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Original Research

Comparative advantages of remimazolam over midazolam in sedation for impacted tooth removal in patients with dental anxiety

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ABSTRACT:
Background: While midazolam is frequently employed to sedate patients experiencing dental anxiety, its limitations can diminish satisfaction for both patients and doctors. Consequently, this study aims to investigate the benefits of remimazolam as an alternative sedative. **Methods**: The study employed a prospective randomized controlled trial design, wherein patients experiencing dental anxiety and scheduled for impacted tooth removal were randomly assigned to either the remimazolam or midazolam groups. Sedation with remimazolam or midazolam occurred before administering the nerve blocker. The predictor variable was the type of sedative, while primary outcome variables encompassed onset time, awakening time, recovery time, and postoperative side effects. Secondary outcome variables included pre- and post-surgery Modified Dental Anxiety Scale scores, patient satisfaction and comfort levels, and doctor satisfaction levels. Additional variables encompassed patient demographics and operation time. **Results**: The study enrolled a total of 166 patients, with 84 assigned to the remimazolam group and 82 to the midazolam group. No significant differences were observed between the two groups concerning demographic features and operation time. Notably, patients in the remimazolam group experienced significantly shorter onset time, awakening time, and recovery time compared to their counterparts in the midazolam group (each $P < .001$). **Conclusion**: Remimazolam offers a quicker onset, swifter recovery, and a reduced likelihood of postoperative side effects in comparison to midazolam. This contributes to heightened satisfaction among both patients and doctors. Consequently, remimazolam presents several advantages over midazolam when it comes to sedating patients experiencing dental anxiety during the extraction of impacted teeth.
Keywords: sedation, remimazolam, midazolam

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INTRODUCTION

Dental anxiety, a complex emotional response characterized by feelings of nervousness and fear associated with dental diagnosis and treatment, poses significant challenges in healthcare. This apprehension often goes beyond a mere discomfort; it can give rise to heightened behavioral sensitivity and reduced tolerance among patients[1]. The consequences of dental anxiety are far-reaching, potentially resulting in the postponement, avoidance, or deliberate interference with essential dental nursing and treatment procedures. This, in turn, escalates the risks of treatment failure, leaving patients in a precarious state of oral health.Furthermore, the psychological impact of unpleasant oral experiences should not be underestimated. The trauma induced by such encounters can be profound, leading to adverse effects on mental well-being. Astonishingly, studies indicate that approximately 48.1% of individuals suffering from severe dental anxiety may develop post-traumatic stress disorder (PTSD) after undergoing dental operations[2]. This PTSD can manifest in various ways, including post-traumatic re-experiencing, avoidance of subsequent oral treatment, feelings of

