmacy with support from a dedicated neuro-pharmacist (as listed above), a laboratory, and a contracts and legal department. We have access to a patient clinic in conjunction with the Department of Neurosurgery.

5.4 Subject Eligibility Criteria

Screening criteria

All acute stroke or cerebral vasospasm patients referred for endovascular intervention will be screened by study investigators for enrollment in this study. The study investigators will clinically evaluate the patient to assess the need for sedation during the procedure. Level of sedation (RASS score) will be used to screen the patients (See 13.1).

Inclusion Criteria

1. Patients with acute ischemic stroke who require endovascular intervention between the ages of 18 and 85, in whom a mNIHSS score can be obtained.
2. Patients with subarachnoid hemorrhage who are referred to cerebral angiography for suspicion for vasospasm between the ages of 18 and 85, in whom a mNIHSS score can be obtained.

Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. History of severe hepatic disease or severe renal disease (GFR<20).
2. Hemodynamic instability.
3. Pregnancy.
4. Known allergy to study drug.
5. Evidence or history of cardia electrophysiology instability including uncontrolled hemodynamically unstable complex atrial/ventricular arrhythmia or conduction block at the time of evaluation with the exception of atrial fibrillation, and heart rate less than 60 systolic blood pressure less than 90.
6. Respiratory compromise requiring intubation.
7. Any medical (including history of cardiac conduction block, major hepatic or renal disease) or laboratory abnormality that may increase the risk associated with the trail participation or drug administration or may interfere with interpretation of trail results.
8. Baseline continuous infusion of sedative.

Recruitment Precedure

The neurointerventional attending physician or fellow will approach the patient or legally authorized representative to explain the aims, risks and benefits of this study. Informed consent will be obtained from the subjects or legally authorized representative. Eligible subjects who have given their consent will be enrolled in this study (See 13.4 Appendices).

5.5 Study Calendar/Schedule

All drug administration takes place within a 6 hour time frame and there will be no return or follow-up visits. As per review of our database, 32 subjects should be enrolled within 9-12 months of contract execution, at the rate of 2-4 per month. This would require 1-2 vials of Precedex per month. One-half of the patients should be enrolled by 6 months and all of the subjects by one year from contract execution. At conclusion of the trial, the manuscript should be completed by 14 months from contract execution and sent to Hospira for review.

5.6 Accrual Goals and Monitoring

According to statistical power analysis, an overall study population size of at least 32 patients is required to achieve primary objectives. According to prior retrospective data, this number will be achieved at approximately one year after initiation of the study. After 6 months and one year, the study population size recruited up to such time point will be assessed.

5.7 Randomization

32 subjects with diagnosis of acute ischemic strokes or cerebral vasospasm will be included in this study. 16 patients will be enrolled in the Precedex arm and 16 patients will be enrolled in the control arm. All subjects who have met all inclusion criteria and no exclusion criteria and are eligible to receive study drug will be randomized. The patients will be randomized in both groups by using a shuffle card technique. The subject will be blinded to the treatment arm to which they were randomized. The

neurointerventionalist team who will be performing the interventional procedure will be informed of the treatment arm.

5.8 General Concomitant Medication and Supportive Care Guidelines
Sedatives: It is well documented that dexmedetomidine has a dose sparing effect when used concomitantly with other medications used for sedation and analgesia. If deemed necessary, supplemental sedatives (opioids or benzodiazepines) will be utilized at lower doses and the dosing interval will be limited to 10 minutes between repeated dosing. Antihypertensives: If antihypertensive therapy is necessary, dosing will be consistent with current practice, and the dosing interval will be limited to 10 minutes between repeated dosing and dose titrations for these agents. Typical Medications: Opioids: Fentanyl; Anxiolytic: Midazolam; Antihypertensive: Labetalol, Hydralazine, and Nicardipine

5.9 Post-therapy Visits
No further visits are part of this trial.

5.10 Criteria for Removal from Study
At all times the patient can withdraw from this study and receive the usual standard of care. If any of the clinical scenarios detailed in the exclusion criteria occur or are discovered, the patient will be removed from the study.

