Does Single Intraoperative Bolus Dexmedetomidine Significantly Reduce Narcotic Requirements During Postoperative Period in Bariatric Patients?

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Protocol

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Introduction: This study will evaluate the postoperative opioid sparing effects of dexmedetomidine given as single bolus dose intraoperativley. Dexmedtomidine is an agonist of α_2-adrenergic receptors sedative medication used by intensive care units and anesthesiologists and is unique in its ability to provide sedation without causing respiratory depression. Recently, it has received attention for its potential for additive analgesia. The study population will be patients undergoing gastric bypass surgery. The study population of bariatric surgery patients was chosen due to high prevalence of sleep apnea and Pickwickian component that can be worsened with opioid analgesia in the postoperative period. The purpose of the study is to test whether the use of a single bolus dose dexmedetomidine in addition to standard dose pain regimen decreases postoperative narcotic requirements when compared to standard dose pain regimen alone. The secondary purpose is to study whether single bolus dose dexmedetomidine reduces respiratory rate, heart rate, systolic and mean blood pressure, patient PCA demand bolus requests and VAS pain scores in the postoperative period. Our overall goal of the study is to establish evidence of dexmedetomidine's role in multimodal pain relief in the bariatric surgery population with the possibility of other patient subgroups to follow.

Primary Objective: The primary objective of the study is to assess if the use of a single bolus dose dexmedetomidine in addition to standard pain regimen given intraoperatively decreases postoperative narcotic requirements when compared to standard pain regimen alone.

Secondary Objective: The secondary objective of the study is to assess if the use of single bolus dose dexmedetomidine decreases respiratory rate, heart rate, systolic and mean blood pressure, patient PCA demand bolus requests and VAS pain scores in the postoperative period.

Potential Benefits to Subjects

a. Increased patient satisfaction and comfort
b. Decreased narcotic requirements
c. Decreased narcotic related side effects including nausea, constipation and respiratory depression
d. Decreased stress response
e. Reduced postoperative blood pressure and heart rate

f. Patient anxiolysis

Study Design: After informed consent is obtained in the Bariatric Surgery Center, patients will be enrolled in the study and assigned a code for the remainder of study. The code will used by pharmacy for block randomization. The code will be associated with MRN for patient identification and data entry by Co-investigators after patient has been discharged from study. On the day of the procedure, preoperative nursing will place sticker on front of patient hard chart clearly marking participation in trial. The control group will receive 1-2 mcg/kg fentanyl IV plus 1000 mg IV tylenol as well 60mL saline delivered over 15 minutes in OR upon notification of surgical closure. The experimental group will receive 1-2 mcg/kg fentanyl IV plus 1000mg IV acetaminophen and 1mcg/kg IV dexmedetomidine deliver over 10 minutes from 60 mL syringe upon notification of surgical closure. Pharmacy will be notified of patient enrollment in trial, use block randomization sheet for assignment to treatment or control group, and prepare medication syringes. Syringes will be delivered to OR for administration by anesthesia personnel upon notification of surgical closure. The investigators, patient, anesthesia staff, PACU nursing OR staff and surgeon will be blinded to medication being administered. Pharmacy will not be blinded to medication as they will have block randomization sheet and assign patient by MRN to a given code. Time interval to extubation from procedure stop will be recorded in EMR by anesthesia personnel. Upon arrival to PACU, patient will immediately receive hydromorphone and be instructed on its usage by PACU nursing. PACU nursing will record HR, RR, BP, and VAS score q15min per PACU routine into EMR. PCA will be interrogated at 30 minute, 1 hour, 90 minute, 2 hour and 4 hour mark by PACU nursing and usage in milligrams will be recorded in chart as nursing note for later review by researchers. Included in PCA data will be total mg of hydromorphone used, number of demand doses given by pump, and number of times patient pushes demand button. Patient will be discharged from study after 4 hour mark per OSA guidelines. Results will be recorded into Redcap online statistics program to ensure data safety. Code and MRN block randomization sheet will be kept under lock and key in pharmacy.

