INPLASY PROTOCOL

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Corresponding author:
Yen Ta Huang

uncleda.huang@gmail.com

Author Affiliation:
Hualien Tzu chi Hospital

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Efficacy and safety of remimazolam for procedure sedation: A meta-analysis of randomized controlled trials with trial sequential analysis

Jhuang, BJ[1]; Yeh, BH[2]; Huang, YT[3]; Lai, PC[4].

Review question / Objective: **Is remimazolam effective and safe for procedure sedation?**
Condition being studied: **Remimazolam is an ester-based benzodiazepine and could be rapidly hydrolyzed by tissue esterases to inactive metabolite. Its onset of action was 1 to 3 minutes and has considerable shorter half-life of the metabolite (0.75 hours) than that of midazolam (2.89 hours) providing adequate moderate sedation but faster recovery after intervention. Food and Drug Administration has approved remimazolam for the induction and maintenance of procedural sedation in adults undergoing procedures lasting.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 August 2020 and was last updated on 13 June 2021 (registration number INPLASY202080043).

INTRODUCTION

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METHODS

Search strategy: Two independent investigators (BJ Jhuang, BH Yeh) systematically searched PubMed, Web of Science, Embase, Airiti Library, Google Scholar and Cochrane Library from inception to June 30, 2020 without language limitation. Keywords using free texts and medical subject headings for search included "remimazolam," "midazolam," "safety," "efficacy," "endoscopy," "bronchoscopy," and "colonoscopy". In addition, we searched ClinicalTrials.gov and European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) for any unpublished or ongoing trials and additional data from published trials.

Participant or population: Patients for procedure sedation.

Intervention: Receiving remimazolam.

Comparator: Receiving midazolam.

Study designs to be included: RCTs.

Eligibility criteria: The exclusion criteria were studies that did not meet the above inclusion criteria; reviews, case reports, or case series; and studies with no relevant data for extraction.

Information sources: Two independent investigators (BJ Jhuang, BH Yeh) systematically searched PubMed, Web of Science, Embase, Airiti Library, Google Scholar and Cochrane Library from inception to June 30, 2020 without language limitation. Keywords using free texts and medical subject headings for search included "remimazolam," "midazolam," "safety," "efficacy," "endoscopy," "bronchoscopy," and "colonoscopy". In addition, we searched ClinicalTrials.gov and European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) for any unpublished or ongoing trials and additional data from published trials. The final list of included studies was decided on by discussion among all authors, with full agreement required before inclusion. We also reviewed reference lists from original manuscripts and published reviews, systematic reviews and meta-analyses to identify trials that were not listed in the original database. Our search strategy aimed to include every randomized controlled trial that investigated the effectiveness of remimazolam on procedure sedation.

Main outcome(s): The data extracted from the eligible studies included demographic data, publication year, sample size, the proportion of male, mean age and the American Society of Anesthesiologists physical (ASA) status were extracted. The primary outcome included procedure success, completion of procedure, and no administration of rescue medication. Secondary outcomes were safety outcomes, including time to recovery, cognition recovery of Hopkins Verbal Learning Test–Revised (HVLT-R) and adverse events.

Quality assessment / Risk of bias analysis: The risk of bias was assessed by two authors (PC Lai and YT Huang) independently using the Risk-of-bias tool 2.0 (RoB 2.0).

Strategy of data synthesis: We used Review Manager (RevMan) version 5.3 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014) for this meta-analysis. Dichotomous outcomes were presented as Risk ratio (RR), and continuous outcomes were presented as mean difference (MD), both with 95% confidence intervals (CIs). A random-effect model was used. Heterogeneities among studies were assessed by the I square (I2) statistics. An I2 higher than 50% represented substantially heterogeneous. Hypothesis and heterogeneity testing were considered as statistical significance if two-tailed $p < 0.05$ and $p < 0.10$, respectively.

Subgroup analysis: If necessary, subgroup analysis will divided by risk of bias and different type of procedure.

Sensibility analysis: Trial sequential analysis (TSA) is a methodology for approaching and quantifying the statistical reliability of data through repetitive and cumulative testing, especially for meta-analyses. TSA was conducted by TSA version 0.9.5.10 beta (Copenhagen Trial Unit, Center for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark). Type I error was set at 5% and type II error was set at 20% in the model.

Language: No limit.

Country(ies) involved: Taiwan.

Keywords: remimazolam, midazolam, sedation.

Contributions of each author:
Author 1 - Bo-Jyun Jhuang - This author helped conduct the literature search, perform the quality assessment of the studies and write the manuscript.
Author 2 - Bo-Han Yeh - This author helped conduct the literature search and write the manuscript.
Author 3 - Yen-Ta Haung - This author helped design the study, conduct the study, analyze the data.
Author 4 - Pei-Chun Lai - This author helped design the study, conduct the study, analyze the data.

Amendments: This study changed to use the latest statement of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA 2020). Besides, we updated the search date to May 31, 2021. Except for trial sequential analysis, we changed the statistical methods for this meta-analysis. Dichotomous and continuous outcomes were presented as odds ratio (OR) and weighted mean difference (WMD), respectively, with 95% confidence intervals (CIs). Statistical analysis was performed using the Microsoft Excel add-in MetaXL 5.3 utilizing the inverse variance heterogeneity model for dichotomous data. The random-effect model with weighted mean difference was used for analyzing the continuous data. Heterogeneities among studies were assessed using the I square (I2) statistics. An I2 higher than 50% represented substantial heterogeneity. For each outcome, we performed further subgroups analysis according to different procedure. To determine the subgroup of adverse events (AEs), we analyzed the AEs of cardiovascular events (hypotension, hypertension, and bradycardia), respiratory events (decreased oxygen saturation), and neurological events (headache). As for the zero event, we further performed sensitivity analysis by Bayesian approach with Markov Chain Monte Carlo method. We used Microsoft-Excel-based NetMetaXL V.1.6.1 to perform WinBUGS 1.4.3 under the setting of random-effect model with vague or informative prior. For publication bias, we presented the Doi plot with Luis Furuya-Kanamori (LFK) index for each endpoint. Values of LFK index outside the interval between -1 and +1 were defined as asymmetry of Doi plot, which may indicate publication bias.