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Title

Tolerability of Sedation with Remimazolam versus Midazolam in Outpatients Undergoing Upper GI or Biliopancreatic Endoscopic Ultrasound in a Non-Anesthesiologist Setting: A Prospective Observational Study (REM-EUS Study)

Centre

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Background

Digestive endoscopy is typically performed under moderate (conscious) sedation, which does not require anesthesiologist involvement, or deep sedation, usually requiring anesthetic support. Deep sedation is often reserved for lengthy, complex, or therapeutic procedures. Effective sedation in digestive endoscopy is crucial for improving procedural quality, which in turn enhances diagnostic yield, therapeutic effectiveness, and patient tolerability.

For moderate sedation, benzodiazepines (e.g., midazolam) are frequently combined with opioids (e.g., fentanyl citrate or meperidine). While propofol is widely used for sedation in digestive endoscopy, its use is often restricted to anesthesiologist-supported procedures due to risks such as respiratory depression. Despite evidence supporting the safe administration of propofol by non-anesthesiologists, this practice remains controversial, particularly in Italy, where a minority of endoscopists administer propofol with nurse assistance, without an anesthesiologist.

Remimazolam (REM), a benzodiazepine derivative approved in the EU in August 2021 for GI endoscopy and bronchoscopy sedation, offers a rapid onset, short duration, and reversibility with flumazenil, positioning it as a promising alternative. Early trials suggest REM may achieve adequate sedation, shorter initiation times, and fewer adverse events than midazolam or propofol, though multiple doses may be necessary due to its short action. Thus, REM is currently used in many centres for sedation in digestive endoscopy. EUS, which provides high-resolution imaging of the gastrointestinal tract, is increasingly important in diagnosing and managing GI and pancreatic conditions. Diagnostic EUS, being brief and generally safe, may be well-suited to REM sedation, although data on REM's tolerability in this context remain limited and mainly focused on demonstrating comparable safety between REM and other sedatives.

Main aim

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To observe and compare patient-reported tolerability of remimazolam versus midazolam (both with fentanyl) in outpatient diagnostic EUS.

Secondary aims

- To evaluate operator's satisfaction
- To determine the incidence of adverse events (AEs) related to sedation, including pain at injection sites, hypotension, respiratory depression, tachycardia, bradycardia, arrhythmia, hypoxemia, and postoperative symptoms (e.g., nausea, vomiting, vertigo, gait abnormalities).
- To conduct subgroup analyses identifying patient subgroups more or less likely to benefit from REM sedation.
- To measure effective sedation rates.
- To compare costs associated with different sedation regimens.

Study design

This is a prospective, monocentric, observational study. Sedation will be administered based on routine clinical practice. REM and midazolam belong to the same pharmacological class and are currently considered interchangeable in clinical practice for moderate sedation in gastrointestinal endoscopy, with no evidence-based preference or indication favoring one over the other. Therefore, the choice of drug will be left to the attending physician's discretion and made according to usual, non-systematic clinical practice. The relatively recent introduction of REM in clinical practice did not allow for the availability of a sufficiently large dataset to conduct a retrospective study.

Inclusion and exclusion criteria

Inclusion Criteria:
- Age > 18 years
- Outpatients undergoing diagnostic EUS (upper GI or biliopancreatic)
- Informed consent obtained

Exclusion Criteria:
- Known allergy to study medications
- Recent upper respiratory infection or asthma attack
- History of sedative or opioid addiction
- Advanced oncologic disease with peritoneal metastases
- ASA score ≥ IV

Data Collection

- Patient Data: Age, sex, ASA score, and any significant pharmacological therapy.
- Procedure Data: Type of EUS (biliopancreatic vs. upper GI tract assessment), use of fine needle

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aspiration (FNA) or fine needle biopsy (FNB).
Data collected will be used to categorize patients for potential subgroup analyses relating to primary and secondary outcomes.

Posology

- REM: Initial dose of 2.5/5 mg REM + 25–100 µg fentanyl, with up to five supplemental doses of 1.25/2.5 mg remimazolam and/or 25–50 µg fentanyl (maximum total dose of 100 µg) every 1–3 minutes as needed.
- Midazolam: Initial dose of 2/2.5 mg midazolam + 25–100 µg fentanyl, with up to five supplemental doses of 1 mg midazolam and/or 25–50 µg fentanyl (maximum total dose of 100 µg) every 1-3 minutes as needed.

