Title: Use of Diphenhydramine as an Adjunctive Sedative for Colonoscopy in Patients Chronically on Opioids

NCT: NCT01967433

Date: 11/15/17

RESEARCH PROTOCOL OUTLINE

Title: Use of Diphenhydramine as an Adjunctive Sedative for Colonoscopy in Patients Chronically on Opioids

Principal Investigator: Salman Nusrat, MD., Dept. of Medicine, Sect. of Digestive Diseases, Assistant Professor of Medicine

Co-Investigator: Mohammad Madhoun, M.D., Dept. of Medicine, Sect. of Digestive Diseases, Assistant Professor of Medicine

William Tierney, M.D., Dept. of Medicine, Sect. of Digestive Diseases, Professor of Medicine.

Donna Zink, M.S., Clinic Project Coordinator, Dept. of Medicine, Sect. of Digestive Diseases

Abstract:

Specific Aims: To access the efficacy of adding diphenhydramine as adjunct to improve sedation and to reduce the amount of standard sedatives used during colonoscopy in patients on chronic opioids. Background: Large number of colonoscopies are performed each year. Use of Sedation increases tolerance and improves outcomes. With increasing use of opioids among general population patient often require large amount of fentanyl and midazolam for adequate sedation. Although effective, these medications have the potential to cause hypotension and respiratory depression especially in high doses. Diphenhydramine with its CNS depressant effect can theoretically provide synergistic effects. We hypothesis use of diphenhydramine will decrease the amount of fentanyl and midazolam (versed) used during colonoscopy and will decrease the duration the procedure and the number adverse effects. Methods: Patient on chronic opioids scheduled to undergo colonoscopy will be randomized to receive 50mg of diphenhydramine or placebo. Amount of sedatives, duration of procedure, adverse effect and quality of sedation (nurse, physician and patient) will be recorded. Two-sided *t*-test will be used to compare the means of

continuous variables in the two groups, and Chi-square test will be used to compare the categorical variables. A *P* value < 0.05 will be considered statistically significant.

A. **Specific Aims**

The primary aim of our study is to determine if addition of Diphenhydramine to Fentanyl and Midazolam will decrease the dose of Fentanyl and Midazolam (versed) used during colonoscopy in individuals on chronic opioids. Secondarily we will be looking at quality of sedation, duration of colonoscopy, time to reach cecum and adverse effects (hypoxia defined as O2 saturation less than 89% lasting for more than 30 seconds, Hypertension 20 mmhg increase in BP from baseline provided this is >140 systolic and 90 diastolic, Hypotension 20 mmhg decrease in BP from baseline provided this <100 systolic or 60 diastolic, Bradycardia a decrease in HR of > 20 provided this is less than 60, Tachycardia a increase in HR of >20 provided this greater than 100 and use of reversal agents i.e Naloxone or Flumazenil).

B. **Background and Significance**

According to an estimate more than 15 million colonoscopies are performed in United States. Patient tolerance is important for successful and safe completion of endoscopic procedure. Sedation not only reduces associated anxiety and pain but also results in increased compliance and willingness to undergo repeat procedures. [i] [ii] During the last two decade sedation frequency has increased both for diagnostic and therapeutic procedures.[iii] Failure to achieve adequate sedation has been a long-standing challenge in the field of gastrointestinal endoscopy. This results in patients discomfort, unsatisfactory examination, incomplete procedures, waste of time and financial loss. Although results have been conflicting factors predictive of difficult sedation

include excessive alcohol use (>40g/day), psychotropic medication, opioid use and anxiety (3-5).[iv] [v] Results of the 2010 National Survey on Drug Use and Health (NSDUH) showed that an estimated 22.6 million (8.9%) of Americans, aged 12 or older, were current or past month illicit drug users. The escalating use of therapeutic opioids shows hydrocodone topping all prescriptions with 136.7 million prescriptions in 2011, with all narcotic analgesics exceeding 238 million prescriptions. Benzodiazepines along with opioids are commonly used for endoscopic sedation.[vi] [vii]However, because of increasing use of both prescription and non-prescription opioids amongst general population and the associated cross tolerance with currently used sedatives, use of diphenhydramine hydrochloride as an adjunctive sedative has been explored and has shown promise. [viii] [ix]Diphenhydramine hydrochloride, an ethanolamine, belongs to the class of histamine 1 antagonist. It is commonly used as an anti-allergic and has CNS depressants effects.[x] However, no study has specifically looked at the use of diphenhydramine as an adjunctive sedative in high risk patients i.e. patient on opioids. We Hypothesis addition of diphenhydramine to midazolam and fentanyl would decrease the usage of benzodiazepines and opioids without compromising the success of the procedure. Thus our study will help identify a medication combination which is effective and save in this challenging population.

