PROTOCOL TITLE: A randomized study of midazolam and fentanyl versus midazolam alone for sedation in gastrointestinal endoscopy

PRINCIPAL INVESTIGATOR:
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STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	N/A
IND / IDE / HDE #	
Indicate Special Population(s)	☐ Children ☐ Children who are wards of the state ☐ Adults Unable to Consent ☐ Cognitively Impaired Adults ☐ Neonates of Uncertain Viability ☐ Pregnant Women ☐ Prisoners (or other detained/paroled individuals) ☐ Students/Employees
Sample Size	772
Funding Source	Self funded
Indicate the type of consent to be obtained	☒ Written ☐ Verbal/Waiver of Documentation of Informed Consent ☐ Waiver of HIPAA Authorization ☐ Waiver/Alteration of Consent Process
Site	☐ Lead Site (For A Multiple Site Research Study) ☐ Data Coordinating Center (DCC)
Research Related Radiation Exposure	☐ Yes ☒ No
DSMB / DMC / IDMC	☐ Yes ☒ No

OBJECTIVES:
This is a noninferiority study designed to examine whether conscious sedation with midazolam alone results in efficacy and safety that is not inferior to the combination of midazolam and fentanyl. English-speaking patients ≥18 years old and ≤75 years old presenting for GI endoscopy planned with conscious sedation using midazolam and fentanyl, will be randomized 1:1 to single agent sedation with midazolam or combination sedation with midazolam and fentanyl. Participants will be blinded to the choice of sedation. Sedation quality and adverse events will be measured with a validated patient-centered measure of procedural sedation quality, the PROcedural Sedation Assessment Survey (PROSAS) [Leffler, et al. Gastrointest Endosc. 2015;81(1):194-203]. Endoscopic quality measures in the 2 study groups will be

collected by retrospective chart review, as an additional metric to ensure the quality of the procedure is not compromised by the choice of sedation.

BACKGROUND:
In the US, endoscopist administered conscious sedation for esophagogastroduodenoscopy (EGD or upper GI endoscopy) and colonoscopy is overwhelmingly performed with Fentanyl and Midazolam. However, there is scant data available to make rational decisions about medication choices for conscious sedation in EGD and colonoscopy. Single agent sedation with Fentanyl has been safely and effectively used [Lazaraki, et al. Surg Endosc. 2007;21(9):1631-6]. However, a significant minority of patients do not tolerate Fentanyl because of nausea and vomiting, decreased respiratory drive and hypoxemia, or hypotension. Rarer side effects of Fentanyl have also been reported, like precipitation of the serotonin syndrome in patients taking SSRIs [Kirschner, et al. Emerg Med. 2010;38(4):477-80]. Combination therapy with Fentanyl and Midazolam may have significantly more hemodynamic side effects than single agent Midazolam [Baris, et al. Can J Cardiol. 2001;17(3):277-81].

It is important to note that single agent midazolam sedation is consistent with the current standard of care and is not uncommonly used with good results when patients report prior adverse reactions to narcotics. However, there are no formal data on the safety and effectiveness of single agent Midazolam conscious sedation for gastrointestinal endoscopy. We propose to conduct a randomized, single blind, noninferiority study to compare the safety and effectiveness of single agent midazolam vs. standard fentanyl/midazolam conscious sedation in consecutive English-speaking patients ≥18 years old and ≤75 years old presenting for EGD and/or colonoscopy planned with conscious sedation using midazolam and fentanyl.

The elimination of fentanyl from conscious sedation without compromising the safety and efficacy of sedation, would represent a significant step forward in decreasing adverse events and increasing patient satisfaction with conscious sedation.

STUDY ENDPOINTS:
The primary endpoint is patient reported satisfaction with the adequacy of sedation as assessed by the previously validated PROSAS questionnaire [Leffler, et al. Gastrointest Endosc. 2015;81(1):194-203]. Secondary endpoints are patient, nurse, and physician reported adverse events as assessed by the PROSAS questionnaire. Additional secondary endpoints will include measures of endoscopic quality to evaluate for any differences in quality measures between sedation groups. These data will be gathered by retrospective chart review and will consist of: cecal intubation rate/time, colonoscopy withdrawal time, and adenoma detection rates.

