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Comparing Time to Readiness for Discharge After Colonoscopy: Propofol and Dexmedetomidine vs Propofol Only Sedation

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1. INTRODUCTION:

Colonoscopy is an important diagnostic screening procedure for colon cancer that is often associated with discomfort therefore requiring moderate to deep sedation of patients. Monitored Anesthesia Care (MAC) sedation is the technique that is widely provided and is considered the standard of practice in the United States for patients undergoing colonoscopy [1]. An ideal sedative agent for ambulatory colonoscopy should have certain properties that include: a rapid onset and offset of action, provide cardiopulmonary stability, have minimal adverse effects, and allow for smooth recovery, and early discharge [4, 5].

Titrated bolus dosing or continuous infusion, of propofol alone, is the commonly used technique for Monitored Anesthesia Care (MAC) in ambulatory colonoscopy. Propofol is chosen because of its rapid onset and short duration of action, a property which is ideal for fast recovery and early discharge in the ambulatory setting. Depending on a patient's comorbidities, age and functional status, there is a wide range of variability in the hemodynamic and respiratory responses with sedative doses of propofol. Careful propofol titration is therefore required to avoid hypotension and hypoventilation. Hypotension and apnea can occur if large doses of propofol are required to complete the procedure [1, 6, 7].

Balanced anesthesia, using a combination of medications with different mechanisms of action can be used as a technique to minimize the total amount of each agent given and their side effects while achieving the desired level of sedation. Dexmedetomidine is one agent that has been used alone or in combination with propofol for sedation during colonoscopy.

Dexmedetomidine is an alpha-2 adrenergic receptor agonist with analgesic and sedative effects [8]. Other desirable effects for this agent include: decrease requirements for other anesthetics and analgesics, minimal respiratory depression, neuroprotection, and decrease in emergence agitation [9-11]. On the other hand, dexmedetomidine has been reported to be associated with prolonged post-operative recovery time due to bradycardia, low mean arterial pressure, and cardiovascular depression [12-14].

While several studies have examined the use of dexmedetomidine in colonoscopy, there is limited evidence on its efficacy when combined with propofol for use in ambulatory colonoscopy. One study that demonstrated the safe use of dexmedetomidine alone for colonoscopy also concluded that its sole use in this setting is limited by its side effects such as, hemodynamic instability, prolonged recovery, and a "complicated administration" [15]. In another study, dexmedetomidine was shown to provide better hemodynamic stability, higher Ramsay sedation scale score, and higher satisfaction scores in comparison to midazolam [16]. A randomized study that compared four different drugs: dexmedetomidine, sufentanil, meperidine and midazolam used in combination with propofol for sedation in colonoscopy showed that patients who received dexmedetomidine and propofol had a higher degree of sedation and shorter time to recover protective reflexes and motor function [4].

Only one study in the literature has directly compared a dexmedetomidine-propofol regimen with propofol alone for sedation during colonoscopy. In this Chinese study, investigators found that oxygen saturation level, and the amount of propofol consumed in patients who received dexmedetomidine-propofol are decreased in comparison with those who received propofol only [17]. The study investigators determined that there was no difference in recovery time between a combination of dexmedetomidine-propofol compared to propofol-only. However, recovery time in the study was defined as time from the last dose of medication to the time when the patient became alert and oriented to their name, age and to time. This definition of recovery does not necessarily mean that the patient is ready for discharge to home, which will be more relevant to the clinical implications of the findings in the ambulatory surgical setting. In the United States, phase 2 recovery from anesthesia and readiness for discharge to home is based on a specific criteria that is defined by the Modified Post Anesthesia Discharge Scoring System (MPADSS), shown in Table 1 (18, 19). Compared to the Aldrete score (Table 2), the MPADSS system does not only provide criteria for discharge from the post anesthetic care unit (PACU), but also provides criteria for "street fitness," such as severity of pain, ability to stand and ambulate, and tolerance of oral fluids so that patients can be discharged to home (20,21).