C. **Preliminary Studies**

Study by Raymond H et al showed addition of diphenhydramine resulted in 10.1% reduction in meperidine and 13.7% reduction in midazolam dose. Sedation scores significantly favor Diphenhydramine. However, only 7/130 patients in the diphenhydramine group were on chronic opioids.

D. **Research Design and Methods**

Study Design:

Prospective Randomized Double Blind Study

Study Center:

Data will be collected from the Oklahoma City Veteran Affair Medical Center (VAMC)

Study Population:

Inclusion Criteria

1. Patients aged 18-75 years undergoing screening, surveillance, diagnostic and therapeutic colonoscopy
2. Patient on chronic opioids defined as at least 5 mg of morphine or its equivalent at least 3 days per week for more than 3 months

Exclusion Criteria

1) Inability to execute informed consent
2) Allergy to Diphenhydramine, fentanyl or midazolam
3) Known or suspected pregnancy
4) Endoscopic procedure without sedation
5) Patient scheduled to have other endoscopic procedures on the same day
6) Prior alimentary tract surgery
7) Severe cardiopulmonary disease (ASA IV)
8) MOI use within 2 weeks of procedure

Recruitment and Consent:

Charts of patients scheduled for colonoscopy at VA Medical Center Oklahoma will be reviewed by provider involved in the care of these patients to identify patient who meet the inclusion criteria. Patients will be consented on the day of the procedure by one the team members in a private room.

Day of Procedure:

After consent is obtained the medical records of the patients will be reviewed and demographic information, co-morbidities, current medication will be extracted and recorded.

On the day of colonoscopy Alcohol use disorder inventory (AUDIT) will be used to screen for alcohol abuse. AUDIT was developed by World Health Organization and has been validated over a period of 2 decades. It consist of 10 questions, each question is scored 0-4 on the basis of subjects alcohol use. It takes about 2-4 minutes to complete.

Subjects will be checked in and prepared according to routine protocols of the VA medical center. Participants will be randomly assigned to receive either 50 mg of diphenhydramine or 10 ml of 0.9% sodium chloride. On the day of colonoscopy randomization will be performed by an independent investigator who is a pharmacist at VA medical center using the website http://www.randomization.com. She will also prepare and dispense medication. Each endoscopy team will consist of an attending gastroenterologist, two nurses either with or without a 3rd year gastroenterology fellow. Medications will be administered by one of the nurses under the direct supervision of the physician.

At the start of procedure baseline vitals will be recorded as per our unit's policy. Research medication will be administered within 3 minutes prior to administration of other medications. Neither the patient nor the medical staff including the endoscopist will be aware of the contents of

the vial. Conscious sedation will be achieved using a combination of intravenous midazolam (versed) and fentanyl as standard sedative. During the procedure vital signs including oxygen saturation will be monitored per standard operating procedures of the endoscopy lab. Procedure related complications, including hypotension, desaturation and cardiac arrhythmia will be managed according to our endoscopy unit policy and protocols.

Following the procedure, the nurse and the fellow or the attending will individually rate the quality if sedation on a Likert scale (optimal sedation score of 7). Qualitative assessment will also be made (Under-sedated, adequately sedated, or over-sedated).

Recovery time will be recorded.

Day Following the Colonoscopy

Twenty-four hour discharge a follow up call will be made and the patients will be asked to evaluate the level of pain (1, no pain; 10 severe pain), and amnesia (10, no memory of the procedure; 1 complete memory).

E. **Statistical Analysis**

Sample Size Calculation**:** Using a mean dose of 94 mcg ± 29.1 for fentanyl (Robertson, DJ et al.) and considering a 15 mcg decrease in dose as significant a sample size of 120 will give a power of 80% at an alpha of 0.05

SAS software (SAS Institute, Cary, NC, USA) will be used for performance of data analyses. Continuous variables will be reported as mean ± SD and categorical variables as percentages. Two-sided *t*-test will be used to compare the means of continuous variables in the two groups

(diphenhydramine versus placebo), and Chi-square test will be used to compare the categorical variables. A *P* value < 0.05 will be considered statistically significant.

F. **Gender/Minority/Pediatric Inclusion for Research**

This protocol includes all adult (over age 18) patients who will be having a colonoscopy as an outpatient. No distinctions based on race or gender is relevant.

G. **Human Subjects**

Criteria for inclusion and exclusion is described are listed above.

After obtaining consent medical records will be reviewed. Data will be gathered during and after colonoscopy as described above.

