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Comparison of intranasal versus intravenous dexmedetomidine in postoperative pain control in traumatic mandibular fractures surgery: a randomized clinical trial

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Abstract: **Objective:** Preparing patients for emergency surgeries requires accurate consideration of their clinical condition and medical history to avoid potential hemodynamic instability and compromise the immune system. This study aims to compare the effects of dexmedetomidine and magnesium sulfate infusions in maintaining stable hemodynamics during emergency orthopedic surgery.Effective pain management in mandibular fractures is crucial due to the complications associated with opioids, such as respiratory depression and re-intubation. Non-opioid methods are therefore important. This study aims to compare the effectiveness, safety, and efficiency of intranasal (IN) versus intravenous (IV) dexmedetomidine (Dex) for reducing acute pain following mandibular surgery.

Methods: This study was a randomized, double-blind clinical trial. All patients underwent general anesthesia, laryngoscopy, and intubation in a standardized manner. For the IN administration group, Dex was prescribed at a dose of 0.2 µ/kg (in the form of drops) half an hour before the start of anesthesia. For the IV administration group, Dex was administered at a dose of 0.5 µ/kg intravenously over ten minutes, half an hour before anesthesia. During the first 24 hours after surgery, pain intensity and the total amount of opioid medication (measured in mg of pethidine) were recorded for each patient.

Results: There was no significant difference in pain intensity between the two groups in the post-anesthesia care unit (P=0.898), one hour (P=0.052) and 24 hours post-surgery (P=0.898). However, pain intensity was significantly lower in the IN Dex group at the second (P=0.044), fourth (P=0.041), sixth (P=0.048), and twelfth (P=0.025) hours. Total pethidine injected in the IN Dex group was significantly lower than in the IV Dex group (P=0.041).

Conclusion: This study underscores the efficacy of IN Dex as a viable alternative for postoperative pain management in traumatic mandibular fracture surgeries.

Keywords: Dexmedetomidine; Intranasal; Intravenous; Postoperative Pain; Traumatic Mandibular Fractures

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1. Introduction

Mandibular fractures, often resulting from blunt trauma, sports injuries, or motor vehicle accidents, are among the most common facial fractures requiring surgical intervention (1). These injuries necessitate precise realignment and fixation to restore function and aesthetics. Postoperative pain management in these patients is particularly challenging due to the extensive nature of the surgery and the rich innervation of the orofacial region (2). Therefore, optimizing analgesic strategies is paramount to improving postoperative outcomes (3,4).

Postoperative pain management is a critical component of patient care following traumatic mandibular fracture surgery (5). Effective pain management not only improves patient comfort but also promotes quicker recovery and decreases the risk of postoperative complications, including chronic pain, delayed healing, and prolonged hospital stays (6). Among the various analgesic options available, Dex has emerged as a promising agent due to its potent analgesic and sedative properties without significant respiratory depression (7).

Dex, a highly selective alpha-2 adrenergic agonist, has gained attention in recent years for its analgesic, anxiolytic, and sedative effects (8). Unlike traditional opioids, Dex provides effective pain relief with a lower risk of respiratory depression, making it an attractive option for postoperative pain management in various surgical settings. Its mechanism of action involves the activation of alpha-2 adrenoceptors in the central nervous system, leading to inhibition of norepinephrine release and subsequent analgesia and sedation (9,10).

IV administration of Dex is a well-established route in clinical practice, providing rapid onset of action and precise titration

of dosage (11).

However, the IV route requires vascular access, continuous monitoring and can be associated with hemodynamic fluctuations such as bradycardia and hypotension. These limitations have spurred interest in alternative routes of administration, such as IN delivery (12).

IN administration of medications offers several advantages, including ease of administration, rapid absorption through the highly vascular nasal mucosa, and avoidance of first-pass metabolism (13). For Dex, the IN route could potentially provide a non-invasive and effective means of delivering the drug, offering similar analgesic benefits to the IV route while minimizing the need for invasive procedures and reducing the risk of systemic side effects (14-16).

Several studies have investigated the pharmacokinetics and pharmacodynamics of IN Dex, demonstrating its efficacy in providing sedation and analgesia in various clinical settings (12,14-15). However, limited data are available specifically comparing the effectiveness of IN versus IV Dex in managing postoperative pain following traumatic mandibular fracture surgery (17).