numbness, and heightened alertness, creating a compounding effect on the patients' overall mental and emotional well-being.In the pursuit of mitigating dental anxiety, midazolam sedation has emerged as a commonly employed strategy. However, its effectiveness is hampered by a slow onset of action, and the presence of active metabolites introduces the potential for adverse postoperative reactions. These reactions, ranging from dizziness and nausea to vomiting and hangover-like feelings, not only compromise the immediate postoperative period but also contribute to a decrease in overall satisfaction among both patients and healthcare providers. Amidst these challenges, remimazolam emerges as a promising alternative[3]. This novel, ultra-short-acting benzodiazepine, recently approved for use in China, presents a spectrum of advantages. Its rapid onset of action, short half-life, minimal impact on respiration and circulation, and a notably low incidence of adverse reactions position it as a potential game-changer in the field of dental sedation. When compared with midazolam, remimazolam demonstrates a smaller volume of distribution, higher clearance, and a shorter half-life, indicating a potential for more precise and controlled sedation. However, despite these promising characteristics, the application of remimazolam in dental sedation remains an area of limited exploration[4]. Further research and clinical studies are essential to unravel the full extent of its benefits and potential drawbacks in the context of alleviating dental anxiety. The integration of remimazolam into dental practice could usher in a new era of improved patient experience, streamlined procedures, and enhanced outcomes, but these advancements must be grounded in a thorough understanding of its efficacy and safety profile within this specific domain of healthcare.This comprehensive study was designed to delve into the nuanced advantages of remimazolam as a sedative when juxtaposed with the conventional choice, midazolam. The fundamental hypothesis underlying this research was grounded in the anticipation that remimazolam would showcase a superior profile characterized by a swifter onset of action, expedited recovery, and a notable reduction in postoperative side effects[5]. The rationale behind these expectations was the potential for such attributes to culminate in heightened satisfaction levels among both patients and attending doctors, thereby influencing the landscape of sedative preferences in clinical practice.In pursuit of these objectives, the study employed a multifaceted approach. Firstly, a meticulous comparative analysis was undertaken, scrutinizing parameters such as onset time, awakening time, recovery duration, and the incidence of postoperative side effects for both remimazolam and midazolam[6]. This approach aimed to discern not only the temporal dynamics of the sedatives but also their respective safety profiles.Secondly, the research delved into the psychological realm by utilizing the Modified Dental Anxiety Scale (MDAS) to gauge and compare anxiety levels in patients both before and after surgery for each sedative. In addition to anxiety levels, the study scrutinized patient-reported satisfaction and comfort levels, providing valuable insights into the subjective experiences of individuals undergoing dental procedures. The inclusion of satisfaction scores reported by the attending doctor further enriched the evaluation, offering a holistic view of the sedation process.Lastly, the investigation extended its purview to physiological parameters, focusing on the impact of remimazolam and midazolam on hemodynamic and respiratory aspects[7]. By closely monitoring vital signs and respiratory functions, the study aimed to unravel the physiological implications associated with each sedative, contributing crucial data for a comprehensive understanding of their effects.In essence, this research aimed to unravel the intricate details of remimazolam and midazolam's performances in a dental sedation context. The anticipated outcomes not only hold the potential to inform clinical practices and guide sedative choices but also contribute to the ongoing evolution of patient-centered care by aligning sedation strategies with parameters such as onset speed, recovery efficiency, patient satisfaction, and physiological considerations.

MATERIALS AND METHODS

To meticulously address the research objectives, a prospective and randomized trial was meticulously designed, focusing on patients grappling with dental anxiety slated for the removal of mandibular impacted third molars under intravenous sedation[8]. The targeted study population comprised individuals aged 18 to 25, falling within the American Society of Anesthesiologists' Physical Status grades I-II, possessing a Modified Dental Anxiety Scale (MDAS) score equal to or exceeding 11. Moreover, inclusion criteria specified a history of tooth removal, a plan for the extraction of a second tooth, an absence of preoperative toothache, and a Pell-Gregory and Winter operation difficulty classification of grade IIIB. However, certain exclusion criteria were implemented to ensure the homogeneity of the study cohort. Patients with severe respiratory or circulatory diseases, ventilation or gas exchange disorders such as sleep apnea, a history of sedative or analgesic abuse, long-term opiate use, or renal and liver dysfunction were excluded from the trial. Additionally, individuals allergic to the study drugs or those with neurological or psychological disorders were not considered for participation.The rationale behind these exclusions was to eliminate confounding variables that could potentially influence the outcomes of interest. Factors such as severe respiratory or circulatory issues, sedative or analgesic abuse, and long-term opiate use were deemed capable of impacting critical parameters such as onset time, awakening time, recovery time, and the incidence of postoperative side effects[9]. By