The patient will be consent on the day of procedure by a team member in a private setting. Information about the study will be provided over the phone in advance and a copy of consent will be mailed to the identified patients for review at least a week prior to the scheduled colonoscopy. A contact number will be provided to address any questions or concerns.

Risk and side effects related to Diphenhydramine as an adjunct to sedation: <1% (Limited to important or life-threatening). Side effects include dry mouth, pupillary dilation, urinary retention, constipation, hallucinations and delirium. Most of these side effects are temporary. QT prolongation leading to cardiac arrhythmia and torsades de pontes is extremely rare. [xi] Study by Raymond H, et al showed complication rate was not significantly different between patient receiving (midazolam + meperidine + Placebo) and (Midazolam + meperidine + diphenhydramine). In addition all complications were mild.

H. **Data and Safety Monitoring**

All data will be abstracted without personnel identifiers like name, social security number, date of birth, medical record number and assigned a code number. The list that matches names with the code number will be kept in a locked file in the research team's office (VA OKC Room # 6A-143). The research records will be kept in a password-protected computer file that only the study team will have access to. The personal computers used will be encrypted to ensure VA policies are met. All mobile devices will be encrypted and that the encryption will be FIPS 140-2 validated. Sensitive information will be transmitted to other research members using secure e-mail only. Research data stored on a mobile device will be backed up regularly and stored securely within VA's protected environment. Study personnel once they are not a part of the research team will lose access to any research study data.

Destruction of Research Records: All data used and maintained as part of a research protocol will be retained indefinitely until scheduled for destruction in accordance with Records Control Schedule (RCS) 10-1. At the completion of the study, the research records will be maintained in password protected computer file to which only the research team will have access to.

Any theft or loss of data or storage media, unauthorized access of sensitive data or storage devices or non-compliance with security controls will be reported to VA research office and IRB within 5 days of the event by the PI.

REFERENCES

[i] Abraham NS, Fallone CA, Mayrand S, Huang J, Wieczorek P, Barkun AN.Sedation versus no sedation in the performance of diagnostic upper gastrointestinal endoscopy: a Canadian randomized controlled cost-outcome study. Am J Gastroenterol. 2004 Sep;99(9):1692-9.

[ii] Zubarik R, Ganguly E, Benway D, Ferrentino N, Moses P, Vecchio J. Procedure-related abdominal discomfort in patients undergoing colorectal cancer screening: a comparison of colonoscopy and flexible sigmoidoscopy. Am J Gastroenterol. 2002 Dec;97(12):3056-61.

[iii] Bergeron P, Enns J, Delima L, Dupuis JY, Wynands JE. Effects of routine premedication for cardiac catheterization on sedation, level of anxiety and arterial oxygen saturation. Can J Cardiol. 1995 Mar;11(3):201-5.

[iv] Cook PJ, Flanagan R, James IM. Diazepam tolerance: effect of age, regular sedation, and alcohol. Br Med J (Clin Res Ed). 1984 Aug 11;289(6441):351-3.

[v] Peña LR, Mardini HE, Nickl NJ. Development of an instrument to assess and predict satisfaction and poor tolerance among patients undergoing endoscopic procedures. Dig Dis Sci. 2005 Oct;50(10):1860-71.

[vi] Keeffe EB, O'Connor KW. 1989 A/S/G/E survey of endoscopic sedation and monitoring practices. Gastrointest Endosc. 1990 May-Jun;36(3 Suppl):S13-8.

[vii] Hirsh I, Vaissler A, Chernin J, Segol O, Pizov R. Fentanyl or tramadol, with midazolam, for outpatient colonoscopy: analgesia, sedation, and safety. Dig Dis Sci. 2006 Nov;51(11):1946-51. Epub 2006 Sep 29.

[viii] Tu RH, Grewall P, Leung JW, Suryaprasad AG, Sheykhzadeh PI, Doan C, Garcia JC, Zhang N, Prindiville T, Mann S, Trudeau W. Diphenhydramine as an adjunct to sedation for colonoscopy: a double-blind randomized, placebo-controlled study. Gastrointest Endosc. 2006 Jan;63(1):87-94.

[ix] Roach CL, Husain N, Zabinsky J, Welch E, Garg R. Moderate sedation for echocardiography of preschoolers. Pediatr Cardiol. 2010 May;31(4):469-73. doi: 10.1007/s00246-009-9622-z. Epub 2010 Jan 3.

[x] Hofmeister EH, Egger CM. Evaluation of diphenhydramine as a sedative for dogs. J Am Vet Med Assoc. 2005 Apr 1;226(7):1092-4

[xi] Husain Z, Hussain K, Nair R, Steinman R. Diphenhydramine induced QT prolongation and torsade de pointes: An uncommon effect of a common drug. Cardiol J. 2010;17(5):509-11