

A COMPARISON OF DEXMEDETOMIDINE AND MIDAZOLAM FOR INTRAVENOUS SEDATION IN OUTPATIENT LOWER THIRD MOLAR SURGERY (RANDOMIZED CONTROLLED TRIAL, SPLIT-MOUTH TECHNIQUE)

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ABSTRACT

The objective of this research was to compare the anxiolytic efficacy of Dexmedetomidine and Midazolam in patients undergoing surgical removal of impacted mandibular third molars. This study was designed as a randomized, double-blind, controlled clinical trial using a split-mouth technique. Twelve participants who qualified for inclusion in the study were randomly allocated to two groups. In Group A, patients received intravenous sedation with Dexmedetomidine (1 µg/kg) before first procedure and Midazolam (0.1 mg/kg) before the second procedure. In Group B, start with Midazolam followed by Dexmedetomidine respectively. A washout period was at least 3 weeks. Anxiety levels were assessed using Corah's dental anxiety scale (CDAS) before sedation and postoperatively once the patient had fully recovered. A three-digit recall test was performed to assess memory. Post-operative pain at 1, 3, 6 hours and the time of first analgesic consumption were recorded. Both Dexmedetomidine and Midazolam were statistically significant reduction in anxiety levels, as evidenced by significant decreases in CDAS from preoperative to postoperative assessments ($p < 0.05$). However, no significant intergroup difference was observed in anxiolytic efficacy. Dexmedetomidine was associated with lower pain scores at all time points and prolonged time to first rescue analgesia compared to Midazolam. A statistically significant difference in amnestic effect was observed in Midazolam group. No nausea or vomiting was observed in either group. However, the small sample size limits the statistical power and generalizability of the findings

Keywords: Dexmedetomidine, Midazolam, Third molar surgery, Anxiety, Sedation

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INTRODUCTION

Dental anxiety is a psychological condition characterized by fear and apprehension related to dental treatment which can adversely influence pain perception and contribute to avoidance of care and delayed treatment, ultimately leading to poorer oral health outcomes (Van Wijk & Hoogstraten, 2009). In addition to its behavioral impact, dental anxiety has been shown to induce measurable physiological stress responses, for example, elevated preoperative cortisol levels have been reported in patients undergoing dental extractions, reflecting an acute stress response with potential perioperative implications (Gadicherla et al., 2018). Management strategies for dental anxiety can be broadly categorized into non-pharmacological and pharmacological approaches (Appukuttan, 2016). Non-pharmacological interventions, including cognitive behavioral techniques, distraction, and effective clinician-patient communication, aim to reduce fear and improve patient cooperation (Hoffmann et al., 2022). However, pharmacological interventions are often required in patients who are unable or unwilling to engage in behavioral strategies (Newton et al., 2012). Pharmacological management of anxiety disorders commonly includes antidepressants (SSRIs and SNRIs), anticonvulsants and benzodiazepines (Katzman et al., 2014). Among these, Midazolam is widely used for procedural sedation due to its rapid onset, short duration and reliable anxiolytic effects when appropriately titrated (Conway et al., 2021). Third molar extraction is one of the most commonly performed procedures in oral and maxillofacial surgery and provides a standardized, reproducible surgical stimulus, making it a reliable clinical model for evaluating conscious sedation techniques (Leitch et al., 2004). Conscious sedation is defined as a drug-induced depression of consciousness in which patients respond purposefully to verbal commands or light tactile stimulation, while maintaining adequate spontaneous ventilation and cardiovascular function (Practice Guidelines for Moderate Procedural Sedation and Analgesia 2018, 2018). Midazolam exerts its sedative and anxiolytic effects through potentiation of γ -aminobutyric acid type A (GABA-A) receptor-mediated inhibitory neurotransmission in the central nervous system (Bohlhalter et al., 1996). Clinically, Midazolam-based sedation has been shown to reduce patient discomfort and improve procedural conditions (Baudet & Aguirre-Jaime, 2019). However, Midazolam is associated with dose-dependent adverse effects, including respiratory depression, oxygen desaturation, hypotension, and delayed recovery (Jun et al., 2019). These limitations have driven the search for alternative sedative agents that provide effective anxiolysis with improved safety and minimal respiratory compromise. Dexmedetomidine is a highly selective α_2 -adrenoceptor agonist developed to overcome the limitations of earlier agents such as clonidine. Its pharmacological effects are mediated through activation of central α_2 -receptors, resulting in inhibition of adenylate cyclase and reduced intracellular cyclic AMP levels (Bhana et al., 2000). It is characterized by distinct sedative properties, including intrinsic analgesic and sympatholytic effects with minimal respiratory depression compared with conventional sedatives such as benzodiazepines (Carollo et al., 2008). Since its approval by the U.S. Food and Drug Administration in 1999 for short-term sedation in critically ill patients, its clinical use has expanded to procedural and perioperative sedation due to its favorable cardiorespiratory profile (Bae, 2017; Bradley, 2000). These properties have prompted increasing interest in their potential role as an alternative sedative agent in settings requiring both anxiolysis and procedural cooperation, including oral and maxillofacial surgery. Therefore, this study aimed to compare the anxiolytic efficacy of Dexmedetomidine and Midazolam in patients undergoing surgical removal of impacted mandibular third molars.