STUDY INTERVENTION(S) / INVESTIGATIONAL AGENT(S):
Midazolam injection is indicated:
• intramuscularly or intravenously for preoperative sedation/anxiolysis/amnesia;
• intravenously as an agent for sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic or endoscopic procedures, such as bronchoscopy, gastroscopy, cystoscopy, coronary angiography, cardiac catheterization, oncology procedures, radiologic procedures, suture of lacerations and other procedures either alone or in combination with other CNS depressants;
• intravenously for induction of general anesthesia, before administration of other anesthetic agents. With the use of narcotic premedication, induction of anesthesia can be attained within a relatively narrow dose range and in a short period of time. Intravenous midazolam can also be used as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia);

• continuous intravenous infusion for sedation of intubated and mechanically ventilated patients as a component of anesthesia or during treatment in a critical care setting

Fentanyl Citrate Injection is an opioid agonist indicated for:
• analgesic action of short duration during the anesthetic periods, premedication, induction and maintenance, and in the immediate postoperative period (recovery room) as the need arises.
• use as an opioid analgesic supplement in general or regional anesthesia.
• administration with a neuroleptic as an anesthetic premedication, for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia.
• use as an anesthetic agent with oxygen in selected high risk patients, such as those undergoing open heart surgery or certain complicated neurological or orthopedic procedures

The proposed study involves 2 drugs that are marketed in the US. The proposed study is not intended to support a new indication for either drug, a change in the labeling of either drug, a change in the advertising of either drug, and is not intended to promote or commercialize either drug. We will use midazolam and fentanyl in ways that are consistent with the current standard of care, despite having never been formally studied in GI endoscopy. As such, the proposed study does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of either drug. Therefore, the proposed study meets all criteria set forth by the FDA for research that can be done without an IND.

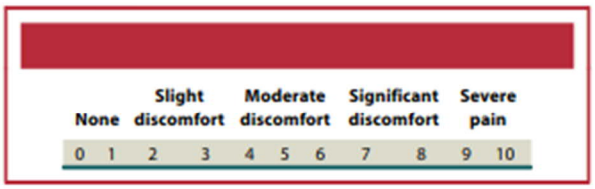
PROCEDURES INVOLVED:
English-speaking patients ≥18 years old and ≤75 years old presenting for EGD and/or colonoscopy planned with conscious sedation using midazolam and fentanyl, will be offered participation in the study. REDCap will be used to randomize consenting participants to sedation with midazolam and fentanyl or midazolam alone. Cluster randomization will be used to ensure that each physician participating in the study has an even distribution of participants randomized to each group. The EGD and/or colonoscopy will then be performed with no other modifications to the procedure(s). All endoscopic procedures will be performed with CO_2 insufflation, the standard method of insufflation at NMH. The decision to break protocol and administer fentanyl to a participant who has been randomized to single agent midazolam sedation, will be made at the sole discretion of the physician performing the procedure. After the procedure, the participant, physician, procedure nurse, and recovery nurse will complete their respective sections of the PROSAS questionnaire shown below.

Typical doses of midazolam range from 5-20 mg titrated in 2-3 mg increments every 2-3 minutes. Typical doses of fentanyl range from 50-200 mcg titrated in 25-50 mcg increments every 2-3 minutes. In the midazolam only group, midazolam will be given in the usual manner with 2-3 mg doses repeated every 2-3 minutes until the desired sedation level is reached. We would expect that the dose of midazolam used in the midazolam only group may be higher than the dose of midazolam used in the midazolam/fentanyl group.

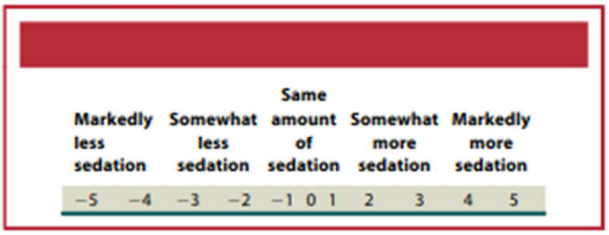
APPENDIX

Patient to complete the following survey by him- or herself with a family member or a nurse

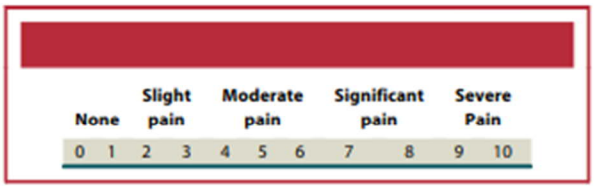
How much discomfort did you experience during the procedure?



