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Dexmedetomidine as a Substitute for Muscle Relaxants in Facilitating Endotracheal Intubation. A Randomized, Controlled Double-Blinded Study

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KEYWORDS

Endotracheal, Dexmedetomidine

Abstract:

Introduction:

Endotracheal intubation is usually achieved by using neuromuscular blocking agents (NMBAs) which are one of the main drugs used in general anesthesia. Several researchers tried performing endotracheal intubation without using NMBAs. The main aim was to find the proper selection and optimum dose of the induction agent to provide suitable conditions for endotracheal intubation without adverse cardiovascular effects. Dexmedetomidine is an alpha-2 receptor agonist with analgesic, sedative, amnestic, and sympatholytic properties. It abolishes the pressor response associated with endotracheal intubation. It showed promising effects in awake fiber-optic, facial trauma, tempo-mandibular joint diseases, and pediatric fields.

Aim: This study evaluated the use of intravenous infusion of a single dose of dexmedetomidine (1.5 µg/ kg) in optimizing the intubating conditions and stress response of intubation.

Methodology: 74 ASA I and II patients were randomized into 2 groups. Group D received 1.5µg/kg of dexmedetomidine as a single IV infusion over 10 minutes. Group C received an IV infusion of normal saline. Intubating conditions were compared in both groups using the previously described scoring system. Hemodynamics was monitored to investigate the effect of dexmedetomidine in blunting the stress response of intubation.

Results: The current study showed that using 1.5 µg/ kg dexmedetomidine as a single IV infusion had a statistically insignificant successful incidence of endotracheal intubation 94.6% compared to 100% of atracurium. Laryngoscopy score, jaw relaxation, and limb movements were comparable between both groups. Incidence of coughing and vocal cord position were significantly different in the D group than C group.

Conclusion: 1.5 µg/kg IV infusion of single-dose dexmedetomidine can be used as a substitute for atracurium in endotracheal intubation in adult patients undergoing GA.

Introduction:

Endotracheal intubation is usually achieved by neuromuscular blocking agents (NMBAs) which are one of the main drugs used during induction of general anesthesia. [1] Despite their frequent use and relative safety, NMBAs still have a few side effects that can be particularly concerning. Both depolarizing and non-depolarizing NMBA may cause allergic reactions and hemodynamic changes due to histamine release or sympathomimetic properties. [2]

Moreover, certain neuromuscular disorders e.g. myopathies, and myasthenia gravis, have different effects on the pharmacokinetics of NMBAs which made the selection, dose adjustment, and reversing the NMBAs used difficult. In such cases, it is recommended to avoid NMBA in patients suffering from these conditions. [3]

Therefore many studies investigated the possibility of performing endotracheal intubation without the aid of neuromuscular blocking agents. Up till the present time, it is still a challenge to find the optimum drug with an optimum dose that can replace NMBAs. [4]

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Dexmedetomidine is a sympatholytic agent with analgesic, amnestic, and sedative properties which enables it to blunt the pressor response resulting from laryngoscopy and endotracheal intubation. These properties have made it more frequently used in the perioperative period as it reduces the anesthetic and analgesic requirements. [5]

Furthermore, there were few trials with promising results evaluating the effect of dexmedetomidine in performing endotracheal intubation without muscle relaxants in certain circumstances i.e. in awake fiber-optic, facial trauma, tempo-mandibular joint disease, and pediatric fields. [6, 7, 8]. But none of them compared dexmedetomidine to NDMR which is the standard practice in endotracheal intubation.

Aim of the study:

This study aimed to assess the effect of intravenous infusion of a one-time dose of dexmedetomidine (1.5 µg/ kg) in optimizing the intubating condition by comparing it to atracurium in adult patients.