LITERATURE REVIEWS

Mandibular third molar impaction is a prevalent developmental condition, primarily resulting from inadequate space within the mandibular arch and a discrepancy between jaw growth and

tooth eruption, typically found between the ages of 17 and 21 years (Hupp et al., 2013). Impacted mandibular third molars are associated with a spectrum of pathological conditions, including pericoronitis, dental caries affecting the adjacent second molar, periodontal disease, and odontogenic cysts or tumors. (Ventä et al., 2004). In the study by (Fan et al., 2013), a loading infusion of Midazolam at 0.005 mg/kg/min and Dexmedetomidine at 0.1 µg/kg/min was administered in minor oral surgical procedures. This was followed by maintenance infusions, titrated to maintain bispectral index (BIS) values within $\pm 10\%$ of the predetermined target. The initial maintenance infusion rates were 0.01 mg/kg/h for Midazolam and 0.2 µg/kg/h for Dexmedetomidine, respectively. Notably, BIS values were lower in the Dexmedetomidine group, suggesting a deeper level of sedation; however, inter-individual variability remains a potential limitation. The study of (Üstün et al., 2006), in which patients receiving Midazolam ($0.4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) or Dexmedetomidine ($4 \text{ µg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) demonstrated comparable levels of conscious sedation (mean Ramsay Sedation Score of 2.9), the investigators did not evaluate patients' anxiety levels preoperatively and postoperatively and the study was restricted to third molar cases with a vertical impaction pattern. In the study by (Cheung et al., 2007), the median dose required to achieve conscious sedation for third molar surgery, as assessed by the Ramsay Sedation Scale, was 0.88 µg/kg for Dexmedetomidine and 0.07 mg/kg for Midazolam. However, the study did not employ a split-mouth design and did not assess patient anxiety levels or the degree of impaction difficulty, thereby leaving potential inter-individual variability as a source of confounding.

Our research strategy is intended to achieve an adequate level of conscious sedation while minimizing dose-dependent adverse effects, particularly hypotension and bradycardia, thereby enhancing the overall safety profile and patient satisfaction

Moreover, to the best of our knowledge, no previous studies have simultaneously assessed patient anxiety using validated subjective measures, such as Corah's Dental Anxiety Scale, in third molar surgery of comparable difficulty while directly comparing Dexmedetomidine and Midazolam within a crossover study design.

Research Hypothesis

Intravenous Dexmedetomidine is more effective than Intravenous Midazolam in reducing anxiety in patients undergoing third molar surgery

