



# The Effects of Lidocaine, Fentanyl, and Remifentanil on Hemodynamics and Intraocular Eye Pressure After Tracheal Intubation: A Randomized Clinical Trial

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## Abstract

**Objectives:** An increased reflex in sympathetic and sympathoadrenal activity caused by tracheal intubation causes an increase in arterial blood pressure, and increased venous pressure causes an increase in intraocular pressure (IOP). The aim of the current study was to compare the effects of lidocaine, fentanyl, and remifentanil to determine which agent was most effective in the prevention of elevated IOP.

**Methods:** The patients were separated into 3 groups (lidocaine, fentanyl, and remifentanil). Heart rate and mean arterial pressure (MAP) were measured and recorded 2 min after the administration of the drugs and at 1, 5, and 10 min after intubation. IOP was measured and recorded in each eye separately by an ophthalmologist preoperatively, at 2 min after drug administration and at 1, 5, and 10 min after intubation.

**Results:** MAP was found to be high ( $122.750 \pm 17.068$ ) in the lidocaine group at 1 min after intubation. In all 3 groups, the right and left eye IOP values were found to be higher at 1 min after intubation than at 2 min after drug administration. Only the difference in the lidocaine group was statistically significant ( $p=0.003$ ). In all 3 groups, the right and left eye IOP values at 5 min after intubation were statistically significantly lower than the values at 1 min after intubation (Group 1:  $p=0.001$ , Group 2:  $p=0.000$ , and Group 3:  $p=0.000$ ).

**Conclusion:** From the results of this study, it was concluded that remifentanil and fentanyl were more effective drugs than lidocaine in the prevention of increased IOP and hemodynamic response to intubation, and there was no significant difference between these two drugs.

**Keywords:** Fentanyl, intraocular pressure, intubation, lidocaine, remifentanil

## Introduction

An increased reflex in sympathetic and sympathoadrenal activity caused by laryngoscopy and tracheal intubation causes an increase in arterial blood pressure, heart rate (HR), and

intracranial pressure, whereas cough, straining, and respiratory tract obstruction as a reason for increased venous pressure cause an increase in intraocular pressure (IOP) (1,2). Although this increase does not create any complications in

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healthy individuals, in patients with chronic elevated IOP and therefore a reduced capacity for aqueous drainage, careful hemodynamic control is necessary during endotracheal intubation and anesthesia induction as they may not have sufficient capacity to compensate for acute IOP increases (3). Therefore, the effects on IOP of the intubation method and the agents used in induction are important.

Previous studies have shown that lowering IOP could decrease the risk of glaucoma (4,5). Postoperative sight loss has been reported following non-ophthalmological operations such as vertebral surgery, cardiothoracic surgery, craniotomy, or abdominal surgery (6). The reason for this has been determined to be ischemic optic neuropathy (7) and one of the most common causes of ischemic optic neuropathy is glaucomatous changes associated with an increase in IOP. Therefore, attention must be paid preoperatively to groups at particular risk of increased IOP.

To eliminate unwanted side-effects associated with intubation, precautions must be taken such as ensuring the depth of the general anesthesia applied, administering topical anesthesia to the laryngeal area under general anesthesia, administering intravenous (iv) lidocaine a few minutes before the procedure, and administering vasodilators which prevent a sympathoadrenal response, alpha-and beta-adrenergic blockers, precurarization, and short-term narcotic analgesics (alfentanil and remifentanil) before anesthesia induction (8).

In the light of this information, it can be seen that IOP is a risk factor that must be taken into consideration in anesthesia, especially in high-risk groups. The method of intubation applied and the agents administered are of great importance in the effect on IOP. In the application of anesthesia before, during, and after the operation, IOP must be kept under control and prevented from increasing (9).

The pharmacological agents most commonly used to prevent hemodynamic response to intubation in anesthesia induction, thereby an increase in IOP are lidocaine, fentanyl, and remifentanil. The aim of this study was to compare the effects of these 3 drugs and to determine the agent most effective for the prevention of elevated IOP.

## Methods

### Ethical Approval and Patient Consent

Approval for this study was granted by the Local Ethics Committee (Decision no: HNEAH-KAEK 2015/36, Dated: 25.05.2015). Written informed consent was obtained from all the patients.

