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Comparison of the effects of dexmedetomidine and remifentanil on potential extreme haemodynamic and respiratory response following mask ventilation and laryngoscopy in patients with mandibular fractures

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Abstract. – OBJECTIVE: The safety profile and efficacy were compared for remifentanil and dexmedetomidine with respect to haemodynamic and respiratory response during mask ventilation and laryngoscopy in patients with mandibular fractures.

PATIENTS AND METHODS: Seventy patients undergoing elective mandibular fracture surgery were randomly assigned to the remifentanil group (Group R, n = 35) or the dexmedetomidine group (Group D, n = 35). The primary outcomes were preoperative pain scores caused by jaw movement; haemodynamic response; intubation score; and side effects, such as the incidence of oxygen desaturation and muscle rigidity. Other side effects, such as tachycardia, bradycardia, hypertension and hypotension, were also compared.

RESULTS: Preoperative pain scores caused by jaw movement were significantly high for both groups, but there were no statistically significant differences between the groups. The incidence of oxygen desaturation and muscle rigidity was significantly lower in Group D than in Group R ($p = 0.025$). No significant differences existed between the groups in terms of intubation score, haemodynamics, and other side effects ($p > 0.05$).

DISCUSSION: Dexmedetomidine and remifentanil had equal effectiveness on the control of haemodynamic response due to mask ventilation and intubation in patients with mandibular fractures. However, at the doses used in this study, dexmedetomidine had a significant advantage over remifentanil in terms of respiratory stability.

Key Words:
Mandibular fractures, Remifentanil, Dexmedetomidine, Opioid complications, Trauma, Pain.

Introduction

The facial deformity that occurs in patients with mandibular fractures poses a risk for successful mask ventilation and orotracheal intubation. Different methods are used to ensure ventilation according to the degree of difficulty in accessing/injury to the airway and the surgical method[1].

Although the degree of difficulty in the airway and the surgical method are of primary concern, trauma in the same area as the mandibular fracture during airway management is a further issue. For patients with fractures of the mandible, the pain may be so severe as to cause trismus[2-5]. In many such cases, mask ventilation or a laryngoscope is used to ensure ventilation. The mandible is a facial bone that is exposed to indirect or direct force during mask ventilation or laryngoscopy. The force applied to provide ventilation for patients with mandibular fractures may lead to a second trauma to a mandible that has already been exposed to trauma. Trauma and pain are also stress factors for the body, leading to haemodynamic responses[6]. Laryngoscopy and tracheal intubation are often associated with tachycardia, hypertension, and arrhythmias due to stimulation of the tracheal structure. The haemodynamic response caused by the trauma may lead to an increase in the reflex haemodynamic response due to stimulation of the tracheal structures.

Opioid agents are frequently used for the prevention of surgical stress. However, most opiates likely have the potency to induce respiratory depression and muscle rigidity[7], both of which may develop during intubation and lead to difficulty

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in intubation of patients with fractures of the mandible. Dexmedetomidine is a highly selective adrenergic $\square_2$ adrenergic agonist; it has sedative and analgesic properties resulting from reduced endogenous norepinephrine release in the brain and spinal cord[8]. In addition, dexmedetomidine causes less respiratory depression than other sedatives or narcotics[9]. Therefore, an extreme cardiovascular response to tracheal intubation may be expected with no complications if dexmedetomidine is used during the induction of anaesthesia in patients with mandibular fractures but no complications.

In this study, we aimed to compare the effects of dexmedetomidine and remifentanil on the control of the haemodynamic and respiratory responses due to mask ventilation and intubation in patients with mandibular fractures.

Patients and Methods

With approval from the faculty Ethical Committee and our patients, 70 American Society of Anaesthesiologists (ASA) physical status I patients who underwent mandibular fracture surgery under general anaesthesia and were between the ages of 18 and 60 were included in the study. Conditions excluding patients from the study included ineligibility for nasotracheal intubation; cardiac, pulmonary, renal, or hepatic disease; pregnancy (at lactation stage); and contraindications to anaesthetics. The patients were randomly assigned to one of the two study groups: the remifentanil group (the R group; n=35) or the dexmedetomidine group (the D group; n=35). The anaesthetist was blinded to the patient's group assignment, and the study data were recorded by a blinded observer.