Optimizing postoperative pain management is crucial for improving outcomes in patients undergoing surgery for traumatic mandibular fractures. Dex, known for its effective analgesic properties, presents a promising option for pain control. This study aims to compare the efficacy of IN versus IV Dex in managing postoperative pain in these patients. Evaluating the effectiveness and safety of IN versus IV administration of Dex could offer valuable insights and potentially broaden the options available for postoperative pain management in this challenging patient population. Ultimately, this study seeks to contribute to the expanding body of evidence on the use of Dex in surgical settings, enhancing patient care and recovery.

2. Methods

2.1. Study design

This study was conducted as a randomized clinical trial with a prospective approach, without a control group in a double-blind manner. It involved patients who were candidates for traumatic mandibular surgery at Imam Reza Hospital, Tabriz, Iran.

2.2. Sampling

To estimate the sample size, we used the results of a pilot study. In this pilot study, we included 5 participants in each group. Based on the results, the pain intensity was 6.44±1.93 in the IN group and 6.31±1.52 in the IV group, with an alpha level of 0.05. The power of the test was 80%, and accounting for a 30% dropout rate, we determined that 35 participants were needed per group. Consequently, we included 70 patients in this study using an available sampling method.

2.3. Eligibility criteria

The main inclusion criteria for the study were: age over 18 years, being a candidate for mandibular fracture surgery due to trauma, a Glasgow coma scale (GCS) score above 14, American society of anesthesiologists (ASA) class I or II, consent to participate, general anesthesia performed by a specialist, and surgery conducted by a single specialist. The exclusion criteria were heart rate less than 60 beats per minute, history of hypertension, use of antihypertensive drugs and beta-blockers, history of heart disease, low blood pressure, allergy to Dex, bleeding exceeding 1000 ml during surgery, receipt of blood products during surgery, use of calcium channel blockers, lactation, hemodynamic instability, and use of blood thinners.

2.4. Randomization

We used Excel software for randomization. Two groups of 35 participants each were defined. We recorded the information of each patient enrolled in the study in Excel, and using the randomization feature of the software, the patients were divided into two groups: IN and IV.

2.5. Blinding

The anesthesiologist administered the study medications therefore could not be blinded during the study. However, the maxillofacial surgeon who recorded the study outcomes, as well as the participants, were unaware of the patient group assignments and were thus blinded throughout the study. Therefore, this study was conducted as a double-blind trial.

2.6. Procedure

All patients underwent general anesthesia, laryngoscopy, and nasal intubation in a standardized manner. In the IN administration group, Dex was administered at a dose of 0.2 μ/kg (in the form of drops) half an hour before the start of anesthesia. For the IV administration group, Dex was administered at a dose of 0.5 μ/kg intravenously over ten minutes, half an hour before anesthesia.

In this study, for postoperative pain management, we exclusively used intravenous pethidine. The dosage was administered based on the visual analog scale (VAS pain scale): for pain levels below 3, patients received 0.25 mg/kg of pethidine; for pain levels between 3 and 6, 0.5 mg/kg was administered; and for pain levels greater than 6, 1 mg/kg of pethidine was given intravenously.

Pain intensity and the total amount of opioid medication (measured in milligrams of pethidine) were recorded for each patient. Pain intensity was assessed using the VAS in the post-anesthesia care unit (PACU) and at the following time points after discharge from recovery: one hour (T1), two hours (T2), four hours (T3), six hours (T4), twelve hours (T5), and twenty-four hours (T6) after surgery. Additionally, the amount of opioid medication required at each of these time points was recorded in milligrams of pethidine.

At the end of the first day, each participant's level of satisfac-

tion with their pain management was assessed. Satisfaction levels were graded as full satisfaction (score 3), partial satisfaction (score 2), or dissatisfied (score 1).

2.7. Data analysis

The collected data were entered into SPSS 27 statistical software. Frequencies and percentages were calculated for qualitative data, while means and standard deviations were computed for quantitative data. Chi-squared tests and t-tests were used to analyze the results for qualitative data. In all cases, a P-value of less than 0.05 was considered statistically significant.