6.0 Statistical Considerations

Procedures will last on average 90 minutes, and a minimum of 30 minutes. We expect all subjects to complete the procedure.

For first aim: In projecting the available power from the proposed design, we expect that at least 30% of subjects in the control arm will eventually be given Midazolam and/or Fentanyl. We conservatively project that if no Midazolam and/or Fentanyl are administered, there will be on average at least 24 one-minute intervals with a recorded motion event during an average length procedure of 90 minutes, and no events will occur if Midazolam and/or Fentanyl are administered. In other words, we expect a proportion of 0.2667 of the one-minute intervals during a procedure to have events. Given our preliminary experience with Precedex, only 2 out of 13 subjects recorded a motion event at all during procedure. For those that did, 10-12 events were observed.

Anticipated Results: Hence, for the usual care arm, the expected number of events in a 90-minute period is 16, given the assumption that 30% receive Midazolam and/or Fentanyl. Equivalently, suppose an expected proportion of 0.267 of the one-minute intervals will have events. For the Precedex arm, suppose conservatively that the expected number of one-minute intervals with events in a 90-minute period is 8; equivalently, suppose the expected proportion of one-minute intervals that will have events is 0.089. A common assumption for count data within a given time period is that they follow a Poisson distribution. The characteristic of the Poisson distribution that is of interest for this power analysis is that the mean and variance are equal. Being conservative, suppose that the variance is four times as large as the mean, and larger than we expect. Note that a hypothesis test to see if the expected number of one-minute intervals with events in a given time period (equivalently, the expected proportions) are equal between Precedex and usual care arms, at two-sided Type I error of 0.05, will have power equal to 0.885 using a two-sample t-test. Hence, we believe that the study should easily have sufficient power for this aim. A nonparametric Mann Whitney test also will be considered.

We will assess correlation between intervals, as the power analysis assumes independent observations. Impact of this assumption will be assessed through fitting a generalized linear mixed model that allows for correlated binary outcomes, and analysis of a treatment effect in the context of that model will be compared with the t-test results. Treatment arm will be denoted by a binary variable, and the corresponding coefficient will be tested to see if it is zero or not. We will assess different covariance structures, and explore including time of interval as a covariate. While we do not expect strong intra-subject serial correlation, presence of correlation would have some effect on power, so it is prudent to be conservative with a larger sample size than is needed to obtain power of 0.80 under the independence assumption for the t-test. The required sample size is actually 13 per arm to attain of power of 0.80, while we have proposed to collect samples of 16 per arm. Moreover, we also assumed that the variances are four times the value of the projected mean. These variance values reflect overdispersion that may occur due to correlated observations, relative to the reference Poisson distributions that were described. Hence, in computing required sample size, we have tried to be conservative in order to account for possible correlation. The projected sample size requirement should provide adequate power under small serial correlation as well. Note also that we will have a very large number of observations over time per subject (on average, around 90 one-minute intervals), which should enhance power for detecting treatment differences in the mixed model. SPSS has a mixed models package that we will employ.

An alternative analytic approach that was considered is the use of contingency table analysis. Treatment arms could comprise two rows, and the columns could represent categories associated with counts of events. However, due to the relatively small projected sample size, the number of categories representing count number of one-minute intervals with an event would have to be restricted in order for each cell to have sufficient number of counts for asymptotic Chi-square analysis to be applicable. This may well reduce observed variability between treatment arms, and hence we believe the proposed approach of comparing these counts through two-sample comparison methods of means (or medians) is preferable and more powerful.