Sample size:

The study of Noh et al. (2017)[9]indicates that the intubating conditions (excellent and good) among patients receiving dexmedetomidine are 100% while that among those receiving placebo is 68.6%. Based on this; a minimum sample size of **32** cases per group (total of 64 cases) is required with power of 90% and alpha error of 0.05. To compensate for the withdrawn cases; the sample size will be increased by 15% to **37** cases in each group (total of 74). PS (Power and Sample Size Program) Version 3.1.2. was used to calculate the Sample size.

Methodology:

The study was designed to be a prospective, controlled, randomized double-blind study. It was carried out in Theodor Bilharz Research Institute; Department of Anesthesia and Surgical Intensive Care unit after approval by the research ethical committee (PT 822) and patient-informed consents were signed. The trial was registered in ClinicalTrials.gov ID: NCT06409377.

74 Adults were enrolled in the study, randomized using randomly generated computerized numbers, and divided into two groups. To achieve double blinding, two investigators played a role in this study. The first one was responsible for drug preparation and administration with no further role in the study. The second investigator who was uninformed of the group's allocation performed endotracheal intubation and data collection. (Figure 1)

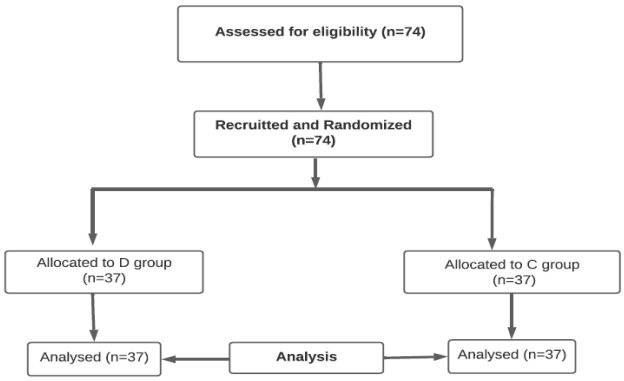

Figure 1: Flow chart.

Patients were allocated according to the randomly generated numbers into 2 groups; each group had 37 patients. The Dexmedetomidine Group (D): Patients received dexmedetomidine (1.5 µg/kg), propofol (2mg/kg), and fentanyl (1 µg/kg). The Control Group (C): Patients received propofol (2 mg/kg), fentanyl (1 µg/kg), and atracurium (0.5 mg/kg).

Inclusion criteria:

1. ASA physical status I, II.
2. Age ranges from 18 to 60 years old for both sexes.
3. Mallampati I and II.
4. Patients are scheduled for elective surgery under general anesthesia and require endotracheal intubation.

Exclusion criteria:

1. Age less than 18 and more than 60 years.
2. Pregnancy.
3. Emergency surgery or full stomach
5. Mallampati III and IV.
4. Renal or Hepatic patients
5. Patients with any cardiac condition.
6. Patients with suspected difficult airway; e.g., high neck circumference, high body mass index (BMI ≥30 kg/m2), airway masses, mouth scars, neck scars, limited neck extension, or history of snoring.
7. Any patient on regular intake of beta-blockers or calcium channel blockers
8. Patients with known allergy or any contraindication to dexmedetomidine,

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9. Patients with psychiatric, neurological, or neuromuscular diseases.

Anesthesia Technique:

All patients were subjected to proper preoperative assessment, including detailed history taking, physical examination, and review of laboratory data before the procedure. Anesthesia and procedural consents were signed by the patients.

Upon arrival at the operative theater, basic monitoring as Electrocardiography (ECG), Non-invasive Blood Pressure (NIBP) monitor, and pulse oximetry were applied. Baseline readings including heart rate (HR), Mean arterial blood pressure (MAP), and arterial oxygen saturation (spo2) were obtained.

According to group allocation and before general anesthetics administration, patients of group D received 1.5 µg/kg dexmedetomidine diluted in 20 ml of normal saline syringe and slowly injected IV over 10 minutes. Patients of the control group received 20 ml of normal saline injected IV over 10 minutes.