Five ml/kg/h of lactated ringer solution were administered intravenously to patients using a 20-gauge cannula. Patients were exposed to standard anaesthetic monitoring, including non-invasive blood pressure (NIBP), electrocardiography (ECG) and peripheral oxygen saturation (SpO_2). Preoperatively, the level of pain was evaluated using the visual analogue scale (VAS) with jaw movement. VAS scores for jaw pain were measured on a scale of 0-10, where 0 represented no pain and 10 represented the worst possible pain imaginable. After a five-minute stabilisation period, basal data for heart rate (HR), mean arterial pressure (MAP) and peripheral oxygen saturation (SpO_2) were recorded.

After evaluating their initial signs, a 1 μg/kg single dose of dexmedetomidine (Precedex®, Meditera, 200 μg/2 mL) was administered to the patients in Group D for 10 min. Patients in Group R received 1 μg/kg of remifentanil (Ultiva®, GlaxoSmithKline, Philadelphia, PA, USA; lyophilised powder, 2 mg) mixed with saline solution 1 minute before anaesthesia induction. After the administration of remifentanil and dexmedetomidine was complete, anaesthesia was induced with propofol 2 mg/kg IV. To facilitate tracheal intubation (TI), 0.6 mg/kg rocuronium was administered. All patients were ventilated using a mask after receiving rocuronium for 2 minutes. The duration from the start of mask ventilation was recorded by an assistant using a chronometer. The period between cessation of the propofol injection and commencement of intubation was recorded as the mask-ventilation time (MVt). Next, male and female patients were intubated nasotracheally as quickly as possible using a Macintosh laryngoscope No. 3 blade and Magill pens. The duration from the commencement of tracheal intubation was recorded by an assistant using a chronometer. Intubation procedures were carried out by the same anaesthetist (TÇ). After nasotracheal intubation, the lungs were ventilated with 50% nitrous oxide in oxygen and 2% sevoflurane. Ventilation was adjusted to maintain the end-tidal CO_2 ($ETCO_2$) between 30 and 40 mm Hg.

The intubation score was graded during intubation and evaluated according to the Consensus Conference on Good Clinical Research Practice in Pharmacodynamic Studies of Neuromuscular Blocking Agents[10]. Five factors were considered in the assessment: ease of laryngoscopy (jaw relaxation, resistance to the laryngoscope), position and movement of the vocal cords, airway reaction, and movement of limbs. The intubation score was considered excellent if all variables were excellent, good if all variables were either excellent or good, and poor if any variable was poor.

MAP, HR, and SpO_2 values were recorded by an assistant after induction; at the end of MVt; and at 1, 3 and 5 minutes after intubation. Hypertension was defined as a MAP increase >20% from the baseline values, and hypotension was identified as a MAP <80 mm Hg or a decrease of <20% from the baseline values. Tachycardia and bradycardia were defined as an HR greater than 120 beats/min or less than 60 beats/min, respectively. Desaturation was defined as an SpO_2 less

than 90%. Muscle rigidity was graded on a scale from 0 to 3, which ranged from no rigidity to virtually impossible to ventilate during mask ventilation. The incidences of hypertension, hypotension, tachycardia, bradycardia, muscle rigidity, and desaturation were recorded throughout the study.

Statistical Analysis

The data were analysed using the Statistical Package for the Social Sciences (SPSS) version 16.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics for demographic data and constant variables were indicated as mean ± standard deviation. Student's t-test was used to compare group quantitative data, and repeated measures analysis of variance (ANOVA) was used to analyse haemodynamic changes over time, using time as the between-subject factor. The chi-square test was used to analyse categorical variables. A p-value < 0.05 was considered statistically significant.

Results

No significant differences existed between the groups in terms of demographic data (Table I). Mandibular fracture locations are indicated in Table II. Preoperative pain scores were similar for both groups (Group D; 7.86 ± 1.55, Group R; 8.06 ± 0.79, $p = 0.561$).