### Patient Selection and Inclusion Criteria

The study included patients aged 18–70 years, who were the American Society of Anesthesiology grade I–II, who were to undergo an elective, non-ophthalmological operation under

general anesthesia. Furthermore, the eyes with refractive error between -8 and +3D, and axial length between 20 mm and 26 mm were only included in the study.

Patients were excluded from the study if they had a history of glaucoma, preoperative IOP measured as >21 mmHg despite no known history of glaucoma, a history of eye surgery or cardiovascular surgery, or a history of systemic hypertension or cardiovascular disease.

### Sample Size

The number of patients to be included in the study sample was calculated with PASS 2008 software using the values in the study by Sator-Katzenschlager et al. (2004) (10). As a result of the calculations, it was concluded that for 95% power, a total of 75 patients was required as 25 patients in each group ( $\mu_1 = 91.3$ ,  $\mu_2 = 78.9$ ,  $\sigma_1 = 13.2$ ,  $\sigma_2 = 16.4$ ,  $r = 0.2$ , and  $\alpha = 0.05$ ). To prevent any problems, it was planned to include 28 patients in each group.

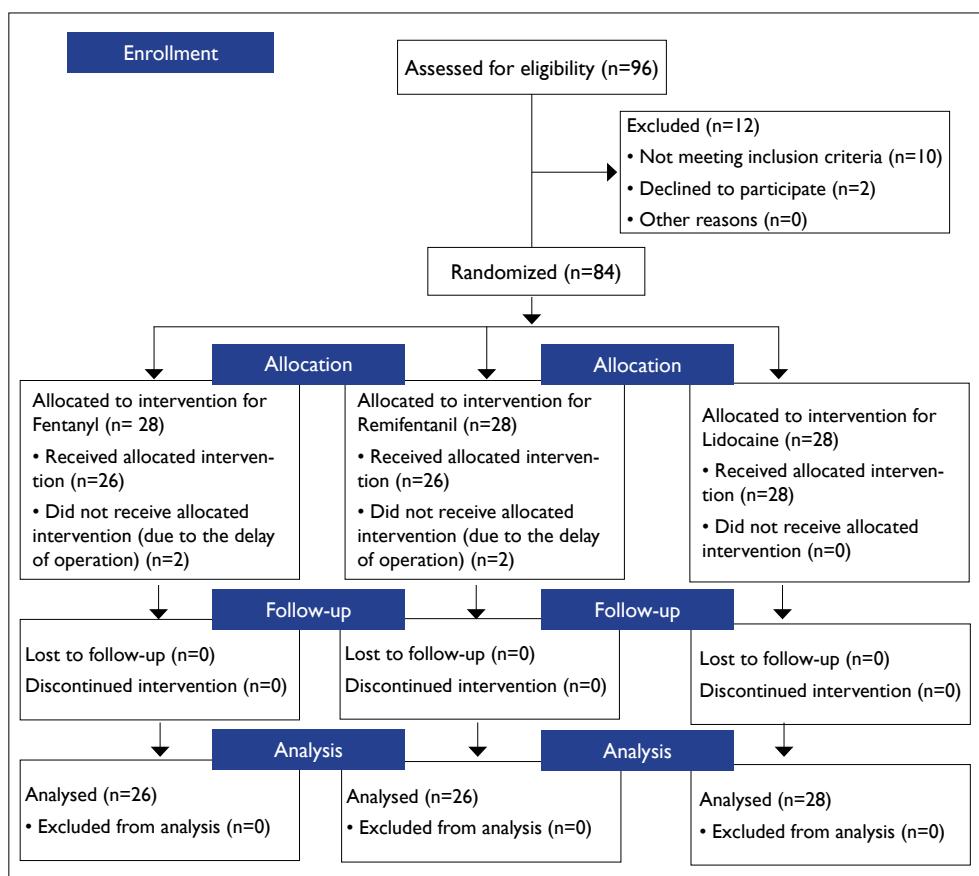
### Patient Groups and Randomization

The study was planned to include 3 groups as the lidocaine, fentanyl, and remifentanil groups. The patients were randomly assigned to the groups and distributed according to the principle of equality. A total of 86 patients were identified as suitable for the study, and of these 10 were excluded as they did not meet the inclusion criteria, and two as they did not wish to participate in the study. It was planned to include 28 patients in each of the groups. As the operations for two patients in the fentanyl group and two in the remifentanil group were postponed, these two groups included 26 patients in each. The lidocaine group included 28 patients (Fig. 1).