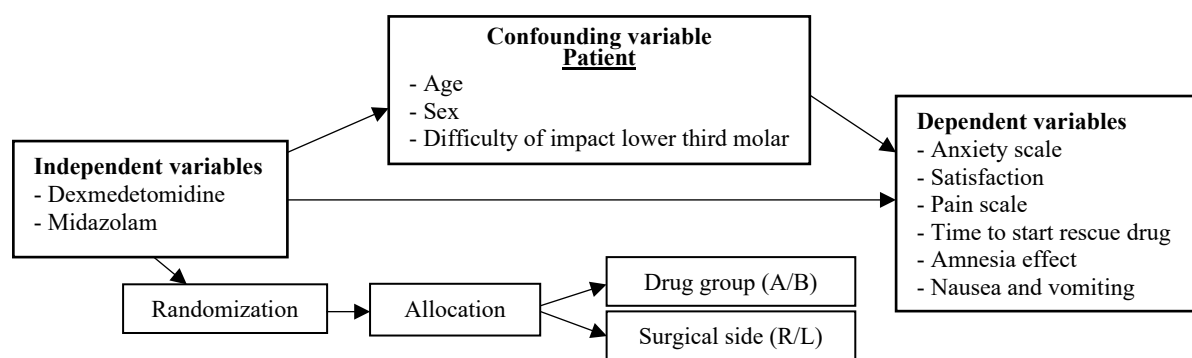


Figure 1 Conceptual Framework

RESEARCH METHODOLOGY

This study was designed as a randomized, double-blind, controlled trial using a split-mouth technique. Both the patients and the surgeons were blinded to the experimental conditions. The study population consisted of patients undergoing mandibular third molar surgery at the Dental Hospital, Faculty of Dentistry, Prince of Songkla University, between June 2025 and March 2026. Inclusion criteria were as follows: patients classified as ASA physical status I or II (either healthy or with well-controlled systemic conditions), aged 18-35 years, weight 40-80 kgs. Thai

patients willing to undergo bilateral impacted mandibular third molar removal, impacted mandibular third molars had a difficulty score of 5-10 (moderate to high), moderate to high dental anxiety (Corah's Dental Anxiety Scale 9-14 points) and absence of signs of infection or pericoronitis. Exclusion criteria: Patients with known hypersensitivity allergy to Dexmedetomidine, Midazolam, Benzodiazepine group, NSAIDs, including COX-2 specific inhibitors; recent use of Benzodiazepines or Antidepressants; clinical history or electrocardiographic evidence of heart block, ischemic heart disease, impaired liver, kidney disease; respiratory system disorders (asthma, sleep apnea syndrome); psychiatric disorders such as schizophrenia and depression; long-term analgesic (over 3 months); breastfeeding or pregnancy patient; drug or alcohol addicted and mental retard. A total of twelve participants were enrolled and randomly allocated into two groups. Participants were randomized into two groups using a computer-generated blocked randomization sequence created with the Sealed Envelope online software ("Create a blocked randomization list"). In Group A, patients received intravenous sedation with Dexmedetomidine 1 µg/kg before first procedure and Midazolam 0.1 mg/kg before second procedure. In Group B, sedation was initiated with Midazolam followed by Dexmedetomidine in the subsequent procedure. For blinding purposes, both Dexmedetomidine 1 µg/kg and Midazolam 0.1 mg/kg were diluted with 0.9% normal saline to a total volume of 20 mL, producing visually indistinguishable, clear solutions. The study drugs were administered as a controlled intravenous infusion via an infusion pump, initiated 10 minutes prior to each surgical procedure. A washout period was at least 3 weeks between the two surgical sessions. The night before the surgical procedure, participants were instructed to fast for a minimum of 8 hours and bring a companion to assist after the procedure. On the day of surgery, baseline dental anxiety was assessed using Corah's Dental Anxiety Scale (CDAS) - revised in Thai version prior to drug administration. The surgical side was randomized by coin toss. The monitoring equipment for vital signs was prepared and supplemental oxygen was administered. A single sedative agent was prepared and administered in accordance with the study protocol under the supervision of the anesthesiology team, who monitored and managed the patient throughout the entire procedure. Patients wore transparent protective goggles to facilitate monitoring of drug-induced reactions. Following administration of local anesthesia, participants were instructed to memorize a three-digit number as part of the amnesia assessment in which digits were presented sequentially, one digit at a time for 5 seconds following drug administration. All procedures were performed by a single operator, a postgraduate student in Oral and Maxillofacial Surgery at the Faculty of Dentistry, Prince of Songkla University, with both the operator and participants blinded to the administered sedative agent and were limited to a maximum duration of 90 minutes. Local anesthesia was achieved using 4% Articaine with epinephrine 1:100,000, with a maximum of 3 cartridges administered per procedure. Following the operation, patients were monitored in the recovery room and recovery status was evaluated using the Modified Post-Anesthetic Discharge Scoring System (PADSS). Patients achieving a score of ≥ 9 were deemed suitable for discharge. Subsequently, participants were asked to complete the following assessments: CDAS, patient satisfaction measured using a visual analog scale (VAS; 0 = unsatisfied, 10 = perfect), recall of the memorized number, the presence of nausea and vomiting, post-operative pain at 1, 3, 6 hours and the time to first analgesic consumption were also recorded, with ibuprofen 400 mg used as the rescue analgesic. Standard postoperative care instructions were then provided. At 7-10 days postoperatively, patients were scheduled for suture removal and follow-up evaluation. Data was analyzed by categorizing participants into the Dexmedetomidine and Midazolam groups. Descriptive statistics were presented as mean of standard deviation (SD) for normally distributed data, and median with interquartile range (IQR) for non-normally distributed data. For inferential statistics, normally distributed data were analyzed using the independent t-test, paired t-test, and repeated measures ANOVA, whereas non-normally