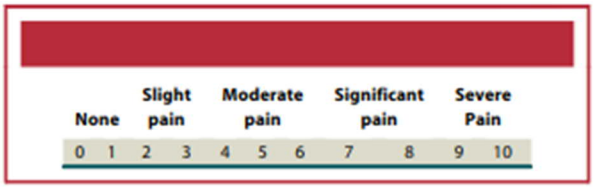
If having this procedure again in the future, how much sedation would you prefer to have?



On a scale of 0-10, how much pain were you feeling before the procedure?



On a scale of 0-10, how much pain are you feeling now?



Do you have any nausea now?

☐ Yes
☐ No

Other comments about your experience?

Procedure Nurse (Name):

Any episodes of O_2 desaturation <90% or leading to intervention?

☐ Yes
☐ No

Any problematic changes in heart rate or blood pressure during intervention? (eg, systolic blood pressure <90, >160; heart rate <50, >120)

☐ Yes
☐ No

Any hemodynamic or respiratory conditions that interrupted the procedure?

☐ Yes
☐ No

Physician (Name):

Please rate the patient's cooperation during the procedure:

☐ Procedure aborted due to lack of cooperation
☐ Procedure delayed/interrupted due to lack of cooperation
☐ Adequately cooperative

Was the exam interrupted in any way due to patient discomfort?

☐ Yes
☐ No

Recovery Nurse (Name):

Did the patient report any pain during recovery?

☐ Yes
☐ No

Did the patient report any nausea during recovery?

☐ Yes
☐ No

The Physician and procedure nurse portions of the PROSAS questionnaire will be completed using REDCap which will collect the data and store it in an encrypted, password protected database. The recovery nurse portion of the PROSAS questionnaire will be completed on a paper form, and the data on the form will be entered into REDCap on the same day, after which the form will be placed in a secure shred bin. The data collected at the time of the EGD and/or colonoscopy will be:

- participant name and date of birth
- date of the procedure(s)
- answers to the PROSAS questionnaire above

After the GI procedure(s) have been completed, the following additional data will be collected by retrospective chart review:

- procedure indications
- preparation quality
- cecal intubation rate/time
- colonoscopy withdrawal time
- endoscopic interventions
- adenoma detection rates
- adverse events
- midazolam and fentanyl doses

DATA AND SPECIMEN BANKING
No specimens will be collected, stored, or banked for this study.

SHARING RESULTS WITH PARTICIPANTS
The results of this study will not directly impact the future health or care of the study participants. Therefore, the results will not be shared directly with the participants or their physicians.

STUDY TIMELINES
Participants involvement in the study is limited to the day of their endoscopic procedure(s). Enrollment is expected to be completed within 2 years and data analysis is expected to be completed within 6 months following the completion of enrollment.

INCLUSION AND EXCLUSION CRITERIA
Inclusion criteria are:
- English-speaking patients
- Patients ≥18 years old and ≤75 years old
- Outpatients presenting for EGD and/or colonoscopy planned with conscious sedation using midazolam and fentanyl
- Patients presenting for endoscopic procedures with no GI fellow or trainee involvement in the procedure

Exclusion criteria are:
- Patients with an allergy or prior adverse event to either fentanyl or midazolam
- Patients who have previously not tolerated endoscopy with conscious sedation and require monitored anesthesia care (MAC)
- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners
- Vulnerable populations, including cognitively impaired adults and adults who are otherwise unable to consent

RECRUITMENT METHODS
Potential participants will be recruited on the day of their endoscopic procedure(s) or at a clinic visit prior to their endoscopic procedure(s) if such an appointment takes place. The purpose of the study and the methods will be explained, all questions will be answered, and the potential participant will verbally acknowledge their understanding and willingness to participate before being presented with a written consent form. Potential participants will have the opportunity to read the written consent form and ask any further questions before they decide whether to sign and participate in the study.

For potential participants seen in clinic, they will be sent home with a copy of the consent form after being given a verbal explanation of the study. On the day of their procedure(s), they can then ask any additional questions and decide whether they wish to participate in the research.

About 100 patients per day are generally seen in the GI endoscopy lab at Northwestern Memorial Hospital. Individual physicians involved in the study will identify appropriate potential participants on their schedule. There will be no advertising or recruitment materials.

COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES
There is no compensation provided to study participants.