Patient Risk Management:

a. Identification of Risk: Because medication is to be given in this study, more than minimal risk will be incurred by the patient. Participation is completely voluntary. Risks include possible allergy or other unanticipated reaction to dexmedetomidine or hydromorphone. Specific side effects to dexmedetomidine include symptomatic bradycardia, sinus arrest, hypertension, hypotension, and excessive sedation. Specific side effects related to hydromorphone are common to all narcotics and include sedation, respiratory depression, upper airway obstruction, constipation, illeus, bradycardia, nausea, and vomiting.

b. Management of Risk: **:** During study period, syringes will be covered with opaque label as to blind surgeon and anesthesia personnel to contents. Label can be peeled off at any time by anesthesia personnel to reveal syringe content in the event of an emergency and medication identification would be necessary for patient safety. Patient would be disqualified from trial if this were to occur. Atropine and glycopyrolate will be in syringes and ready for use as part of standard emergency drug regimen in case of hypotension or bradycardia experienced by patient throughout study period. Dexmedetomidine or saline will not be administered to patient if systolic blood pressure is less the 90mmHg, mean arterial pressure less than 60, or if heart rate less than 50 bpm. Rescue hydromorphone will be available in form of IV hydromorphone 2mg PRN q5mins if PCA dosing fails to control pain. Patient will be disqualified from study if rescue medication was given. Medications will only be administered by trained anesthesia personnel.

Trained PACU nurses under guidance of staff anesthesiologist will oversee PCA usage. Trained pharmacy staff will prepare all medications for use. Emergency resuscitation equipment and drugs including atropine and narcan will be immediately available at all.

c. Confidentiality: The records of this study will be kept confidential. The investigators will not include the name of any patient involved in the research. Patients will be assigned a code number upon enrollment in study. Code numbers will be used for block randomization in pharmacy to randomly assign patient to treatment groups. Pharmacy staff will have access to patient chart and MRN for purpose of recording which drug was given, control or experimental. Block randomization sheet containing MRN and code numbers for patient will be kept under lock in key by pharmacy personnel. The sheet will be kept for official study documentation. A document listing the code associated with a specific patient and their MRN will be stored in redcap only to be viewed by the co-investigators for data analysis. The patient's code number will be used on all other documentation to protect patient privacy. The investigators and statistician will be the only person who will have access to this data.

d. Patient Data Safety Plan: Researchers will access the code sheet at 25, 50, 75, and 100 patient enrolment points to record pertinent clinical data for analysis. Included in the interval analysis will be medical futility and critical detrimental patient events to assure patient safety throughout trial. Times. Specifically, study personnel will look for instances of symptomatic bradycardia or other heart rhythm disturbances, oversedation, respiratory failure, hypotension or other unforeseen critical event. Patients will be provided with study personnel contact information in case adverse event possibly related to study were to occur after discharge from study All data will be entered and safely stored in redcap, an online secured server maintained by School of Public Health

Number of Subjects: 100 subjects (50 subjects assigned to control group and 50 to treatment group)

a. Subject Characteristics: The participants in the study will include 100 bariatric surgery patients at WVUH Ruby Memorial Hospital who choose to participate in the study after informed consent is obtained.

b. Selection Criteria: Patients must be undergoing bariatric surgery at WVUH Ruby Memorial. They must be ASA class III of lower. They must be between the age of 18 to 65 years old.

c. Exclusion Criteria: Hydromorphone or dexmedetomidine allergy. ASA class IV or higher. Emergency surgery. Long term narcotics usage defined as > 2 weeks. Long term sedative (benzodiazepine, clonidine, hydroxyzine) usage defined as greater than 2 weeks Bradycardia defined as HR < 50bpm, SBP < 100mmHg, Tachy-Brady Syndrome, 1st, 2nd or 3rd degree heart block, Junctional Rhythm. Severe renal or hepatic dysfunction. Protected populations will be excluded from study including obstetrical patients, prisoners, students, or mentally handicapped.