distributed data were analyzed using the Mann-Whitney U test and Wilcoxon signed-rank test. A p-value of less than 0.05 was considered statistically significant.

RESEARCH RESULTS

A total of 12 participants were enrolled in the study, participants were randomly allocated to Group A (Dexmedetomidine first) or Group B (Midazolam first) with six participants in each group. In this study, a split-mouth design was employed, whereby each participant served as their own control. Consequently, no statistically significant differences were observed in baseline characteristics and baseline anxiety level between the two groups ($p > 0.05$). The study population consisted of 3 male and 9 female participants. The mean age of the participants was 21.92 ± 3.03 years with a mean body weight of 54.54 ± 10.66 kg and a mean height of 162.33 ± 6.66 cm. The mean body mass index (BMI) was 20.53 ± 2.77 kg/m². The average baseline anxiety score was 11.67 ± 1.83 , as shown in table 1.

Table 1 Demographic Data of Study Participants (Mean $\pm$ SD)

Parameter	P-Value
Sex	
Male (%)	3 (25%)
Female (%)	9 (75%)
Age (Mean $\pm$ SD)	21.92 ± 3.03
Weight (Mean $\pm$ SD)	54.54 ± 10.66
Height (Mean $\pm$ SD)	162.33 ± 6.66
BMI (Mean $\pm$ SD)	20.53 ± 2.77
Including anxiety screen (Mean $\pm$ SD)	11.67 ± 1.83

No statistically significant differences were observed between the groups in terms of procedural duration, volume of local anesthesia administered or the level of impaction difficulty ($p > 0.05$), as shown in Table 2.

Table 2 Surgical duration, volume of local anesthetic administered and difficulty of tooth impaction between Dexmedetomidine and Midazolam groups

Parameter	Dexmedetomidine	Midazolam	P-value [†]
Operating time: minutes (Median $\pm$ IQR)	39.33 ± 7.71	38.08 ± 8.12	0.703
Volume of local anesthesia (ml) (Median $\pm$ IQR)	3.40 ± 0.20	3.50 ± 0.20	0.977
Pederson's difficulty index (Median $\pm$ IQR)	6.00 ± 1.00	5.00 ± 1.00	0.443

Anxiety levels were assessed before sedation and after participants had fully recovered, using CDAS with results expressed as Mean $\pm$ SD. Both pharmacological interventions demonstrated efficacy in reducing anxiety when comparing pre- and post-procedural measurements. Both Dexmedetomidine ($p < 0.001$) and Midazolam ($p = 0.012$) showed statistically significant differences, with Dexmedetomidine producing lower anxiety scores. Intergroup comparisons revealed no statistically significant differences between the two treatment groups. As shown in Table 3.