WITHDRAWAL OF PARTICIPANTS
The only intervention being studied is the withholding of fentanyl for half of the study participants. Since sedation with midazolam alone is also consistent with the standard of care, there are no anticipated circumstances that would require participants to be withdrawn from the study without their consent. However, if any unanticipated circumstances arise, the decision to break protocol and administer fentanyl to a participant who has been randomized to single agent midazolam sedation, will be made at the sole discretion of the physician performing the procedure.

If a participant voluntarily withdraws from the study prior to completing their endoscopic procedure(s), their procedure(s) will proceed according to usual care. If a participant voluntarily withdraws from the study after completing their endoscopic procedure(s) but before completing the PROSAS questionnaire, no further data will be collected on that participant and they will be excluded from the analysis. If a participant voluntarily withdraws from the study after completing the PROSAS questionnaire but before retrospective review of the medical record, the PROSAS data will be included in the analysis but no retrospective data will be collected for that participant.

RISKS TO PARTICIPANTS
Risks include increased pain, increased procedure time, and decreased quality of the procedure if sedation is inadequate. However, to mitigate these risks, the physician performing the procedure can break protocol to administer fentanyl at his/her discretion.

Risks of midazolam include respiratory depression, rare incidences of respiratory or cardiac arrest, hiccups, over-sedation, hypotension, headache, drowsiness.

Risks of fentanyl include respiratory depression, rare incidences of respiratory or cardiac arrest, drowsiness, sedation, nausea, vomiting, headache, hypotension, rare incidence of serotonin syndrome in patients taking serotonergic medications. Symptoms of serotonin syndrome include agitation, hallucinations, tachycardia, fever, muscle twitching or stiffness, nausea, vomiting, diarrhea.

Standard risks of upper endoscopy include reactions to the medications used for sedation (nausea, vomiting, hypotension, or respiratory depression), bleeding from a biopsy or polypectomy site, and a risk of perforating the GI tract (in an estimated 1 of every 2,500 to 11,000 upper endoscopies). Standard risks of colonoscopy include reactions to the medications used for sedation (nausea, vomiting, hypotension, or respiratory depression), bleeding from a biopsy or polypectomy site, and a risk of perforating the GI tract (in an estimated 1 of every 1,000 to 3,000 colonoscopies). It is not known whether the use of midazolam alone for sedation, increases or decreases these risks.

POTENTIAL BENEFITS TO PARTICIPANTS
Study participants randomized to receive single agent sedation with midazolam will avoid any possibility of side effects from fentanyl. Common side effects of fentanyl include nausea (up to 45%) and vomiting (up to 33%), hypotension (≥1%), and respiratory depression (≤4%) [from Elsevier Clinical Pharmacology online database. https://www.clinicalkey.com/pharmacology/monograph/245?sec=monadve, search date 12/18/2020].

DATA MANAGEMENT AND CONFIDENTIALITY
Statistical analysis will be performed with the assistance of Kwang-Youn A Kim, Associate Professor in the Department of Preventive Medicine at Northwestern University, and a member of the Northwestern Biostatistics Collaboration Center. Power calculation based on noninferiority test with 80% power to detect an equivalence within 10% (with 95% confidence intervals), shows that 772 participants will be needed.

The Physician and procedure nurse portions of the PROSAS questionnaire will be completed using REDCap which will collect the data and store it in an encrypted, password protected database. The recovery nurse portion of the PROSAS questionnaire will be completed on a paper form, and the data on the form will be entered into REDCap on the same day, after which the form will be placed in a secure shred bin. The data collected at the time of the EGD and/or colonoscopy will be:

- participant name and date of birth
- date of the procedure(s)
- answers to the PROSAS questionnaire

After the procedure(s) have been completed, additional data will be collected by retrospective chart review:

- procedure indications
- preparation quality
- cecal intubation rate/time
- colonoscopy withdrawal time
- endoscopic interventions
- adenoma detection rates
- adverse events
- midazolam and fentanyl doses

The study data will be stored in an encrypted, password protected database, and will be accessible only by the principal investigator. Once the dataset is complete, the data will be deidentified by removing names and dates of birth before being shared for statistical analysis.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS
An interim safety analysis will be performed after 300 participants have been enrolled, in order to detect any statistically significant differences in adverse events in the 2 study groups. The adverse events of interest are:
- bleeding
- perforation
- death
- oxygen desaturation <90% requiring intervention
- systolic blood pressure less than 90 mmHg
- interruption or termination of the procedure due to patient discomfort or lack of cooperation

- instances of subjects randomized to midazolam alone who were subsequently deemed to require fentanyl
Any statistically significant safety signals will be reported to the IRB for consideration of the appropriateness of stopping the trial.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS
The study data will be stored in an encrypted, password protected database, and will be accessible only by the principal investigator. Once the dataset is complete, the data will be deidentified by removing names and dates of birth before being shared for statistical analysis.