implementing stringent exclusion criteria, the aim was to ensure that the study unfolded under consistent conditions, thus safeguarding the validity and reliability of the findings. This methodological rigor was crucial in minimizing potential confounders and enhancing the ability to draw meaningful conclusions regarding the satisfaction levels reported by both patients and doctors participating in the study. In this randomized trial, patients were allocated to either the remimazolam or midazolam sedation groups through a randomization process. Preoperatively, all participants were instructed to abstain from food for 9 hours and refrain from consuming beverages for 3 hours before the scheduled operation[10]. No preoperative treatment was administered to any of the patients. Upon being situated in the dental chair, baseline measurements, including electrocardiogram, noninvasive mean arterial pressure (MAP), heart rate (HR), and arterial oxygen saturation (SpO2), were recorded. Oxygen was administered via a nasal catheter at a rate of 2 L/minute, and an infusion channel was established in the dorsal hand vein. The initial intravenous dose for remimazolam was set at 5 mg, while for midazolam, it was 2 mg. Once the Ramsay sedation score reached 3 points, nerve block anesthesia was implemented by injecting 2% lidocaine into the inferior alveolar, lingual, and buccal nerves. Surgical procedures commenced upon the onset of the nerve block's anesthesia effect, with the Ramsay score maintained at 3 points throughout the operation. Additional doses of 2.5 mg for remimazolam and 1 mg for midazolam were administered as needed. Post-operation, patients rested in the chair for a minimum of 30 minutes and were discharged after achieving a postanesthetic discharge scoring system (PADSS) score of 9 or 10. In cases where full recovery was not achieved within 2 hours post-procedure, 0.5 mg of flumazenil was administered as an antagonist[11,12]. Postoperative care included oral antibiotics, re-examination, and stitch removal one week later. All surgeries were consistently performed by the same doctor in the clinical operating room of the Department of Oral and Maxillofacial Surgery, conducted before 9:00 AM to minimize disturbance to other patients.Various parameters were recorded for each patient, encompassing onset time (from drug injection to a Ramsay score of 3 points), awakening time (from surgery completion to the first eye opening), recovery time (from the first eye opening to PADSS scores of ≥ 9 points), and the incidence of postoperative side effects at 4, 8, 12, and 24 hours after surgery. Additional recordings included MDAS scores before and after surgery, comfort and satisfaction levels scores for patients, and the satisfaction levels scores reported by the doctor. The satisfaction and comfort levels were assessed using a 10-point scale, where a higher score indicated a greater level of satisfaction or comfort[13]. Furthermore, HR, MAP, and SpO2 readings were documented at specific time points during the procedure to monitor hemodynamic and respiratory parameters. These time points included entry into the operating room (t1), 5 minutes after entry (t2), nerve block administration (t3), the beginning of the operation (t4), 5 minutes after the start of the operation (t5), and the conclusion of the operation (t6).

RESULTS

In this study, a total of 166 patients were systematically assigned to either the remimazolam group (n = 84) or the midazolam group (n = 82) through a random allocation process. The baseline characteristics and operation times for both groups are outlined in Table 1. Notably, no substantial differences were observed in age, gender, height, body weight, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status, or operation duration between the two groups. A meticulous bivariate comparison of these covariates, stratified by sedation status, revealed no statistically significant differences. It is noteworthy that all procedures were executed successfully in every patient, underscoring the robustness of the study's design and implementation.

Table 1: Demographic Characteristics And Other Variables For The Study Groups

Variable	Remimazolam	Midazolam
Age (years)	22	23.1
Gender		
- Female	52 (61.9%)	46 (56.1%)
- Male	32 (38.1%)	36 (43.9%)
Height (cm)	161.6	163.9
Body weight (kg)	56.2	57.5
BMI (kg/m^2)	21.3	21.3
ASA physical status		
- I	35 (83.3%)	36 (87.8%)
- II	7 (16.7%)	5 (12.2%)
Operation time	31.5	32.2

Table 2: Comparison Of The Onset, Awakening, And Recovery Times

Variable	Remimazolam	Midazolam	P-Value
Onset time (minute)	0.57 (0.53-0.63)	9 (8-12)	0.001*
Awakening time (minute)	6 (5-7)	26 (23-30)	0.001*
Recovery time (minute)	5 (4-6)	20 (17-26.5)	0.001*

All patients underwent successful procedures. Table 2 illustrates the commencement, awakening, and recovery durations for both groups. Notably, these intervals were significantly shorter in the remimazolam group. Postoperative side effects were carefully monitored at various time intervals, specifically 4 hours, 8 hours, 12 hours, and 24 hours after surgery. In the cohort that received midazolam, participants reported a range of symptoms, including 12 cases of headache, 8 instances of dizziness, 6 occurrences of nausea, 4 reports of vomiting, and 8 cases of postoperative hangover feelings. In contrast, the remimazolam group experienced notably fewer side effects, with only 6 cases of dizziness[14,15].This discrepancy in the incidence of postoperative side effects between the two groups was statistically significant, as indicated by a p-value less than 0.001. The data underscore the potential advantages of remimazolam in mitigating postoperative discomfort and highlight its favorable profile in comparison to midazolam in this specific context.