Table 3 Comparison of pre- and post-operative anxiety of Dexmedetomidine and Midazolam

	Dexmedetomidine	Midazolam	P-value [†]
Pre surgical anxiety	12.58 ± 3.03	12.83 ± 1.75	0.807
Post surgical anxiety	8.75 ± 3.72	10.00 ± 3.46	0.403
Mean difference	3.83 ± 2.44	2.83 ± 3.24	0.403
P-value [†]	<0.001*	0.012*	

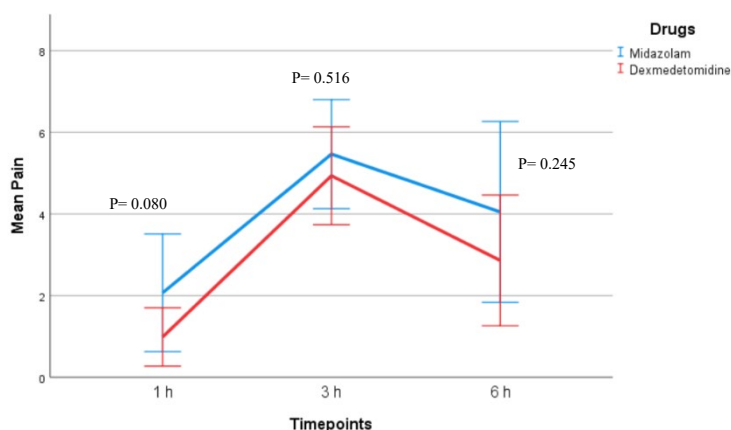
*p<0.05, Paired Samples Test

Pain levels following the procedure were assessed at 1, 3, and 6 hours using VAS scores. Dexmedetomidine reported lower pain scores at all time points when compared to the Midazolam group. However, no intergroup differences reached statistical significance ($p > 0.05$), as illustrated in Table 4 and Figure 1.

Table 4 Post-operative pain score at 1, 3, 6 hours

Time (hours)	Pain score (Mean ± SD)		P-value [†] (Intergroup)
	Dexmedetomidine	Midazolam	
1	0.99 ± 1.13	2.07 ± 2.27	0.080
3	4.94 ± 1.89	5.46 ± 2.10	0.516
6	2.86 ± 2.52	4.05 ± 3.49	0.245

Adjustment for multiple comparisons: Least Significant Difference

**Figure 2** Line graph of postoperative pain scores with intergroup p-values.

Within-group comparisons revealed a statistically significant pain score between hours 1 and 3 ($p = 0.001$), hours 1 and 6 ($p = 0.005$) and between hours 3 and 6 ($p = 0.033$) in Dexmedetomidine group. In Midazolam group, pain scores demonstrated a statistically significant difference only between hours 1 and 3 ($p = 0.001$), no significant differences were observed between hours 1 and 6 or hours 3 and 6 ($p = 0.082$ and 0.313 , respectively). As shown in Table 5.

Table 5 Intragroup P-value[†] comparison of each drug across different time points

Comparing time point (Hours)	Dexmedetomidine	Midazolam
1, 3	0.001*	0.001*
1, 6	0.005*	0.082
3, 6	0.033*	0.313

Adjustment for multiple comparisons: Least significant Difference

The time to start rescue analgesia, defined as the interval from the end of surgery to the onset of intolerable pain requiring pharmacological intervention, was longer in Dexmedetomidine group (213.83 ± 46.14 minutes) than in Midazolam group (190.42 ± 54.91 minutes). However, the difference was not statistically significant ($p = 0.270$), as shown in Table 6

Table 6 Time to start rescue drug (Mean $\pm$ SD)

Parameter	Dexmedetomidine	Midazolam	P-Value
Time to start rescue drug (Minutes)	213.83 ± 46.14	190.42 ± 54.91	0.270

* $p < 0.05$, Independent sample test

Amnestic effects were evaluated using a three-digit recall test. In Midazolam group, 75% ($n = 9$) recalled no digits, 16.7% ($n = 2$) recalled one digit and 8.3% ($n = 1$) recalled two digits. In contrast, the Dexmedetomidine group showed partial preservation of memory, with 16.7% ($n = 2$) recalling one digit and 83.3% ($n = 10$) recalling all three digits. This difference between groups was statistically significant ($p < 0.05$), indicating a less pronounced amnestic effect with Dexmedetomidine compared to Midazolam. Patient satisfaction scores were 8.05 ± 2.63 in the Dexmedetomidine group and 8.10 ± 1.38 in the Midazolam group with no statistically significant difference between the two groups. At the administered doses of Midazolam and Dexmedetomidine, no patients exhibited post-operative nausea or vomiting as adverse effects, as shown in Table 7.