Procedural Tolerability Assessment

- Patient Perspective: Patients will complete the PRO-STEP Scale (doi: 10.1016/j.gie.2020.12.038.) both one hour and 24 hours after the procedure. This scale is currently used as part of routine clinical practice to assess procedural tolerance.
- Endoscopist Perspective: Endoscopists will complete a – A simple 1-10 scale, but with more defined categories like "Easy," "Moderate," and "Difficult" procedural conditions.

Procedure

Enrollment from February to June 2026. Procedures will be conducted by experienced endoscopists meeting international core EUS curriculum requirements. Sedation levels will be monitored by an assistant endoscopist or by a nurse using the Modified Observational Alertness/Sedation Assessment (MOAA/S) scale at regular intervals until three consecutive scores of 5 are reached, indicating readiness for EUS initiation.
Supplemental doses (up to five) will be allowed if MOAA/S scores >1 or patient movements occur. Failure of sedation will be defined as the need for more than five supplemental doses during the procedure.
During the procedure, vital signs (blood pressure, SpO2, heart rate and ECG) will be assessed and recorded every 5 minutes.
After the procedure, patients will be transferred to the recovery room. Recovery time (from the last sedative administration to awakening), VAS at rest, any additional analgesics, and sedation-related adverse reactions will be recorded. Patients will be discharged after 2 hours if their postanesthetic discharge score is ≥9.
This protocol had been endorsed by the anesthesiology department.

Definitions

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- Respiratory Depression: Respiratory rate <8 breaths per minute and/or oxygen saturation <90%.
- Hemodynamic Events: Decrease in MAP or HR >20% of baseline or systolic BP ≤80 mmHg.

Anesthesiologist assistance will be summoned for serious adverse events as necessary.

Outcomes

Primary Outcome:
Difference in tolerability/satisfaction scores among patients and endoscopists.

Secondary Outcomes:
- Time to loss of consciousness (MOAA/S score ≤1).
- Recovery time (defined by a Modified Aldrete score ≥ 9)
- Differences in adverse event rates between RG and SG.
- Number of supplemental doses needed after successful induction.
- Subgroup analysis results

Statistical analysis

Sample size calculation

In the absence of a formal validation of the minimal clinically important difference (MCID) for the PRO-STEP scale, we adopted a margin of 1.5 points, consistent with the literature on analogous subjective scales assessing comfort and sedation tolerability (e.g., VAS, NRS), where differences of 1 to 2 points are commonly considered clinically relevant [Paspatis et al., 2011; Riphaus et al., 2012]. With a power of 80% and an alpha of 5%, a minimum sample size of 63 patients per group is needed. Based on our current procedural volume (six elective outpatient EUS procedures per week), we anticipate completing enrolment within six months.

The sample size calculation refers to the primary outcome comparison and is not intended to ensure baseline equivalence between treatment groups, which will be empirically assessed and addressed through appropriate statistical adjustment.

Statistical Analysis:

Baseline characteristics of patients receiving the two sedative/anesthetic agents will be summarized and compared to assess potential imbalances between treatment groups due to the observational, non-randomized study design.

Continuous variables will be reported as mean ± standard deviation (SD) or median and interquartile range (IQR), as appropriate, and compared using Student's t-test or Mann–Whitney U test according to data distribution.

Categorical variables will be reported as absolute numbers and percentages and compared using the chi-square test or Fisher's exact test, when appropriate.

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In addition to hypothesis testing, standardized mean differences (SMDs) will be calculated for all baseline variables to quantify the magnitude of between-group imbalance, with an SMD > 0.1 considered indicative of a potentially meaningful imbalance. Should relevant baseline differences be observed, adjusted analyses will be performed to account for potential confounding factors. Specifically, multivariable regression models will be used to evaluate the association between sedative agent and study outcomes, adjusting for clinically relevant baseline covariates (e.g., age, ASA score, comorbidity burden, procedure type and duration). All tests will be two-sided, and statistical significance will be set at $p < 0.05$. Analyses will be performed using SPSS version 22.0.

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