MVt was similar in both groups with a mean duration of 143 ± 10 and 145 ± 19 seconds in Groups D and R, respectively ($p = 0.715$). The mean intubation time (TIt) was similar for both Groups (51 ± 10 seconds in Group D and 58 ± 10 seconds in Group R) ($p = 0.170$).

MAP, HR, and SPO_2 are presented in Table III. No differences appeared in the baseline measurements between groups. There was a relative increase in MAP and HR values after MVt in both groups, but these differences were not significant between the groups. HR and MAP were similar for Group R at all times as compared to Group D from the first minute after intubation to the fifth minute after intubation ($p > 0.05$). SPO_2 values measured after induction were relatively high for Group D as compared to Group R. However, there were no statistically significant differences among the groups. SPO_2 values measured after MVt and intubation were similar for Group D as compared to Group R (p□0.05 for all times).

The quality of intubation was similar between groups ($p = 0.202$). There were 24 excellent intubation scores in the dexmedetomidine group and 17 in the remifentanil group. The rate of clinically acceptable scores (excellent or good) was 34 in the dexmedetomidine group and 32 in the remifentanil group.

Adverse effects are shown in Table IV. For Group R, the occurrence of muscle rigidity was significantly higher than that observed in Group D. Muscle rigidity appeared in 0% of the patients

Table I. Patient characteristics.

	Group D N (%)	Group R N (%)	p
Age (years)	32.18 ± 6.28	28.54 ± 5.26	0.456
Sex (F/M)	11/24	8/27	0.592
Weight (kg)	73.88 ± 9.78	69.11 ± 7.39	0.239
Height (cm)	168.50 ± 6.88	167.25 ± 7.44	0.777

R group, remifentanil group; D group, dexmedetomidine group. n is number of patients.

Table II. Anatomic sites of fractures.

	Group D (n = 35)	Group R (n = 35)	p
Right parasymphysis + left condyle	9 (25.7%)	14 (40.0%)	0.247
Symphysis + bilateral condyle	3 (8.6%)	0 (0.0%)	
Right corpus + left condyle	9 (25.7%)	5 (14.3%)	
Left parasymphysis + right condyle	11 (31.4%)	12 (34.3%)	
Left corpus + right condyle	3 (8.6%)	4 (11.4%)	

R group, remifentanil group; D group, dexmedetomidine group. n is number of patients.

Table III. Haemodynamic variables.

Group	Baseline	After induction	After MV	Minutes after TI		
				1 (min)	3 (min)	5 (min)
Group D						
MAP	101.96 ±13.8	87.10 ± 10.7	111.60 ± 11.2	119.67 ± 10.7	108.53 ± 17.8	101.30 ± 9.5
HR	77.66 ± 8.3	73.06 ± 9.4	80.26 ± 9.7	90.83 ± 13.5	87.53 ± 6.5	78.97 ± 9.9
SpO2	97.45 ± 1.4	97.08 ± 1.6	98.34 ± 0.5	98 ± 1.1	99.00 ± 0.8	99.08 ± 0.6
Group R						
MAP	100.82 ± 11.4	89.44 ± 9.8	109.13 ± 8.7	115.34 ± 12.8	102.33 ± 10.4	98.63 ± 13.5
HR	80.96 ± 15.5	78.03 ± 14.3	84.65 ± 16.8	95.86 ± 9.6	90.97 ± 7.4	81.61 ± 12.8
SpO_2	97.34 ± 1.4	93.45 ± 2.0	96.46 ± 1.9	98.17 ± 1.3	98.73 ± 0.8	98.91 ± 1.5

Mean arterial pressure (MAP), heart rate (HR) in beats per minute (bpm) and oxygen saturation (SpO_2) changes (between-groups), ($p > 0.05$). R group, remifentanil group; D group, dexmedetomidine group.

in Group D and in 17.1% (six patients) of Group R patients during mask ventilation ($p = 0.025$). The prevalence of desaturation during mask ventilation and intubation was significantly higher in Group R (17.1%) than in Group D (0%) ($p = 0.025$). For Group R, the occurrence rates of hypotension and tachycardia were relatively higher, while hypertension and bradycardia were relatively lower in comparison with Group D. However, no statistically significant differences existed among the groups.