DISCUSSION

Dental anxiety can have detrimental effects, such as lowering the pain threshold, intensifying the traumatic nature of wounds, and prolonging the duration of dental operations[16]. Extensive research indicates that employing sedation during dental procedures can significantly mitigate these adverse effects associated with anxiety. Sedation techniques have gained popularity in dental treatments, particularly for intricate procedures, and are often favored by dentists, especially for complex cases such as third molar surgery.The extraction of the mandibular third molar ranks among the most frequently performed surgeries in oral and maxillofacial surgery departments. Due to its complexity, this procedure can induce considerable trauma, making patients more susceptible to anxiety. In this study, we specifically focused on assessing the sedative efficacy of remimazolam in patients with a mandibular impacted third molar, particularly those classified with an operation difficulty of grade IIIB according to the Pell-Gregory and Winter scale[17-21].The objective of our investigation was to compare the advantages of remimazolam as a sedative against midazolam. Our hypothesis centered on remimazolam demonstrating a rapid onset of action, swift recovery, and a low incidence of postoperative side effects. We anticipated that these qualities would culminate in heightened satisfaction scores among both patients and medical professionals[22,23].The study aimed to comprehensively compare remimazolam and midazolam across several key parameters. Firstly, it sought to evaluate the onset time, awakening time, recovery time, and the incidence of postoperative side effects associated with each sedative. Secondly, the investigation focused on the pre- and post-surgery Modified Dental Anxiety Scale (MDAS) scores, patient satisfaction and comfort levels, and the satisfaction levels reported by the attending doctor[24,25]. Lastly, the study examined hemodynamic and respiratory parameters.The findings of the study supported the initial hypothesis, demonstrating that remimazolam sedation exhibited a rapid onset of action, swift recovery, and a lower incidence of postoperative side effects compared to midazolam sedation. Notably, both patients and doctors reported higher satisfaction scores with remimazolam sedation than with midazolam sedation. Previous research has highlighted that factors such as pain, bleeding, and past experiences with tooth removal contribute significantly to patient anxiety. Unpleasant oral treatments can lead to psychological trauma, potentially exacerbating existing dental anxiety. Sedation and hypnosis, as shown by Wolf et al, have the potential to reduce fear and anxiety, preventing avoidance behavior and promoting adherence to necessary dental treatments[26,27]. Additionally, sedation can alleviate pain, minimize bleeding during extractions, and contribute to better and faster wound healing, thereby alleviating pre-existing dental anxiety. Importantly, the present study revealed that MDAS scores after surgery were significantly lower in both the remimazolam and midazolam groups compared to scores before surgery. This positive shift in patient experience aligns with the findings of Hierons[28], indicating an improvement in the overall perception of tooth extraction, particularly when sedation was introduced for individuals who had not previously accepted this approach.Pain and anxiety are known to trigger the release of endogenous catecholamines, leading to heightened blood pressure and heart rate (HR). Yamashita et al's study demonstrated that addressing dental anxiety in patients can effectively suppress sympathetic activities, resulting in a significant reduction in both blood pressure and HR. Consistent with this finding, our present study observed that Mean Arterial Pressure (MAP) and HR values in both the remimazolam and midazolam groups exhibited significant reductions at various points during the dental procedure[27-29]. Specifically, these reductions were noted at the nerve block, the commencement of the operation, 5 minutes after the operation commenced, and at the conclusion of the operation, in comparison to the baseline values recorded upon entry into the operating room and 5 minutes thereafter. Furthermore, MAP and HR values in both groups

were also significantly lower 5 minutes after entering the operating room compared to the values recorded at the time of entry. This pattern suggests that both remimazolam and midazolam contribute to a notable reduction in sympathetic activity, thereby positively impacting blood pressure and HR throughout the course of the dental procedure[30].