Then all patients were pre-oxygenated with four to five breaths of 100% oxygen. In the control group; intravenous induction of anesthesia was done using propofol (2 mg/Kg), fentanyl (1 µg/Kg), and atracurium (0.5 mg/Kg). While in the D group propofol (2 mg/Kg), fentanyl (1 mg/kg), and normal saline were used. After 3 minutes of mask ventilation with 2% sevoflurane, endotracheal intubation (ETI) with an 8 mm endotracheal tube for male patients and a 7 mm endotracheal tube for female patients was performed by an experienced anesthesiologist.

After endotracheal intubation was done, the endotracheal tube cuff was carefully inflated with 3cm of air. The correct position of ETT was confirmed by the presence of ETCO2 waves and bilateral auscultation of equal air entry on the chest. Following endotracheal intubation, the first investigator administered Atracurium 0.5 mg /Kg to the dexmedetomidine group and normal saline to the control group. Maintenance of anesthesia was done using sevoflurane 2%, and a mixture of oxygen and air (1 L/min - 1 L/min) in both groups. End-tidal carbon dioxide partial pressure (etCO2) level was kept between 35 and 40 mmHg by adjusting mechanical ventilation parameters.

Intubating conditions were evaluated using a previously described scoring system (Table 1) [10], which included 5 variables: Ease of laryngoscopic insertion, vocal cords state, coughing, limb movement, and jaw relaxation status.

Table 1: The scoring system of the intubating conditions.

Score	1	2	3	4
Laryngoscope:	Easy	Fair	Difficult	Impossible
Vocal cords position :	Open	Moving	Closing	Closed
Coughing reflex:	None	Slight	Moderate	Severe
Jaw Relaxation status:	Complete	Slight	Stiff	Rigid
Limb movement status:	None	Slight	Moderate	Severe

The score was interpreted into 3 categories: excellent, acceptable, and poor conditions:

- Excellent conditions: had a score of 1 for all the 5 factors.
- Acceptable conditions: had a score of 2 for any of the 5 factors.
- Poor conditions had a score >2 for any of the 5 factors.

Successful intubations were defined as excellent and acceptable conditions while failed intubations were defined as poor conditions.

Patients who experienced any of the following conditions: closed vocal cords, a rigid jaw that made it impossible to insert a laryngoscope, excessive limb movement, and severe coughing during the laryngoscopy or intubation, Atracurium (0.5 mg/kg) was administered to allow laryngoscopy and endotracheal intubation.

The MAP, Spo2, and HR were recorded at the following times: baseline (T0), after the end of IV infusion (T1), immediately following induction of general anesthesia (T2), instantly before endotracheal intubation (T3), directly after endotracheal intubation (T4), 3 minutes following endotracheal intubation (T5), and 5 minutes after endotracheal intubation (T6).

Hemodynamic changes were managed as follows: If the mean arterial pressure decreased by 20% from the baseline reading, ephedrine bolus 5 -10 mg IV was given. If the heart rate decreased to 45 beats/ min IV atropine 0.5mg was administrated.

Primary outcome:

Comparing the rate of successful intubations between the dexmedetomidine group and the atracurium group, which was defined as both excellent and acceptable conditions.

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Secondary outcomes:

1- Pressor response to tracheal intubation is defined as an increase in the heart rate by 20% or more from baseline 1 min after ETT.

2- Hypotensive episodes (MAP ≤ 20% from baseline)

3- Bradycardia episodes (HR ≤ 50)

4- Hypertensive episodes (MAP ≥20% baseline for >1 minute)

5- Tachycardic episodes (HR ≥20% baseline for >1 minute).

6- Hypoxic episodes (SPO2 ≤ 95% for 1 minute).

7- Postoperative sore throat.

8- Laryngeal spasm or bronchospasm.