Discussion

The mandible is one of the most often broken facial bones, along with the nose and zygomatic bone, by virtue of its anatomical position[11]. Regional and general techniques are used in the management of anaesthesia[12]. For patients undergoing general anaesthesia, intubation technique is determined by the degree of difficulty in the airways and the intended surgical field. Nasotracheal intubation with direct laryngoscopy is often preferred in patients with no contraindications to avoid blocking the surgical site[13-15]. Intubation with conscious fibre-optic bronchoscopy is performed in patients with a limited range of mouth opening. However, awake intubation is not without significant complications[16] and can be unpleasant for the patient. İn addition, a fibre-optic bronchoscope is not always available at every institution. Submental and retromolar intubation techniques are used in patients with mandibular fractures accompanied by nasal bone and skull base fractures who are undergoing maxillomandibular fixation to prevent the complications of tracheostomy[17,18], but requisite experience is essential in applying these methods.

Previous studies have reported that the major source of bone pain is mechanical distortion, and bringing the periosteum to its normal position reduces the pain. In addition, the mineralized bone and bone marrow have sensory and sympathetic innervation[19,20]. Increasing inflammatory mediators reduces the pain threshold at the trauma site. In the present study, preoperative pain scores caused by jaw movement were significantly high for both groups.

Table IV. Adverse effects.

	Group D N (%)	Group R N (%)	p
Hypertension	8 (22.9)	4 (11.4)	0.171
Hypotension	1 (2.9)	3 (8.6)	0.614
Tachycardia	3 (8.6)	5 (14.3)	0.710
Bradycardia	4 (11.4)	2 (5.7)	0.673
Muscle rigidity	0	6 (17.1)	*0.025
Desaturation	0	6 (17.1)	*0.025

*Significant at the level of $p < 0.05$ (between groups comparisons). R group, remifentanil group; D group, dexmedetomidine group. n is number of patients.

In order to provide effective mask ventilation, it is essential that the mask fits the patient's face and open airway. The patient's mandible must be used as a support when performing this procedure. In addition, factors such as facial asymmetry and oedema may prevent the facemask from fitting to the face, giving rise to air leakage. To prevent this effect, more force must be applied to the mandible. In the same way, during direct laryngoscopy, a force is applied indirectly to the mandible at a right angle to reveal the tracheal structures. In particular, oedema causes an increase in the force applied to the mandible during laryngoscopy by inhibiting the flexion of the muscles and reducing the duration of intubation. The forces exerted can place pressure and movement on the fracture line. The pain caused by tissue damage reveals endocrine and metabolic responses, which may be too small to disturb the normal physiological condition or could affect the entire system either directly or indirectly.

Dexmedetomidine is a selective □2 adrenergic agonist, and remifentanil is an opioid; these two medications are used for diverse situations that include emergent agitation, controlled hypotension, and prevention of haemodynamic response to intubation[21-25]. However, the influences of dexmedetomidine and remifentanil for haemodynamic and respiratory response during mask ventilation and laryngoscopy in patients with mandibular fractures are not clear. In patients with mandible fractures, the bone that has already been exposed to trauma undergoes a second trauma during the induction of anaesthesia, along with stimulation of the supraglottic and tracheal regions. In the present study, according to the baseline values a relative increase in blood pressure and heart rate values after mask ventilation was detected in both groups, but no difference was noted between the groups. The haemodynamic response caused mask ventilation to increase the most in patients with mandibular fractures in the first minute after initiation of the intubation procedure. According to the baseline values, there was a significant increase in blood pressure and heart rate values during the first minute after intubation in both groups, but no difference between the groups was observed. Hypertension developed in eight (22.9%) patients who received dexmedetomidine. In the remifentanil group, hypertension emerged in four (11.4%) patients. When given by rapid intravenous injection, dexmedetomidine can exert a biphasic effect on arterial blood pressure, which starts with transient hypertension and is followed by a longer-lasting reduction in blood pressure[26,27]. While tachycardia developed in five (14.3%) patients of the remifentanil group, it was observed in three (8.6%) members of the dexmedetomidine group. However, the hypertension and tachycardia were not statistically significant among the groups. The most common side effects of dexmedetomidine are hypotension and bradycardia, and they occur more frequently during the loading period. Similarly, some complications of remifentanil, such as unexpected hypotension or bradycardia, could occur during endotracheal intubation. In the present study, while bradycardia developed in the dexmedetomidine group in four patients (11.4%), it was observed in two patients (5.7%) in the remifentanil group during the mask ventilation and intubation process; no significant difference existed between the groups. The prevalence of hypotension was also similar between the groups.