For the secondary analyses: It will be of interest to determine if capability for neurological exam peri and post procedure is preserved. We will count the number of exams for which capability is preserved, out of the 5 exams conducted for each subject once the procedure has begun. We will estimate and report 95% confidence intervals for the proportion of preserved exams per procedure for subjects who are administered Precedex. We expect that at worst, based on our preliminary experience with Precedex, that for subjects in the Precedex arm, at least 60% to 80% of exams will have such capability preserved. Hence, we expect confidence interval half-widths to be between 0.240 and 0.196. For the control arm, we expect that those receiving Midazolam and/or Fentanyl will not have neurologic exam preserved, while those who do not will have all of their exams preserved. Hence, on average, we expect around 75% of exams to be preserved in the control arm. We will also estimate 95% confidence intervals for the respective proportion for this group, which should have similar interval lengths as for the Precedex group, as well as compare proportions between these groups using two-sample z-test. We do not expect to find statistically significant differences. Another secondary outcome of interest that will be analyzed similarly is the proportion of RASS exams for each subject that are in a bandwidth of 0 to -1. We will statistically compare the respective averages of the proportions across arms as well. Finally, we will also compare secondary outcomes across arms for mortality and symptomatic hemorrhage rates, peri-procedural complications, recanalization time, and use of additional sedatives.

7.0 Adverse Events

7.1 Definition.
A serious adverse event (SAE) is defined as any untoward medical occurrence that: (1) results in death, or (2) is life-threatening (at the time of the event), or (3) requires inpatient hospitalization or prolongation of an existing hospitalization, or (4) results in persistent or significant disability or incapacity, or (5) is a congenital anomaly/birth defect.

Abnormal results of diagnostic procedures are considered to be adverse events (AEs) if the abnormality: (1) results in study withdrawal (2) is associated with a serious adverse event (3) is associated with clinical signs or symptoms (4) leads to additional treatment or to further diagnostic tests (5) is considered by the investigator to be of clinical significance.

7.2 Adverse Event Grading:
Grade is used to denote the severity of the adverse event.

1 – Mild
2 – Moderate
3 – Severe
4 – Life-threatening or disabling
5 – Fatal

Adverse Event Attribution: Attribution is used to determine whether an adverse event is related to a study treatment or procedure.

Attribution categories are:
Definite – AE is clearly related to the study treatment or procedure.
Probable – AE is likely related to the study treatment or procedure.
Possible – AE may be related to the study treatment or procedure.
Unlikely – AE is doubtfully related to the study treatment or procedure.
Unrelated – AE is clearly NOT related to the study treatment or procedure.

7.4 Expected Adverse Events
Hypotension: Any decrease in blood pressure to <90Hg systolic or <60mm Hg diastolic will be considered hemodynamically unstable. At this time point medication will be titrated down to lower dose and 250cc normal saline intravenous fluid will be administered. Blood pressure will be re-evaluated in 3-5 minutes interval. If subject's blood pressure still remains unchanged then medication will be stopped and subject will be treated with intravenous normal saline boluses and may need administration or additional vasopressors.

Bradycardia: A decrease in heart rate to <60 beats per minutes from the subject's baseline heart rate will be considered as bradycardia secondary to medication use. At this time point medication will be titrated down to lower dose. If subject heart rate still remains unchanged or interval decrease in heart rate is observed then medication will be stopped. Glycoprrolate or atropine via intra venous injection may be used to counteract drug-induced or vagal reflexes and their associated arrhythmias.

Mortality and Morbidity: Any periprocedural death or morbidity that cannot be attributed to any other cause and if directly related to any adverse event mentioned in Precedex pharmaceutical manual as a side effect will be defined as mortality or morbidity secondary to medication use.

7.4 Adverse Event Reporting
It is the responsibility of the investigator to document all adverse events (AEs) which occur during the course of the study.

8.0 Data Management; Administration

In order to protect confidentiality the subject will be assigned an identification number. This number will be used on all data from the subject and will be used for documentation purposes. Data management for the optimal entry, processing, storage, and retrieval for this protocol's data will be accomplished by the principal investigator. The database will be located on a computer or in a locked cabinet in a locked office. This computer will be secured, accessible only by the research team. A second, secured, copy of the protocol data will be stored in a locked room accessible only by the research team. For quality control, auditing, and checking data for integrity, there will be a regular accounting of data periodically performed.

9.0 Drug Quantity and Financial Expectations

16 patients are expected to be enrolled in the Precedex arm, with one vial being required per patient, as well as 5 extra vials. The fixed Administrative and IRB costs would be expected as the initial payment. Otherwise, it is anticipated that payment will occur as the total divided quarterly or monthly.

10.0 References

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