Statistical analysis:

IBM SPSS® Statistics version 26 (IBM® Corp., Armonk, NY, USA) was used to perform the statistical analysis. Numerical data was expressed as mean ± standard deviation or median and interquartile range. Categorical data was expressed as frequency and percentage. The relation between qualitative variables was evaluated using Pearson's Chi-square test or Fisher's exact test. Intubating conditions scores were analyzed using the Mann-Whitney *U* test. The incidence of successful intubations and excellent intubation conditions between groups were compared using the Fisher exact test. Comparison of quantitative variables between the two groups was done using the Student t-test as the data was tested for normality using the Kolmogorov-Smirnov test and Shapiro-Wilk test and was found to be normally distributed. All tests were two-tailed. A p-value < 0.05 was considered significant.

Results:

Demographic data of both groups including age, sex, ASA, Mallampati classification, and BMI showed no statistically significant difference between both groups. (Table 2)

Table 2: Demographic data of the studied groups:

		Group D (N=37)	Group C (N=37)	Test value	P value
AGE (y) (mean ± SD)	:	40.2 ± 12.8	41.5 ± 12.0	0.441	0.661
SEX (N& %)					
➢ Male	:	15 (40.54%)	14 (37.83%)	0.057	0.812
➢ Female	:	22 (59.45%)	23 (62.16%)		
ASA (N & %)					
➢ I	:	26 (70.27%)	19 (51.35%)	2.779	0.096
➢ II	:	11 (29.72%)	18 (48.64%)		
Mallampati (N& %)					
➢ I	:	13 (35.13%)	15 (40.54%)	0.230	0.811
➢ II	:	24 (64.86%)	22 (59.45%)		
BMI (mean ± SD)	:	22.86 ± 1.62	22.15 ± 1.75	1.830	0.071

Data were presented as mean ± SD or N & % as appropriate.

Regarding the intraoperative hemodynamics; there was no statistically significant difference between the mean values of the MAP of the D group and C group throughout the studied interval. (Figure 2) The comparison of mean HR measurements between the D and C groups showed no statistically significant difference except for the T1 value (post-infusion) which was statistically significantly higher in the C group than the D group with a p-value < 0.005. (Figure 3)

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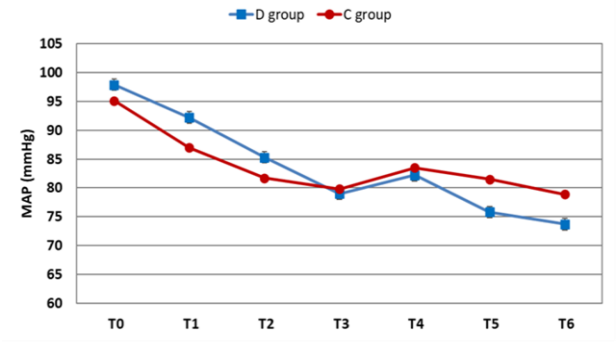

Figure 2: Comparison of mean values of MAP.

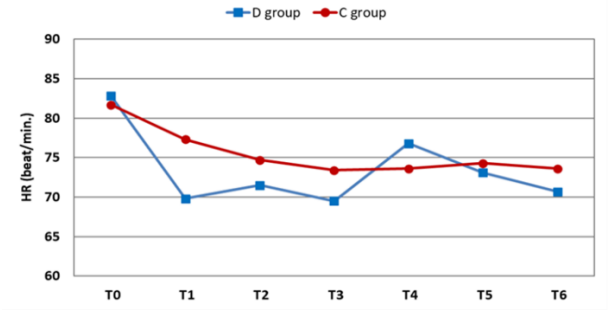

Figure 3: Comparison of mean values of HR.

The intraoperative events showed the following;

Concerning the number of intraoperative hemodynamic episodes; there was no statistically significant difference between both groups in all items; Intraoperative hypotensive episodes occurred in 8 patients of the D group versus 4 patients in the C group. Intraoperative hypertensive episodes occurred only in 2 patients of the C group. None of the patients in both groups had hypoxic episodes.