2.8. Ethical considerations

This study was conducted after obtaining ethical approval from the ethics committee of Tabriz University of Medical Sciences (NO:IR.TBZMED.REC.1402.341) and registering in the Iranian clinical trial system (NO: IRCT20190325043107N40). Participation in this study was entirely voluntary, with no costs incurred by the patients. Any drug side effects that occurred were addressed and resolved as quickly as possible.

3. Results

The mean age of the study participants was 44.24±6.81 years. The mean body mass index (BMI) was 25.14±3.88. The majority of participants were men (55 participants, 78.57%). The trauma mechanism for all participants was an accident. The ASA classification for 52 participants was I. Comparing the demographic information between the two groups indicated no statistically significant differences.

In the PACU (P=0.898) and one hour after recovery (P=0.052), there was no statistically significant difference in pain intensity between the two groups. However, pain intensity was significantly lower in the IN Dex group at the second (P=0.044), fourth (P=0.041), sixth (P=0.048), and twelfth (P=0.025) hours. Additionally, 24 hours after surgery (P=0.898), there was no statistically significant difference in pain intensity between the groups (Figure 1).

The comparison of injectable pain killers, based on milligrams of pethidine, between the two study groups indicated that in the first hour after surgery (P=0.889), there was no significant statistical difference in the average amount of pethidine injected. However, at the second (P=0.044), fourth (P=0.041), sixth (P=0.040), twelfth (P=0.025), and twenty-fourth hours after surgery (P=0.048), the amount of pethidine injected in the IN Dex group was significantly lower than in the IV Dex group. Additionally, the average total (P=0.041) pethidine injected in the IN Dex group was significantly lower than in the IV Dex group (Table 2).

At the end of the study, the comparison of satisfaction levels between the two methods indicated that patients receiving IN Dex were significantly more satisfied after the first 24 hours post-surgery than those receiving IV Dex (P=0.033) (Figure 2).

4. Discussion

The management of postoperative pain following traumatic mandibular fracture surgery is critical for patient comfort and recovery (11). Dex, an alpha-2 adrenergic agonist, has emerged as a promising alternative due to its sedative and analgesic properties with minimal respiratory depression (5) This study aimed to investigate whether the routes of administrations specifically comparing IN versus IV Dex —affects postoperative pain intensity and opioid consumption.

The study initially found no statistically significant difference in pain intensity between the IN and IV Dex groups immediately post-surgery, both in the PACU and one hour after discharge from the recovery unit. This suggests that both routes of administration provided comparable immediate pain relief, aligning with previous studies that have demonstrated Dex 's efficacy in early postoperative pain management (17-19).

However, the study observed a notable divergence in pain intensity from the second hour post-surgery onwards. At the second, fourth, sixth, and twelfth hours, patients receiving IN Dex reported significantly lower pain intensity compared to those receiving IV Dex. This sustained reduction in pain intensity with IN administration highlights its potential advantage in providing prolonged analgesic effects during the critical hours following surgery. The absence of a significant difference at 24 hours post-surgery suggests that the initial benefits of IN Dex primarily influence acute postoperative pain control.

The study also evaluated opioid consumption between the two groups, measured in milligrams of pethidine administered. Initially, during the first hour post-surgery, no significant difference in opioid use was observed between IN and IV Dex groups. However, from the second hour onwards, patients in the IN Dex group required significantly lower amounts of pethidine compared to the IV group. This trend persisted throughout the postoperative period up to twenty-four hours, where the total amount of pethidine administered was significantly lower in the IN Dex group.

The reduced opioid consumption in the IN Dex group aligns with its superior pain control efficacy observed in the study (18). Dex's mechanism of action involves binding to alpha-2 adrenergic receptors in the central nervous system, resulting in decreased sympathetic outflow and pain transmission modulation (19). IN administration offers advantages such as rapid absorption through the highly vascular nasal mucosa, bypassing hepatic first-pass metabolism, and achieving faster onset of action compared to IV administration (20). These pharmacokinetic advantages likely contribute to the observed lower opioid requirements and enhanced pain relief in the IN Dex group (21).