d. Recruitment Source: Bariatric surgery patients at WVUH Ruby Memorial will be recruited in bariatric surgery clinic or pre-operatively by anesthesia personnel. Dr. Quinlin performs 3 to 4 laproscopic gastic bypasses per week with a conservative estimate of 200 operations year. Our

goal is 50% patient participation after voluntary participation rights and exclusion criteria have been applied.

e. Recruitment Methods: Subjects that meet above criteria will be asked if they wish to participate in study. Risks and benefits of the study will be explained.

f. Potential Problems: Problems involving subject identification and recruitment by anesthesia personnel should be minimum. Education post-operative staff on PCA usage data recording will likely be the largest barrier.

Informed Consent: Patients undergoing bariatric surgery at WVUH Ruby Memorial will be asked about voluntary participation in the study during preoperative visit to Bariatric Surgery Center. Risks and benefits relating to the study will be explained to patient by Kristen Rosati, Physician Assistant at WVU Bariatric Surgery Center. Information will be given to patient after all questions and concerns have been addressed. Patient will be given opportunity to consider trial participation and informed consent process would take place on subsequent visit. After inclusion and exclusion criteria have been assessed, the patient will then have informed consent form reviewed with them and sign informed consent form if they wish to participate. Patient will be enrolled in study from this point forward.

Statistical Methods: Descriptive statistics will be calculated for both groups, including means (SD) and frequencies (percentages) where appropriate. Comparisons between the two groups with respect to binary outcomes will be done via chi-square tests, and odds ratios (95% confidence intervals) will be reported to quantify the magnitude of the differences observed. The majority of the primary outcomes are continuous in nature, and more than likely many will be skewed, including cumulative hydromorphone usage. However, given the sample size (over 30 per group), t-tests comparing the means of these outcomes will be able to be used. In the event sample size targets are not reached, nonparametric tests (i.e., Mann-Whitney U) will be utilized. Statistical significance will be set at alpha = 0.05. All data will be exported from REDCap and analyzed via SAS (version 9.3). Power analysis reveals 50 enrolled patients per group will provide 90% power (alpha = 0.05) to detect a difference of 0.66 standard deviations between the two groups. Unfortunately, no reliable standard deviation estimates of our primary outcome, cumulative hydromorphone at 240 minutes post-arrival to PACU, are available in the literature. A conservative estimate from the Tufanogullari et al. paper (Anesthesia and Analgesia, 2008, 106: 1741-1748) for the standard deviation of cumulative morphine in one day (not hydromorphone) is about 30 in either group. Given our calculations for this hypothetical outcome, we would have sufficient power to see a difference of 20mg in cumulative morphine between the two groups, which would amount to a 40% reduction given a mean morphine level of 50mg in the control group. Since we will be focusing on hydromorphone and not morphine over a shorter period of time, both the mean and SD of our primary outcome should be considerably smaller in a similar fashion, but the percent reduction that we would be able to detect statistically should remain the same. For our secondary outcome of the VAS pain score, which is known to have a SD of about 3 in this population, 100 patients will provide 90% power to detect a difference of 2 units in pain score at any given time point.

Primary Endpoint: The primary endpoint will be cumulative patient hydromorphone PCA usage in the 4 hour postoperative period.

Secondary Endpoints: Respiratory rate, heart rate, systolic and mean blood pressure, patient PCA demand bolus requests and VAS pain scores in the postoperative period.

Timeline to Endpoints: We anticipate a one year course for data collection to achieve our goal sample size. Twelve weeks are estimated to be need for statistical calculation and results analysis.

Costs: The subjects of this study will not incur any costs as a result of their participation. Funding for dexmedetomidine will be provided by Hospira.

Compensation and Incentives: There will be no compensation or incentives offered for anyone involved in this research project.

Literature Review

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