We did not find any study in the literature that has definitively assessed whether dexmedetomidine-propofol prolongs readiness for discharge in the ambulatory setting when compared to a propofol-only regimen for sedation.

Some practitioners at the SUNY Downstate Medical Center have started combining dexmedetomidine with propofol for sedation of patients undergoing colonoscopies. Due to the importance of rapid recovery and patient turnover in an ambulatory surgery setting, we plan to conduct a prospective randomized double-blind study on patients scheduled to undergo colonoscopy to compare the combination regimen of dexmedetomidine-propofol to a propofol-only regimen and determine whether there are any differences in recovery time and readiness for discharge as defined by the Modified Post Anesthesia Discharge Scoring System (MPADSS) scale.

2. OBJECTIVES

We will prospectively compare a group of patients randomized to receive propofol and dexmedetomidine to another group of patients randomized to receive propofol alone. We hypothesize that there will be no significant difference in the time to readiness for discharge between the two groups using the MPADSS discharge scale.

3. STUDY DESIGN AND METHODS

This is a prospective study to compare in a randomized double blind trial the following outcome measures:

Primary outcome:
1. Readiness for discharge time:
From the time of last administration of sedative medication to the time for the patient to attain Modified Post Anesthesia Discharge Scoring System (MPADSS) score of 9-10. The evaluation of time to discharge will involve the assessment of patients every 10minutes. Since almost every patient is discharged within an hour, the measure is very granular; we propose therefore to dichotomize it as discharge within 30min, yes or no.

Secondary outcomes:
1. Total propofol consumption per group (mg/kg)/duration of procedure in minutes
2. Side effects:
    a. lowest intraoperative % drop in MAP from baseline
    b. sustained bradycardic episode (HR<50 for at least 5 minutes) intraoperatively, to be reported as a yes/no event
    c. number of apneic episodes, intraoperatively, requiring positive pressure ventilation. To be reported per group

A. Type of study

This is a non-inferiority prospective randomized double blind study.

B. Patient selection

i. Requested Sample Size: Up to 150 people will be screened until the study achieves 100 cases (excluding screen failures and withdrawals) - 50 patients to receive intravenous Dexmedetomidine 0.3 ug/kg followed by propofol; 50 patients to receive propofol-only plus placebo.

ii. Inclusion and Exclusion Criteria:

Inclusion criteria:

- All patients scheduled to undergo colonoscopy at SUNY Downstate Medical Center.

Exclusion Criteria

- < 18 years old
- > 75 years old
- Cognitively Impaired patients (Cognitively impaired patients are excluded from the study because our primary outcome involves a very strict discharge criteria that requires the patient to respond to and perform tasks on our pre-existing discharge scale checklist. These may be impossible to assess or will be difficult to standardize for patients whom are Cognitively Impaired.)
- Pregnancy
- Patients who use a wheelchair or ambulates with crutches (Patients using a wheelchair are excluded from the study because our primary outcome involves a very strict discharge criteria that requires the patient to respond to and perform tasks on our pre-existing discharge scale

checklist. These may be impossible to assess or will be difficult to standardize for patients whom who use a wheel-chair).

- Limited exercise tolerance (as this could represent active coronary disease)
- Total body weight greater than 150 kg (due to maximal dose of drug available in randomized syringes containing study drug)
- Propofol, soy or glycerol allergy
- Significant renal impairment
- Significant hepatic impairment
- Inability to read or write in English

iii. Method for Screening For Eligibility:

- Screening for Cognitively Impaired patients
  - pre-existing clinical diagnosis of cognitive impairment in medical history
- Screening for pregnancy
  - Based on urine or serum HCG pregnancy test done as part of routine preoperative evaluation prior to administration of anesthesia.
- Screening for renal impairment
  - Based on glomerular filtration rate <60 using routine preoperative basic metabolic panel.
- Screening for other issues
  - As documented in health records or reported by the patient

iv. Inclusion of Vulnerable Populations: Minors will not be included. Pregnant women will not be included. Cognitively Impaired individuals will not be included. To mitigate undue influence of patients recruited by their provider, a member of the research team who is not directly involved in the anesthetic management of the patient will be responsible for recruiting and consenting the patients for this research study. Minorities and women will be included, but are not specifically being targeted for inclusion. Since a significant percentage of our patient population are minorities, it is important to include this group in our research study. Minorities will receive the same recruitment and randomization process as non-minorities. We will emphasize their right to withdraw from the study at any point and encourage them to ask questions about any issues of concern.

v. Recruitment Procedures: Study staff will recruit participants through direct subject contact. This would occur after the patient has been evaluated and consented for anesthesia by a different anesthesia clinical team member that is not involved in the study. Recruitment will be done in the preoperative area separate by a study staff who is not directly involved in the clinical management of the patient.

vi. Discontinuation of Study Subject/Withdrawal: The study may be discontinued at any time. The participant can opt out at any time. The PI can withdraw the participant for reasons such as: participant meets one or more of the exclusion

criteria listed above or it is determined that participation in the study will be harmful to the participant.

C. Procedures and Data collection

Randomization procedure:

Patients will be randomized, 50 patients in each group by using an electronically generated randomization table to determine the patient's group assignment (random assignment similar to a flip of a coin). One group will receive intravenous Dexmedetomidine 0.3 ug/kg followed by propofol, and the other group will receive propofol-only plus placebo. The level of sedation in each subject will be monitored by use of a Bispectral Index (BIS) monitor. The anesthesiologist will not be allowed to view the BIS monitor until after the first dose of propofol is administered. This is to ensure that the anesthesiologist is not provided with information that may allude to which arm the patient was randomized to. Additional doses of propofol will be given at the discretion of the anesthesiologist based on level of sedation to maintain a BIS level of approximately 60.

The anesthesiologist will be blinded to the study group of each subject and will receive a premixed syringe containing either dexmedetomidine or placebo but labelled as dexmedotimidine 4 mcg/ml. Randomization will be performed by a research pharmacist who will determine the patient's group assignment based on an electronically generated randomization table. This investigator will then give the respective pre-labeled syringe to the anesthesiologist and record the patient's assignment in a password protected electronic data collection sheet. It will not be necessary to un-blind the care providers if an adverse event occurs because the management of likely adverse events are independent of the treatment arm and are based on clinical signs and findings in the evaluation of the patient.

Data to be gathered from all participants will include: age, gender, body mass index (BMI); American Society of Anesthesiologists (ASA) classification; duration of procedure; procedure start and end times, time of the initial dose of sedatives given as well as the time of the last dose of medication administration. The total dose of propofol administered will also be recorded.

Recovery will be assessed using the Modified Post Anesthesia Discharge Scoring System (MPADSS). This criteria is chosen because it has been proven as an efficient system that guarantees safe discharge. [18, 19]. This should be reliable and valid for use in this study because the purpose is to determine the point where patients have sufficiently recovered from sedation to be safely discharged from the ambulatory post anesthesia care unit. Data will be recorded immediately at the end of the procedure and every 10 minutes until the patient meets discharge criteria. Discharge criteria will be defined as a score of 9 or greater in the MPADSS scale. In

addition, we will also record the immediate postoperative Aldrete score (Table 2) in the operating room. The Aldrete score can be used to follow the awakening process of patients after an anesthetic experience as well as to determine eligibility for discharge from the PACU to the hospital ward. This method is accepted by the Joint Commission of Accreditation of Health Care Organizations in the United States and by similar regulatory agencies internationally [20]. We plan to report and compare the immediate post-operative Aldrete score as average score in each study group upon immediate assessment postoperatively.

Vital signs will be recorded preoperatively, immediately at the end of the procedure and also at 10 minute intervals until the patient meets the discharge criteria as previously described. Postoperative requirement for medical interventions to correct vital signs, to treat pain or nausea will also be recorded. The individual recording the data will also be blinded to the group assignments to avoid bias.

