A COMPARATIVE STUDY BETWEEN INHALATIONAL SEVOFLURANE SEDATION WITH INTRAVENOUS MIDAZOLAM SEDATION FOR UPPER ENDOSCOPY PROCEDURE

21st MARCH 2018

OBJECTIVES

1. To determine whether Sevoflurane is more superior sedative agent in terms of:
    a. Scoring of memory test
    b. Side effect occurrence/ depth of sedation
    c. Haemodynamic stability
    d. Recovery time/ discharge time
    e. Patient satisfaction and comfort
    f. Endoscopist (user) satisfaction scoring.
2. To determine the time recovery and discharge for Sevoflurane as compared to midazolam.

HYPOTHESIS

1. Sevoflurane provides deeper depth of sedation, better surgeon's satisfaction and better patient comfort towards the upper gastrointestinal endoscopy as compared to midazolam.
2. Time needed recovery and discharge is significantly shorter with Sevoflurane as compared to midazolam.

NULL HYPOTHESIS

1. Sevoflurane is not more superior in terms of providing better patient comfort, better surgeon's satisfaction or depth of sedation during upper gastrointestinal endoscopy as compared to midazolam.
2. There are not statistically significant difference in time needed for induction, recovery and discharge of the patient between Sevoflurane and midazolam.

METHODOLOGY

RESEARCH DESIGN

This study will be carried out using a randomized control trial study design.

[Research ID: 42799; NMRR ID: 2018321-6154]

SUBJECTS AND SAMPLING

Patients undergoing elective upper gastrointestinal endoscopy.

STUDY SITES

The study will be carried out over a period of 1 year commencing from 1st of June 2018 until 30th November 2019 in University Malaya Medical Center.

SAMPLE SIZE CALCULATION

Estimation of sample size is based on two mean sample calculation. According to the study done by *Montes t al (2000)* the mean of time to awakening under sevoflurane group was 5.79 ± 3.18. By using the two means formula, a minimum of 55 subjects will be needed in this study in order to compare mean difference of outcome between Sevoflurane and Midazolam at 80% of the power of the study and 0.05 as level of significance. The calculation was calculated using G power software 3.0.10. Hence the total number of patients to be collected will be rounded up to 60 patients.

INCLUSION AND EXCLUSION CRITERIA

INCLUSION CRITERIA:

1. ASA I to II
2. Patients who are not taking sedative agents prior to procedure.
3. Patients who are able to give consent for the procedure.

EXCLUSION CRITERIA

1. Patients with ischaemic heart disease, respiratory diseases and cerebrovascular disease.
2. Patients who are taking opioid or sedative medications 24 hours before procedure.
3. Patients with previous history of adverse effects to Sevoflurane or Midazolam.
4. Pregnant patients.
5. Patients with airway obstructions.
6. Patients with features of difficult airway such as limited neck extension, small mouth opening of less than 3 cm, mallampati score of more than 3.
7. Patients who are at risk of aspiration. Impaired gag reflex, presence of neurological disorders and impaired physical mobility.

PROCEDURAL METHOD

1. Obtain written informed consent from patients during recruitment of patients.
2. All patients are fasted at least 6 hours prior to procedure with no opioid or sedative agents given.
3. Three psychometric tests are performed on the patient before the sedation (or before entering the procedural room) and after the completion of procedure.
4. The memory test includes immediate and delayed recall test. It involves showing patients a cardboard with 9 objects for 30 seconds and patients were asked to recall immediately and after 20 minutes later for delayed recall test. The number of correct recalls is noted. Another test that is similar to the digit symbol substitution test is the "posting box task" test. This test involves patient putting 6 shaped bricks through

appropriately shaped holes of a box as quickly as possible using one hand and the best time for two attempts will be taken. Lastly a Stroop Test will be done to whereby printed words are colored differently from the meaning of the words. The words and colours have to be read out aloud. The reaction time and error rate will be recorded.

5. Patients were randomly allocated to receive either Sevoflurane or Midazolam
6. All patients were given time to familiarize with the nasal mask and nasal breathing with 4L/min oxygen alone.
7. All patients will be monitored with and electrocardiograph (ECG), non-invasive blood pressure, pulse oximetry and capnography.
8. 2 observers are needed. One observer will be unblinded to the test whereas the second observer will be blinded to the test.
9. The first observer who was not blinded to the identity of the drug will be present at the procedural site will perform frequent clinical assessment of the depth of sedation.
10. The second observer who was blinded to the identity of the drug will have to obtain baseline test scores and repeat these tests at the end of the procedure and subsequently post operatively at the recovery area.
11. All drug syringes were concealed under a cloth and nose clip will be worn to omit any scent of Sevoflurane to ensure blinding of the second observer.
12. Blood pressure, heart rate, oxygen saturation and frequency of ventilation are assessed prior to start of the procedure. Pulse oximetry and heart rate are continuously monitored where blood pressure frequency of ventilation are monitored every 1-2 minutes up to 10 minutes from the time of drug administration or until maintenance is reached and subsequently monitored every 5 minutes after.
13. Level of sedation is monitored using Observer's Assessment of Alertness/Sedation scale (OAAS scale). The unblinded observer will assess the level every minute and titrate the medication (Sevoflurane, Midazolam) to achieve a score of 3.