Regarding HR there was no statistically significant difference between both groups, 2 patients in the D group versus a single patient in the C group had bradycardic episodes. Single patients in each of the D group and C group had tachycardic episodes. Stress response to tracheal intubation showed no statistically significant difference between the mean HR of the D group (74.6 ± 9.6) versus (78.8 ± 9.9) in the C group. (P value: 0.066)

The intubating conditions of both groups showed the following;

The overall incidence of successful intubations was comparable between the D group (94.6%) and the C group (100%) with a P-value (0.493). Only 2 patients in the D group had failed tracheal intubation in the D group and 0.5 mg/kg atracurium was administered to enable tracheal intubation. (Figure 4)

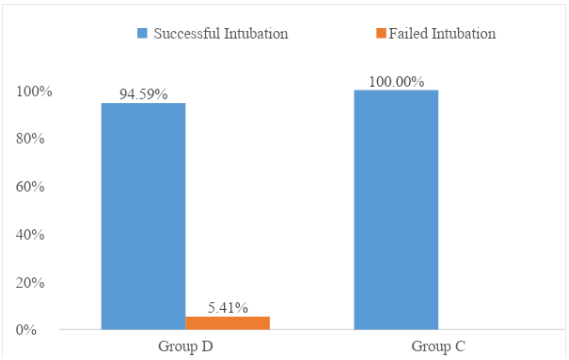

Figure 4: Overall Incidence of Successful intubations done by Fisher exact test.

The detailed criteria of the intubating conditions showed the following;

Regarding the laryngoscopy score; all 37 patients in the D group had easy laryngoscopy while 36 patients in group C had easy laryngoscopy and only 1 patient had fair laryngoscopy. P-value (0.493) (Table 3)

There was a significant difference between the two groups in vocal cords score; 30 patients had open vocal cords in the D group versus 37 patients in the C group. While 6 patients had moving vocal cords and only 1 patient had closing vocal cords in the D group. (P-value 0.006) (Table 3)

The coughing score showed statistical significance between the study groups; 22 patients in the D group versus 35 patients in the C group had no coughing in response to tracheal intubation. 13 patients in the D group versus 2 patients in the C group had slight coughing. 1 patient in the D group had moderate coughing while severe coughing occurred only in a single patient in the D group (P-value < 0.001). (Table 3)

All 74 patients of both D and C groups had complete jaw relaxation conditions. (Table 3)

The limb movement score showed that 34 patients in the D group versus 37 patients in the C group had no limb movements in response to endotracheal intubation. Only 3 patients in the D group had slight limb movement during endotracheal intubation.

P-value (0.079). (Table 3)

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Table 3: Detailed criteria of intubation:

Variable Group	Laryngoscopy Score		Vocal Cords Score		Coughing Score		Jaw Relaxation Score		Limb Movement Score	
	D	C	D	C	D	C	D	C	D	C
1	37	36	30	37	22	35	37	37	34	37
2	0	1	6	0	13	2	0	0	3	0
3	0	0	1	0	1	0	0	0	0	0
4	0	0	0	0	1	0	0	0	0	0
Mean Rank	37.00	38.00	41.00	34.00	44.05	30.95	37.50	37.50	39.00	36.00
Mann-Whitney	666.00		555.00		442.00		684.50		629.00	
P-value	0.317		0.006*		0.000*		1.000		0.079	

Table 3: Detailed criteria of the intubating conditions done by Mann-Whitney Test and represented as mean ranks.

Analyzing the Laryngoscopic grade of both groups showed that 30 patients (81.0%) of the D group versus 26 patients (70.2%) of the C group had Laryngoscopic grade I, while 7 patients (18.9%) of the D group versus 11 patients (29.7%) of the C group had Laryngoscopic grade II. There were no statistically significant differences between both groups (P- value: 0.278).

None of the 2 groups ' patients experienced laryngeal or Broncho-spam during tracheal intubation. Also, there was no incidence of postoperative sore throat detected in both groups.