4. STUDY SITE:
SUNY Downstate Medical Center, Brooklyn, NY

5. STATISTICAL CONSIDERATIONS

This study is characterized as a 2-arm, randomized non-inferiority trial.

A. Principal outcome of interest:
The evaluation of time to discharge will involve the assessment of patients every 10minutes. Since almost every patient is discharged within an hour, the measure is very granular; we propose therefore to dichotomize it as discharge within 30min, yes or no.

B. Sample size considerations:
We project from past experience that in the single-drug arm, probability of patient discharge within 30min will be 0.90. We project that the same probability will apply to the two-drug arm; but we assert that if this number were as low as 0.70, the extra inconvenience to all concerned would be minimal; in other words, this differential represents a threshold of clinical significance, and we aim to demonstrate with reasonable certainty that the actual differential is smaller. Assuming equal numbers of subjects in each study arm, the power of the Pearson chi-square test to detect a differential as small as this is 90% for N=37 per arm, given a 2-tailed test and significance level of 0.05. However, that test is not always accurate for low prevalences, so we aim instead for N=50 per arm, which should yield an expected frequency of 5 or more in each cell of the 2x2 table that constitutes the principal analysis. Outcomes will be evaluated with the fisher's exact test and the Mann-Whitney U test for non-parametric variables as detailed below.

We project that we can consent about 4 patients per week into the study, which suggests that the enrollment window will be about 6 months.

C. Data analysis plan:
Subjects' biometric, demographic and medical history characteristics as listed above will be recorded and summarized in a 2-way table, *i.e.*, broken down by study arm membership, showing quartiles and min-max values for scored quantities, numerators and denominators with %s for classified quantities.

There are 3 outcomes of interest:

1. discharge within 30min;
    a. Specifically looking at whether there is a statistically significant difference in the number of patients discharged within 30 minutes in both treatment groups.
2. mg propofol administered per kg bodyweight per minute of procedure;
3. change in mean arterial pressure from pre-procedure baseline to lowest value observed during procedure.
    a. Difference in hemodynamic variables in blood pressure will serve as evidence of whether patients in the experimental group tolerated the study drug combination better than patients in the control group.

Presentation of outcome summary data will be conducted as described above. Fisher's exact test will be used to evaluate the first outcome; a supplementary Mann-Whitney test of between-arm difference in distribution of actual discharge times will be conducted. Mann-Whitney tests will be used for the other two outcomes. Given that this is a randomized study with decent sample sizes, we do not propose to construct regression models that attempt to control for differences between study arms. And given the nature of the intervention under evaluation, "intent to treat" considerations are essentially irrelevant.

6. RISKS

There is an occasional risk of a bradycardia following administration of dexmedetomidine. This is usually self-limited and resolves within a few hours particularly given the very small dose of dexmedetomidine needed for this study. If the heart rate is significantly slow, a small dose of glycopyrolate can be administered with expected immediate effect. Risk of glycopyrolate include tachycardia and dry mouth, however we do not expect these side effects because very small doses of glycopyrolate are required to correct the bradycardia.

There is also an occasional risk of hypotension following administration of dexmedetomidine. If the blood pressure is significantly low, a small dose of ephedrine can be administered with expected immediate improvement in blood pressure. Risks of ephedrine include tachycardia but this is usually self-limited and does not require treatment particularly given the small dose of ephedrine required to correct the hypotension from dexmedetomidine.

Furthermore, the bradycardia and hypotension are usually self-limited, easily treated and will be readily detected with the use of standard ASA monitors required for routine colonoscopy and while in the recovery room.

There is also a potential for feelings of coercion or undue influence because of the recruitment of participants from the study team's own patient population. To mitigate this undue influence, recruitment and informed consent will be performed by a member of the research team that is not directly involved in the clinical care of the patient.