- Group I: Lidocaine Group; 1,5 mg/iv lidocaine was administered 2 min before intubation.
- Group II: Fentanyl Group; 2 mcg/kg/iv fentanyl was administered 2 min before intubation.
- Group III: Remifentanil Group; 1 mcg/kg/iv remifentanil was administered 2 min before intubation.

The person administering the drug was blinded to which drug was being used. All the measurements and values were recorded by an anesthetist blinded to the groups.

At 30 min before admission to the operating room, all the patients were administered 0.5 mg intravenous (iv) atropine and 2 mg intramuscularly (im) midazolam as premedication. When the patient was transferred to the operating table, HR, non-invasive blood pressure, and saturation monitorization were applied. Anesthesia induction was provided with 2.5 mg/kg/iv propofol and 0.1 mg/kg/iv vercuronium. At 3 min after the administration of vercuronium, the patient was intubated using a Macintosh laryngoscope. The intubation was performed by a 5th-year resident with good experience of intubations, blinded to the drug groups. No complications were experienced at the stage of intubation. Anesthesia was



**Figure 1.** Flow diagram.

maintained with inhaler of 1% sevoflurane and 50%  $\text{N}_2\text{O}$ -50%  $\text{O}_2$  mixture.

HR and mean arterial pressure (MAP) were measured and recorded at 2 min after drug administration and at 1, 5, and 10 min after intubation. Bradycardia developed in two patients, who were then administered 0.5 mg iv atropine. No tachycardia table was developed that required intervention.

### IOP Measurement Device Protocol

IOP was measured and recorded in each eye separately by an ophthalmologist blinded to the groups using applanation tonometry (Tono-Pen Avia, Reichert Technologies). To prevent infection spread, the tip of the tonometer was covered with a separate cover (Ocu-Film Tip Covers) for each patient before taking the measurements. IOP was measured and recorded a total of 5 times; preoperatively, at 2 min after drug administration, and at 1, 5, and 10 min after intubation.

### Statistical Methods

Data obtained in the study were analyzed statistically using SPSS software. Conformity of the data to normal distribution was examined with the Kolmogorov-Smirnov test. Descriptive statistical methods of number, percentage, and mean $\pm$ standard deviation values were used in the data evaluations. In the comparison of qualitative data, the Pearson's

Chi-square test was used. In the comparison of quantitative data, the Kruskal-Wallis test was applied to the comparisons of more than two groups, and the Mann-Whitney U-test was used to determine from which group the difference originated. The Wilcoxon signed-rank test was used in the comparisons of parameters within groups. The results were evaluated in a 95% confidence interval. A  $p<0.05$  was accepted as statistically significant.

### Results

Evaluation was made of a total of 80 patients who met the study inclusion criteria. No perioperative complications or side effects that required exclusion from the study were observed in any patient. No statistically significant difference was determined between the groups in respect of demographic data and comorbidities ( $p>0.05$ ). The demographic data and comorbidities of the patients are shown in Table 1.

The MAP values at 1 min after intubation were statistically significantly higher in the lidocaine group at  $122.750\pm17.068$  mmHg, compared to  $105.040\pm19.751$  mmHg in the fentanyl group and  $108.960\pm20.419$  mmHg in the remifentanil group (Table 2).

No statistically significant difference was determined between the groups in respect of the preoperative right and

**Table 1.** Demographic characteristics of the patients

	Fentanyl		Remifentanil		Lidocaine		P
	n	%	n	%	n	%	
<b>Gender</b>							
Female	15	57.7	17	65.4	21	75.0	0.403
Male	11	42.3	9	34.6	7	25.0	
<b>ASA grade</b>							
1	13	50.0	12	46.2	15	53.6	0.862
2	13	50.0	14	53.8	13	46.4	
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	42.6	10.3	40.9	11.2	48.0	12.7	0.086
Weight (kg)	76.7	12.9	74.5	14.9	73.6	12.9	0.764

ASA:American Society of Anesthesiologists; SD: Standard Deviation.