The observed reduction in anxiety levels, as reflected in the decreased blood pressure and heart rate during the dental procedure, could be attributed to the psychological counseling and thorough explanations of the surgical procedures provided by the medical team after the patients entered the operating room. Alenezi and Aldokhayel's[31] research has emphasized that unfamiliar environments and a lack of knowledge about surgical procedures can significantly contribute to dental anxiety. Consequently, a proactive approach involving comprehensive communication before the operation, along with efforts to increase patients' familiarity with the environment and enhance their understanding of the surgical procedures, can play a pivotal role in alleviating patient anxiety. This underscores the importance of creating a supportive and informed atmosphere for patients undergoing dental procedures, positively impacting their psychological well-being and physiological responses.Midazolam, a benzodiazepine with sedative, anxiolytic, muscle relaxant, and anticonvulsant properties, is commonly employed in dental procedures, particularly for highly anxious or phobic patients. Notably, it is known for inducing pronounced amnesia, particularly concerning the memory of local anesthesia, when compared to other drugs. Studies by Zanette et al[32], Barends, and Salem et al have demonstrated its effectiveness and safety, especially when administered intranasally for geriatric patients and children with high dental fear. However, midazolam has some limitations. Its active metabolites contribute to prolonged sedation and unpredictable recovery, necessitating consideration in patients with impaired liver and kidney functions[33]. Additionally, midazolam is associated with a slow onset of action (2 to 5 minutes) and a notable incidence of postoperative adverse reactions, including dizziness, nausea, and vomiting. Research on oral midazolam preceding intravenous sedation has reported side effects such as dizziness in 69.6% of patients, nausea, and vomiting in 43.8% within the initial 2 hours after treatment, and tremors in 47.9% of patients[34]. Moreover, studies by Wang et al and Dave have highlighted potential postoperative behavioral changes, cognitive dysfunction, restlessness, and agitation associated with midazolam. In summary, while midazolam is frequently used in dental settings, its drawbacks, including prolonged sedation, potential adverse effects, and limited suitability for patients with liver and kidney dysfunction, suggest that it may not be an ideal sedative in all situations.

CONCLUSION

Remimazolam emerges as a superior choice in the realm of sedation for dental procedures, particularly during the extraction of impacted teeth, when compared to midazolam. The distinct advantages it offers, including a rapid onset of action, swift recovery period, and a reduced likelihood of postoperative side effects, collectively position it as a more favorable option for both patients and healthcare providers.The accelerated onset of action of remimazolam ensures a prompt initiation of the sedative effects, allowing for a smoother transition into the dental procedure. This is especially crucial in addressing the time-sensitive nature of dental treatments, contributing to a more efficient and streamlined operation. The swifter recovery associated with remimazolam further enhances its appeal, minimizing the overall duration of sedation and promoting a quicker return to baseline functionality for patients.One of the key distinctions lies in the reduced incidence of postoperative side effects with remimazolam when compared to midazolam. This not only enhances the overall patient experience by mitigating potential discomfort but also contributes to a more positive perception of the sedation process. The lower occurrence of side effects is particularly significant in the context of dental anxiety, where minimizing any adverse experiences is paramount for patient comfort and satisfaction.The collective impact of these advantages translates into heightened satisfaction levels reported by both patients and healthcare providers. Patients undergoing dental procedures, especially those involving the extraction of impacted teeth, often experience anxiety and apprehension. Remimazolam's efficacy in addressing these concerns, coupled with its favorable recovery profile, contributes to an overall positive experience for the patient.In conclusion, remimazolam's superior characteristics make it a preferred sedative option over midazolam in dental settings. Its rapid onset, quick recovery, and reduced likelihood of postoperative side effects collectively position it as a valuable tool in enhancing the sedation experience for patients undergoing procedures such as the extraction of impacted teeth, ultimately leading to increased satisfaction among both patients and healthcare providers.

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