In addition, there is the potential for a breach of confidentiality given the collection of protected health information in this study. The medical record number will be the only information on the data sheet linking the protected health information to the patient. Additionally, information will be stored in a password protected document.

We do not expect any other additional risks to the subject beyond that which is expected for a routine outpatient colonoscopy procedure. The proposed study does not deviate from standard of care and patients in each study group will be receiving the same quality of anesthesia that they would otherwise receive whether or not they are enrolled in our study. Currently, anesthesiologists at SUNY Downstate Medical Center have the choice to use a combination of the drugs dexmedetomidine and propofol as a method of sedation or use the drug propofol alone. This investigation simply allows us to collect and analyze data on the current practices to improve the standard of care.

The investigators believe that the benefits of the knowledge gained from this study outweigh the risks of performing it. Results of this study could encourage more anesthesiologists to employ this technique of balanced anesthesia that minimizes the side-effects of each drug administered with a predictable expectation of how patients will recover from the treatment.

7. BENEFITS

Although no direct benefits will apply to the subjects being studied, the results of this investigation could encourage more anesthesiologists to employ this technique of balanced anesthesia that minimizes the side-effects of each drug administered with a predictable expectation of how patients will recover from the treatment.

8. INFORMED CONSENT

Informed consent will be obtained from each subject by a member of the research team in the pre-operative area after the anesthesiology consent and evaluation has been completed by a separate clinical team member that is not involved in the study. Patient's PHI will be protected in compliance with IRB and HIPA regulations.

9. CONFIDENTIALITY

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Patient data will be entered into a password protected electronic spreadsheet. Only the

investigators, who have been invited to participate in the study and who are registered with the IRB as well as have documented completion of all IRB, HIPAA, and CITI certifications will have access to the file and password. Electronic records will be stored for five years after study conclusion on the agreed upon investigator's laptop computer, after which time they will be deleted. These records will be encrypted and password protected.

10. ADVERSE EVENT REPORTING

If there is a breach in confidentiality, adverse event, or violation of IRB or HIPAA regulations, the IRB will be notified in a timely manner as required by SUNY DMC policy and appropriate actions taken thereafter.

11. FOLLOW-UP AND RECORD RETENTION

Electronic records will be stored for five years after study conclusion on the agreed upon investigator's laptop or desktop computer that is stored in the investigators office at the hospital. These records will be encrypted, password protected and available only to the investigators invited to participate in the study and who have fulfilled all requirements outlined by IRB and HIPAA policies. Five years after the study is closed with the IRB, all documents will be deleted.

12. CONFLICTS OF INTEREST

All investigators have no conflict of interests in regards to the proposed study.

Table 1

Modified Postanesthestic Discharge Scoring System (Score ≥ 9 for discharge)	
VITAL SIGNS	
• Within 20% of preop value	2
• 20 – 40% of preop value	1
• 40% of preop value	0
AMBULATION	
• Steady gait/no dizziness	2
• With assistance	1
• None/dizziness	0
NAUSEA/VOMITING	
• Minimal	2
• Moderate	1
• Severe	0
PAIN	
• Minimal	2
• Moderate	1
• Severe	0
SURGICAL BLEEDING	
• Minimal	2
• Moderate	1
• Severe	0

Table 2

Modified Aldrete Score System	
Activity: Able to move (voluntarily or on command)	
• Four extremities	2
• Two extremities	1
• No extremities	0
Respiration	
• Able to breathe deeply or cough freely	2
• Dyspnea, shallow, or limited breathing	1
• Apnea	0
Circulation	
• BP+/- 20 mm Hg of preop level	2
• BP +/- 20 – 50 mm Hg of preop level	1
• BP +/- 50 mm Hg of preop level	0
Consciousness	
• Fully awake	2
• Arousable on calling	1
• Unresponsive	0
Oxygen saturation	
• SpO2 >92%	2
• Needs supplement O2 to maintain SpO2>90%	1
• SpO2 <90% with oxygen	0

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