Dexmedetomidine causes fewer cases of respiratory depression than other sedatives or narcotics[28,29]. In contrast, previous studies indicate that doses of remifentanil as low as 0.25 μg/kg/min can lead to significant dose-dependent respiratory depression[30]. In addition, most opiates likely have the potency to induce muscle rigidity. Hogue et al[31] reported that muscle rigidity occurred in 7% of patients during the induction of anaesthesia at a 0.1 μg/kg/min remifentanil infusion rate. When rigidity occurs during anaesthesia induction, signs include flexing of the upper limbs, extension of the lower limbs, immobility of the head, rigidity of the chest and abdomen, and vocal cord and jaw closure. The anaesthesiologist may observe that the patient is difficult and sometimes impossible to ventilate[32-37]. The highly selective $\square_2$ adrenergic agonist dexmedetomidine is capable of inducing muscle flaccidity and anaesthesia in rats and dogs. Dexmedetomidine can also prevent alfentanil-induced muscle rigidity in a dose-dependent fashion[38]. In the present study, six patients (17.1%) developed muscle rigidity in the remifentanil group. Mandibular fractures can lead to muscle spasm, swelling, trismus, and inflammation. Therefore, muscle rigidity caused by remifentanil may be more apparent in patients with mandibular fractures. In reviewing the literature, no study on this topic that might be used for comparison has been found. In the present study, muscle rigidity caused desaturation in six

patients, which was managed via anaesthetic breathing circuit and facemask within 30 seconds. Dexmedetomidine did not significantly alter SpO_2.

The intubation score was similar between the groups. This finding may result from the effects of rocuronium[39]. During the intubation, desaturation developed in six group R patients who experienced desaturation during mask ventilation. A two-minute wait is enough to assess the intubation condition after rocuronium injection. In our study, we limited the mask ventilation time to two minutes in order to shorten the time during which pressure was applied to the traumatic area. However, limiting the mask ventilation time to two minutes may cause insufficient partial oxygen pressure (PaO_2), which occurred after rocuronium injection in six patients during the intubation process. Nasotracheal intubation is a relatively longer process than conventional orotracheal intubation. In these patients, desaturation may result from insufficient blood oxygenation with mask ventilation before the nasotracheal intubation process. A score of 60 mm Hg or higher for PaO_2 is enough to produce an SpO_2 value of 90% or more. We did not evaluate the blood gas in our patients before intubation and did not determine the PaO_2. SpO_2 was measured using pulse oximetry. The value of SpO_2 was 95% or more before intubation in these six patients.

In general, traffic accidents are reported as a causal factor in more than 60% of maxillofacial fractures; assault, sports injuries, and accidents at work compose the other main causes. According to the type and severity of the trauma, mandibular fractures can be seen alone or may be accompanied with general body trauma[40]. In the study conducted by Teoman et al[41], damage to various organ systems was detected in 36% of 753 patients with mandibular fractures; cranial, orthopaedic, thoracic, and intra-abdominal injuries were seen in 154, 137, 64, and 34 of these patients, respectively. Respiratory depression and muscle rigidity induced by remifentanil may lead to unwanted complications in patients with mandible fractures accompanied by other organ damage.

Conclusions

Dexmedetomidine and remifentanil were equally effective in controlling the haemodynamic response attributable to mask ventilation and intubation in patients with mandibular fractures. However, at the doses used in this study, dexmedetomidine had a significant advantage over remifentanil in terms of respiratory stability during mask ventilation and intubation. Larger studies will be needed to confirm these results in patients with mandible fractures.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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