Table 7 Recall number

	Digits recalled	Midazolam	Dexmedetomidine	p-value [†]
Amnesia	0	9 (75%)	0(0%)	<0.001*
	1	0(0%)	2 (16.7%)	
	2	1(8.3%)	0(0%)	
	3	2(16.7%)	10 (83.3%)	

* $p < 0.5$, Fisher-Freeman-Halton Exact Test

DISCUSSION & CONCLUSION

This study employed a split-mouth technique, which reduces intergroup confounding by allowing each participant to serve as their own control (Spineli & Pandis, 2023). Accordingly, both groups were comparable with respect to baseline characteristics, including sex, age, body weight, height, and baseline anxiety levels. Furthermore, all bilateral mandibular third molar surgeries were performed by a single operator to minimize inter-operator variability and potential bias related to surgical experience. However, as the split-mouth design necessitates two separate surgical interventions, the initial procedure may influence the patient's subsequent perception and experience, either positively or negatively, thereby potentially affecting anxiety levels during the second intervention. To address this potential source of bias, the study was further designed as a crossover trial, thereby mitigating the impact of carryover effects and reducing residual confounding (Antczak-Bouckoms et al., 1990).

Anxiety levels were reduced in both groups when comparing preoperative and postoperative measurements, consistent with findings by (Gadicherla et al., 2018) reported that cortisol levels increased during the preoperative phase, reflecting acute psychological stress experienced by patients and subsequently decreased following the intervention, supporting the reduction in anxiety questionnaire observed in the present study. Postoperative pain scores at 1, 3, and 6 hours were consistently lower in the Dexmedetomidine group compared with the Midazolam group, with a prolonged time to first rescue analgesic requirement. These findings support the intrinsic analgesic properties of Dexmedetomidine, mediated via central α_2 -adrenergic receptor activation, which inhibits presynaptic release of excitatory neurotransmitters such as substance

P and glutamate, thereby attenuating nociceptive transmission (Vuyk et al., 2015). Consistent with these findings, (Labafchi et al., 2023) and (Lopez et al., 2018) reported reduced postoperative pain and opioid requirements, highlighting its opioid-sparing effect. In addition, Dexmedetomidine has been shown to improve block quality, prolong analgesia, and reduce postoperative analgesic needs across various surgical settings (Devasya & Sarpangala, 2015; Ye et al., 2015). Furthermore, Its α_2 -adrenoceptor-mediated vasoconstrictive effect may further enhance local anesthetic efficacy, suggesting its potential as an adjunct alternative to epinephrine, particularly in patients with increased cardiovascular risk (Ouchi et al., 2014). The amnestic effect, objectively assessed using digit recall testing following sedation, serves as a reliable indicator of a drug's capacity to impair memory consolidation and short-term retention. In the present study, this effect was predominantly attributable to Midazolam, whereas Dexmedetomidine primarily contributed to sedation and anxiolysis (Wakita et al., 2012). Midazolam exerts its amnestic effects through positive allosteric modulation of the GABA-A receptor, enhancing chloride influx and inducing neuronal hyperpolarization. This process indirectly inhibits NMDA receptor activation by maintaining the Mg^{2+} block, thereby reducing calcium influx and suppressing long-term potentiation (LTP), a key mechanism underlying memory formation (Tokuda et al., 2010). Pharmacologically induced amnesia may provide clinical benefits by reducing patients' recall of distressing intraoperative experiences, particularly among those who prefer limited awareness. However, this effect is not universally desirable, as some patients may perceive postoperative memory impairment as disorienting or psychologically unsettling which potentially leading to dissatisfaction. In contrast, Dexmedetomidine produces a comparatively weaker amnestic effect, which may allow partial intraoperative recall and influence patient satisfaction in certain individuals. The bidirectional perception of drug-induced amnesia, being beneficial for some patients yet undesirable for others, may partly explain the absence of a statistically significant difference in overall patient satisfaction observed between groups. Notably, at the administered doses, neither Midazolam nor Dexmedetomidine was associated with postoperative nausea or vomiting. In conclusion, Dexmedetomidine and Midazolam both effectively reduced anxiety. However, Dexmedetomidine demonstrated superior analgesia with prolonged pain control and minimal amnestic effect, whereas Midazolam exhibited a stronger amnestic effect but less analgesic efficacy. These findings should be interpreted with caution due to the limited sample size.

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Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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