The questions on the PROSAS questionnaire are not of a personal nature, but rather a gauge of the participant's satisfaction with the sedation and level of discomfort during their procedure. None of the additional data collected retrospectively after the completion of the endoscopic procedure(s) is of a personal nature, but rather consists of general markers to measure procedure quality. These retrospective data consist of: procedure indications, preparation quality, cecal intubation rate/time, colonoscopy withdrawal time, endoscopic interventions, adenoma detection rates, adverse events, midazolam and fentanyl doses. The research team will access the electronic medical record to collect the retrospective data.

COMPENSATION FOR RESEARCH-RELATED INJURY
There is no compensation for research-related injury. Both sedation regimens being used in this study are consistent with the standard of care.

ECONOMIC BURDEN TO PARTICIPANTS
There are no costs that participants will be responsible for because of participation in the research.

CONSENT PROCESS
When possible, the consent process will begin at a clinic visit if the potential participant has such a clinic visit. In the clinic setting, the potential participant will be sent home with a copy of the consent form after being given a verbal explanation of the study. On the day of their procedure(s), they can then ask any additional questions and decide whether they wish to participate in the research. For potential participants who did not require a clinic visit prior to their procedure(s), consent will be obtained in the GI endoscopy lab during the course of the pre-procedure check-in process, in tandem with the conversation in which the physician explains the details, risks, and benefits of the scheduled procedure(s). Potential participants will be provided time to ask questions and review the written consent form before making a decision regarding study participation. The consent process is anticipated to take 10-15 minutes. Only English-speaking patients will be considered for study inclusion. All physicians involved in the consent process will speak English. As part of the consent process, it will be reinforced to potential participants that their decision whether or not to participate in the study will not otherwise affect their care. In order to ensure that potential participants understand what they are consenting to, they will be asked to briefly verbally summarize their understanding of the study before signing the consent form.

NON-ENGLISH-SPEAKING PARTICIPANTS
Non-English-speaking patients will not be included in the study.

PROTECTED HEALTH INFORMATION (PHI AND HIPAA)

Since participant names and dates of birth will be collected, and since the electronic medical record will be used to retrospectively collect data after the completion of the endoscopic procedure(s), HIPAA Authorization will be obtained from all participants.

QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE

Per the power calculation referenced above, 772 participants will be needed. Each of the approximately 15 general gastroenterology physicians at Northwestern Memorial Hospital performs endoscopic procedures on approximately 800 patients per year. Using conservative estimates, if only 3 physicians participate in the research, and if only 20% of potential participants consent to participate in the study, 480 participants could be enrolled in 1 year. Therefore, a 2 year study enrollment period is feasible.

REDCap will be used to randomize participants and to collect the prospective data elements for the research, consisting of participant name, date of birth, date of endoscopic procedure(s), and answers to the PROSAS questionnaire. REDCap will automate and simplify this phase of data collection and immediately secure all protected health information (PHI). Only the principal investigator will have access to the data until it is deidentified prior to statistical analysis.

During the enrollment phase of the research, the research will not require a significant investment of time outside of the time required to initially train the nurses and physicians who will be participating in the research, and the time required to conduct the informed consent process with potential participants. Training of nurses will be performed by the principal investigator during one of the twice monthly meetings of the GI nurses. Training of physicians will be performed via either in-person or video meetings.

Once enrollment is complete, the principal investigator, with the assistance of an Internal Medicine resident to be selected at a later date, will collect the retrospective component of the data (procedure indications, preparation quality, cecal intubation rate/time, colonoscopy withdrawal time, endoscopic interventions, adenoma detection rates, adverse events, midazolam and fentanyl doses). This phase of the research would be expected to require about 100 hours of work, likely spread across 6 months. There are no special facilities required to complete this work aside from a computer with access to the Northwestern Medicine network.

Once the dataset is complete, statistical analysis will be performed in collaboration with Kwang-Youn A Kim, Associate Professor in the Department of Preventive Medicine at Northwestern University, and a member of the Northwestern Biostatistics Collaboration Center. Intention to treat and per protocol analyses will be performed.