The findings of this study are consistent with prior research investigating Dex in various surgical contexts. The studies by Wang et al (22). and Shams et al (23). have reported similar outcomes, demonstrating reduced opioid consumption and improved pain management with IN Dex compared to

Table 1

Variables	Groups (n=70)		P value
	IN groups (n=35)	IV groups (n=35)	
Age *	45.85±5.67	43.16±5.57	0.459
High (cm) *	165.56±12.88	171.36±12.96	0.782
Weigh (kg) *	86.27±2.63	44.24±6.81	0.369
BMI *	44.24±6.81	88.75±2.45	0.445
Sex** |Male	27 (77.14 %)	28 (80 %)	0.603
|Female	8 (22.85 %)	7 (20 %)	
ASA** | I	25 (71.42 %)	27 (77.14 %)	0.759
|II	10 (28.57%)	8 (22.85 %)	

IN: Intranasal; IV: Intravenous; BMI: Body mass index; ASA: American society of anesthesiologists; *: T test; **: Chi squared test

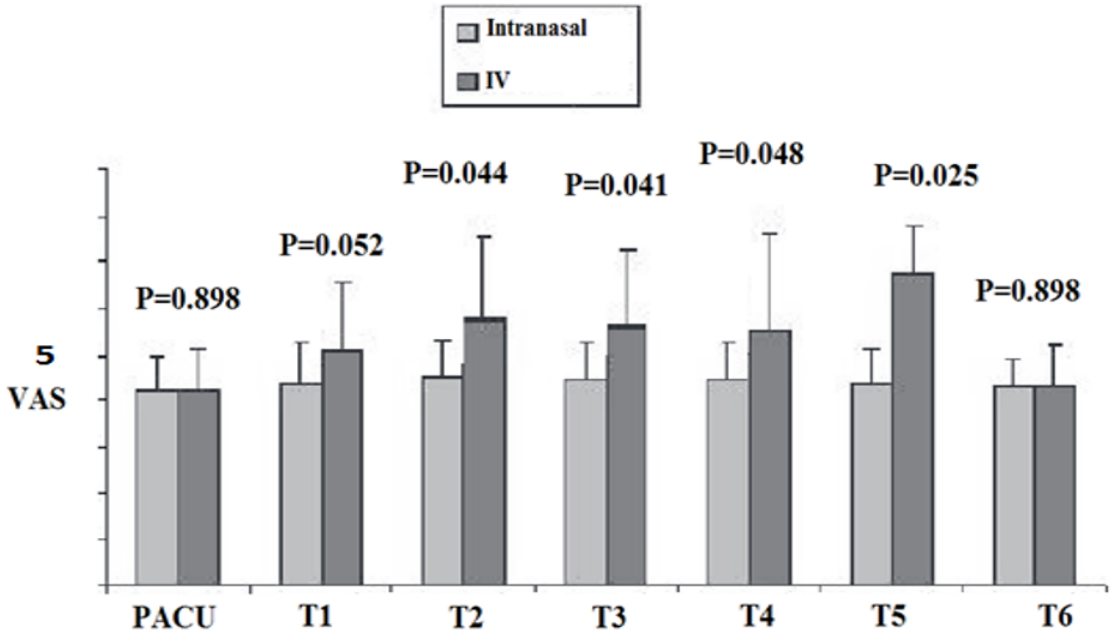

Figure 1 Comparison of pain intensity between two groups during the first 24 hours after surgery. T1: one hour after surgery, T2: two hours after surgery, T3: four hours after surgery, T4: Six hours after surgery, T5: 12 hours after surgery, T6: 24 hours after surgery

Table 2 Comparison of the mean amount of pethidine injected between the two study groups

Variables	Groups (n=70)		P value*
	IN groups (n=35)	IV groups (n=35)	
First hour after surgery	8.03±3.96	8.29±2.85	0.889
Second hour after surgery	12.45±3.52	18.74±2.45	0.044
Fourth hour after surgery	15.52±3.85	21.41±4.13	0.041
Sixth hour after surgery	20.63±3.57	31.85±4.89	0.040
Twelve hours after surgery	22.48±3.35	35.52±5.78	0.025
Twenty-four hours after surgery	19.94±3.59	28.96±4.45	0.048
Total pethidine during 24 hours	18.41±3.15	29.63±4.12	0.041

IN: Intranasal; IV: Intravenous; *: T test

IV administration in abdominal and orthopedic surgeries, respectively. Mechanistically, the enhanced bioavailability and rapid onset of IN Dex contribute to its efficacy in acute pain control, supporting its potential broader application in perioperative settings (24).