14. Maintenance level was defined as three consecutive OAAS score of 3 and subsequent assessment will be done every 5 minutes after.
15. The inhalational anaesthetic agent and oxygen will be delivered via an anaesthetic circuit with a vaporizer (Sevotec 3, Ohmeda, Streeton UK) with a nasal mask.
16. All the patients will receive IV Fentanyl 30mcg STAT dose prior to the initiation of sedation and also 10mls of Lignocaine 1% to gargle for about 2 minutes for analgesic and local anaesthesia purposes.
17. Patients who are allocated for Sevoflurane will be given initial oxygen flow of 8L/min and then Sevoflurane was introduced at a concentration of 0.2% and was increased stepwise by 02% for every 30s up to a maximum of 1.0 minimum alveolar concentration (MAC; 2.05% end tidal). Patient's deepest sedatin was recorded and adjusted to achieve optimal OAAS as mentioned above.
18. Inadequate or over sedation was treated by reducing or increasing the Sevoflurane concentration dial by 0.2 – 0.6% until the desired effect is reached. Vital signs are monitored as mentioned above.
19. Patients who are allocated for Midazolam will be given the similar nasal mask delivering 8L/min oxygen. However, Sevoflurane will not be introduced to these patients.
20. Midazolam is titrated slowly to achieve OAAS score of 3 but no more than 2.5mg is to be given within 2 minutes period to patients selected to be in Midazolam group.
21. Inadequate sedation is treated by giving slow titration of the medication based on the unblinded observer's judgement. Over sedation is treated by withholding the midazolam and continuing oxygen supplementation until the patient returned to the desired sedation level. No other sedative agents are allowed to be given to the patient or else patient will be excluded from this study.

22. Incidence of side effects such as excitation, headache, apnea, airway obstructions are recorded. Patients who experiences severe excitation disinhibition as defined in the investigator's opinion as agitation. Uncontrollable patient movements that causes unsafe procedural conditions and conversion to general anaesthesia is needed.
23. Post procedural recovery scoring are taken which includes:
    a. Time taken from the point that the procedure ended to the first OAAS score of 5
    b. Time taken from (a) to meeting discharge eligilibility.
24. Discharge eligibility includes:
    a. Awake, alert, and achieving baseline orientation
    b. Minimal nausea, vomiting
    c. Pain score of less than 3, well controlled
    d. Room oxygen saturation of 95% and above or if achieve baseline saturation.and
25. The blinded observer assess post procedural cognitive functions and return of the preoperative baseline cognitive functions is assessed by the similar assessment test as mentioned above.
26. The cognitive tests are done at baseline (prior to entering the procedural room), at 10 minutes post procedure and 30 minutes after if unable to achieve baseline scores at 10 minutes post procedure.
27. The endoscopist will evaluate the patient's cooperation and satisfaction towards the type of sedation using Numerical Rating Scale of 0 – 10.
28. Patient's opinion regarding the type of sedation and its side effects are also taken.
29. The data collected will be entered and analysed using SPSS.

STATISTICAL ANALYSIS PLAN

Data obtained from this investigation was then analyzed using a statistical package for social sciences, SPSS version 24.0 to make inference and draw robust conclusions. In brief, a descriptive statistics of all variables were initially done to evaluate the distribution, normality and homogeneity of the data. Frequency and percentage were reported for distribution of categorical variables and Mean ± Standard Deviation to report numerical variables. Independent T test and Mann Whitney test were used to analyse mean difference of numerical outcome between the groups depending on the normality of data distribution. Fisher's Exact test was used to determine the proportion difference of categorial outcome between the groups. Any P- value of less than 0.05 is considered statistically significant.

UNIVERSITY OF MALAYA MEDICAL CENTRE

PARTICIPANT INFORMATION SHEET

Study Title: A comparative study of inhalational Sevoflurane sedation with intravenous Midazolam sedation for upper endoscopy procedure.

Version No: 1.0

Version Date: 21/3/2018

We would like to invite you to take part in a research study. Before you decide whether to participate, you need to understand why the research is being done and what it would involve. Please take time to read the following information carefully; talk to others about the study if you wish.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Attention to the investigator: Please fill in simple layman language as you would speak to research subjects.

1. What is the purpose of this study?

This study is done to determine whether Sevoflurane is a more superior agent as compared to Midazolam in terms of patient comfort, depth of sedation, speed of recovery and time of discharge.