Discussion:

The current study showed that the use of a one-time dose of dexmedetomidine 1.5 µg/ kg IV infusion over 10 minutes had a successful tracheal intubation incidence of 94.6% comparable to 100% in the atracurium group.

To the best of the authors' knowledge, this study is the first to compare the intubating conditions of a drug against the usually used NDMR as a control for endotracheal intubation.

The optimum intubating conditions are usually evaluated through two aspects; the Laryngoscopic scoring system and the ability of the drug to blunt the pressor response of intubation. Dexmedetomidine was nearly as effective as Atracurium in both of these aspects.

All patients in both groups had easy insertion of laryngoscopy and complete jaw relaxation. Moreover, limb movement was comparable in both groups despite its slight occurrence in 3 patients of the dexmedetomidine group. Despite the significant difference between both groups concerning vocal cords movement and coughing reflex, it didn't prevent successful tracheal intubations in (94.6%) of the patients.

Our results came in agreement with Lingxin Wei et al. (2015) who found that a single dose of 1 µg/kg dexmedetomidine improved intubating conditions in children versus remifentanil (2 µg/kg) without muscle relaxants in both groups. We had a relatively higher percentage of patients who had successful tracheal intubation (94.6%) in comparison to 90 % in their study. A key distinction in our study is the selection of adult patients, who generally pose more challenging intubation conditions. Moreover our study compared dexmedetomidine against NMB atracurium which assures its efficacy. [11]

Hanci et al. (2010) showed that propofol and dexmedetomidine administration inhibited the airway reflexes; i.e.: coughing, and diaphragmatic movements in response to endotracheal intubation without NMBA more effectively than propofol and fentanyl. [12]

Several drugs were studied concerning the feasibility of endotracheal intubation without muscle relaxants.

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Opioids especially remifentanil, propofol, and ketamine were employed with variable outcomes.

E. Erhan et al. (2003), compared the intubating conditions using alfentanyl versus varying dosages of remifentanyl (2, 3, and 4µg/kg). They found the success rate to be 45% versus 20%, 75%, and 95% respectively [13]. The highest percentage of excellent intubating conditions; comparable to our results concerning dexmedetomidine; was noticed with the highest dose of remifentanyl 4µg/kg. This high dose is relatively not the common practice in induction of GA due to the relative risks of such dose; muscle stiffness, and delayed recovery. Also in this study, patients received multiple drugs as adjuvants (opioids and benzodiazepines), which is not suitable for day-case surgeries and might had synergistic effects that led to increasing the success percentage.

S. Demirbilek, et al. 2004 demonstrated that adding 0.5mg/kg ketamine to 3µg/kg and 4µg/kg remifentanil during induction of general anesthesia with 2mg/kg propofol achieved 90% and 100% excellent intubating conditions respectively. The high success rate could be attributed to the usage of multiple induction agents, yet these combinations couldn't preserve the hemodynamics and wouldn't be preferred for day-case surgeries. [14]

Another finding of the current study was that dexmedetomidine blunted the stress response to endotracheal intubation when a loading dose of 1.5 µg/kg was slowly administered over 10 minutes. This finding was consistent with several previous results which supported the notion that preoperative administration of dexmedetomidine significantly blunt the stress response of endotracheal intubation. [15, 16, 17]

Dexmedetomidine also showed a stable hemodynamic profile throughout the study despite that it was previously reported that it has a biphasic hemodynamic profile as the high-loading doses might cause hypertension and bradycardia while the low-loading doses might cause hypotension. [18, 19]

The main limitation of the current study is that all the enrolled patients were classified as Mallampati I or II. Thus further studies are required in patients with suspected difficult airway management.

In conclusion; we assume that an IV infusion of 1.5µg/kg dexmedetomidine may be used effectively as an intubating agent instead of atracurium. Also, the used regimen of dexmedetomidine showed a stable hemodynamic profile with effective blunting of the stress response.

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