The implications of this study highlight the clinical relevance of route-specific Dex administration in optimizing postoperative pain management for traumatic mandibular fractures: IN Dex offers sustained pain relief with reduced opioid use, minimizing adverse effects and promoting early recovery. By mitigating opioid-related complications such as respiratory depression and gastrointestinal disturbances, IN Dex enhances perioperative safety. Lower opioid consumption and potentially shorter hospital stays associated with IN Dex

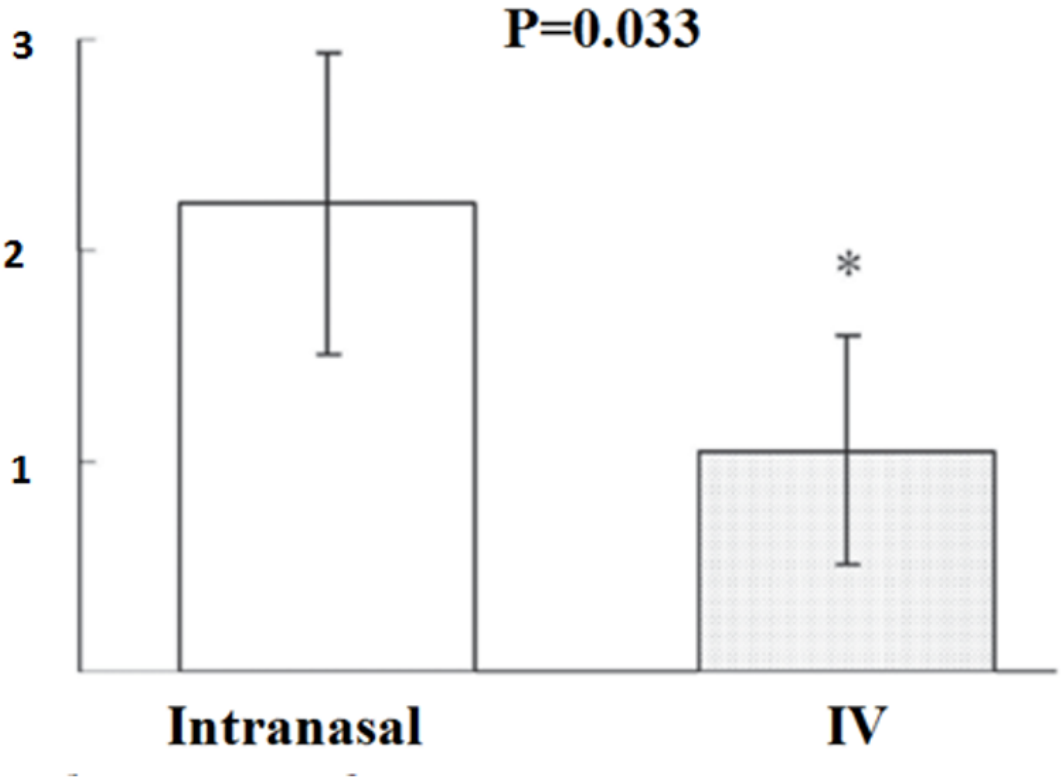

Figure 2 Comparison of satisfaction levels between the two study groups

may lead to cost savings and resource optimization.

5. Conclusion

In conclusion, this study underscores the efficacy of IN Dex as a viable alternative for postoperative pain control in traumatic mandibular fracture surgeries. By demonstrating superior pain management and reduced opioid requirements compared to IV administration, these findings support the integration of IN Dex into clinical practice to optimize perioperative care and enhance patient outcomes. Continued research efforts will further refine its role in modern surgical anesthesia and pain management strategies, ultimately improving patient care and surgical outcomes.

6. Declarations

6.1. Acknowledgement

None.

6.2. Authors' contribution

All authors contributed equally to the manuscript.

6.3. Conflict of interest

None.

6.4. Funding

None.

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