2. Why is this study important?

This study is important so that a medication that has faster recovery, safer therapeutic window and higher patient acceptance can be determined for future upper endoscopy procedure.

3. What type of study is this?

This is a randomized control trial design study where 60 patients will be randomly selected to receive either intravenous Midazolam sedation (Set 2) or inhalational Sevoflurane sedation (Set 1) during upper endoscopy procedure. Each patient will be assigned to a number (e.g. candidate number 1 is numbered as 1 and so on). Hence a total number of 60 will be selected for the research. These numbers are then keyed into a research randomizer application provided by https://www.randomizer.org/. 30 random non repeating numbers will then be placed into each set. Both of these medications are commonly used for sedation during our daily practices in the operation theatre and procedural room.

4. What is the procedure that is being tested? (If applicable)

Not applicable

5. Does the investigatory product contain cultural sensitive ingredients eg: bovine or porcine? (if applicable)

No

6. Why have I been invited to participate in this study?

You are invited to participate in this study as you are planned for upper endoscopy procedure and will be given sedation for comfort when undergoing the procedure.

7. Who should not participate in the study?

1. Patients who have previous adverse effects to either Midazolam or Sevoflurane.
2. Patients who are taking opioid or sedative medications 24 hours prior the procedure.
3. Pregnant patients.
4. Patients with heart problems, respiratory diseases and previous history of stroke.

8. Can I refuse to take part in the study?

Yes.

9. What will happen to me if I take part?

You will be attended by an Anaesthesiologist or Anaesthesiology Medical Officer throughout the procedure. Sedations will be titrated by them as well and your vital signs are closely monitored.

10. How long will I be involved in this study?

You will be followed up until you are deemed suitable for discharged home after the procedure.

11. What are the possible disadvantages and risks?

Most of the adverse effects are mild to moderate in nature and are transient.
For Sevoflurane inhalational agent, the possible risks are as stated below.

- Adverse effects during induction period (onset of anaesthesia to start of procedure)
  - Common (>1% and < 10%)
    - Cardiovascular system: Low heart rate 5%, hypotension 4%, increased in heart rate 2%
    - Respiratory system: Airway spasm 8%, breath holding attacks 8%, cough 5%
    - Nervous system: agitation 7%

- Adverse effects during awakening
  - Very common (>10%)
    - Digestive system: Nausea 25%, vomiting 18% (may be due to multifactorial – can be due to other medications and procedure)
    - Cardiovascular system: Hypotension 11%
    - Respiratory system: cough 11%

  - Common (>1% and < 10%)
    - Body as a whole: Fever 1%, shivering 6%, headache 1%
    - Cardiovascular system: Hypertension 2%, low heart rate 5%, increased heart rate 2%
    - Nervous system: somnolence 9%, agitation 9%, dizziness 4%m increased salivation 4%
    - Respiratory system: Breath holding attacks 2%

  - Uncommon (<1%)
    - Body as a whole: pain
    - Cardiovasculr system: heart block, cardiac arrest, arrthymias
    - Nervous system: anxiety, confusion, insomnia
    - Respiratory system: low oxygen saturation, wheezing, airway spasm
    - Metabolism and nutrition: deranged liver enzymes

For intravenous agent, Midazolam, the possible risks are as stated below:

- Incidence > 10%
  - Decrease in breathing volume and respiratory rate
  - Apnea
  - Variation in blood pressure and heart rate

- Incidence < 10%
  - Nausea and vomiting 2.6%
  - Headache 1.5%

- Drowsiness 1.2%
- Oversedation 1.6% (antidote Flumazenil will be given and titrated to effect)

12. What are the possible benefits to me?

Benefits of this procedure include safer and smoother induction, better comfort during the procedure for patients, earlier awakening and sooner discharge to home.

13. Who will have access to my medical records and research data?

Primary and co investigator

14. Will my records/data be kept confidential?

Yes.

15. What will happen to any samples I give? (If applicable)

Not applicable

16. What will happen if I don't want to carry on with the study?

You can choose to drop out from the study.

17. What if relevant new information about the procedure/ drug/ intervention becomes available? (If applicable)

The drugs that are used in this study have been available in the market for a substantial period of time. They are also commonly used in the daily practices as a form of sedative medication and also maintanence of anaesthesia. Any new informations will be disclosed to the patient and one may choose to continue or drop out from the study.

18. What happens when the research study stops? (If applicable)

Your treatment will be continued with the standard protocol for sedation as commonly practiced in our setting.

19. What will happen to the results of the research study?

The results will be sent for publication in national or international journal or presented at national or international conferences.

20. Will I receive compensation for participating in this study?

No.

21. Who funds this study?

UMMC research unit.

22. Who should I contact if I am unhappy with how the study is being conducted?

Medical Research Ethics Committee
University of Malaya Medical Centre
Telephone number: 03-7949 3209/2251