**Table 2.** Mean arterial pressure

	Fentanyl		Remifentanil		Lidocaine		P
	Mean	SD	Mean	SD	Mean	SD	
Preoperative	101.40	12.147	99.620	13.002	103.430	15.000	0.439
2 min after drug injection	100.120	9.492	97.230	14.035	105.110	14.038	0.103
1 min after intubation	105.040	19.751	108.960	20.419	122.750	17.068	0.002
5 min after intubation	91.230	16.712	90.420	17.360	100.820	14.381	0.040
10 min after intubation	81.770	10.539	90.540	14.860	95.820	13.112	0.001

SD: Standard Deviation, min: Minutes.

left eye IOP values (right eye IOP: p=0.728; left eye IOP: p=0.557) (Tables 3 and 4).

In all 3 groups, the right and left eye IOP values were found to be higher at 1 min after intubation than at 2 min after drug administration. Only the difference in the lidocaine group was statistically significant (p=0.003) (Tables 3 and 4).

In all 3 groups, the right and left eye IOP values at 5 min after intubation were statistically significantly lower than the values at 1 min after intubation (Group 1: p=0.001, Group 2: p=0.000, and Group 3: p=0.000). No significant change was observed in the values between 5 and 10 min after intubation in any of the groups (Tables 3 and 4).

## Discussion

To date, various drugs have been used to prevent an increase in IOP related to intubation and hemodynamic changes. Some of these drugs which have been shown to be effective are lidocaine, fentanyl, and remifentanil.

In a study by Memiş et al. (11) of 50 cases undergoing elective surgery, iv administrations were made 3 min before

intubation of 0.8 mg/kg esmolol to Group I, 10 mcg/kg alfentanil to Group II, 2 mcg/kg fentanyl to Group III, 1.5 mg/kg lidocaine to Group IV, and 10 ml physiological saline to Group V, and lidocaine was reported to be ineffective in the prevention of cardiovascular responses developing during intubation.

In the current study, 1.5 mg/kg lidocaine was administered approximately 5 min before intubation, and this was observed to be more effective in suppressing the hemodynamic responses which develop after intubation compared to the drugs in the other groups.

Steven et al.(12) compared the efficacy of esmolol, lidocaine, and a placebo in the prevention of tachycardia and hypertension associated with tracheal intubation. Fentanyl and lidocaine were seen to be insufficient in protection against increased heart rate. All 3 drugs, with no statistically significant difference between them, were found to be effective in protecting against increased systolic blood pressure.

O'Hare et al. (13) reported that the hemodynamic response to intubation could be kept in balance with the ad-

**Table 3.** Right eye intraocular pressure

	Fentanyl		Remifentanil		Lidocaine		P
	Mean	SD	Mean	SD	Mean	SD	
Preoperative	17.190	3.889	16.620	2.913	16.500	2.887	0.728
2 min after drug injection	15.880	3.421	14.420	3.190	15.070	3.527	0.346
1 min after intubation	16.690	5.884	15.000	5.044	17.640	4.863	0.179
5 min after intubation	13.270	3.628	11.810	3.805	13.040	3.554	0.240
10 min after intubation	12.380	2.669	11.850	2.541	12.290	3.332	0.854

SD: Standard Deviation, min: Minutes.

**Table 4.** Left eye intraocular pressure

	Fentanyl		Remifentanil		Lidocaine		P
	Mean	SD	Mean	SD	Mean	SD	
Preoperative	17.580	3.797	16.800	2.769	16.680	3.019	0.557
2 min after drug injection	15.730	3.672	14.560	3.124	14.930	3.630	0.545
1 min after intubation	16.540	6.313	15.160	5.047	17.640	4.832	0.184
5 min after intubation	13.420	3.466	12.080	3.696	12.960	3.543	0.350
10 min after intubation	12.580	2.715	11.760	2.554	12.290	3.332	0.693

SD: Standard Deviation, min: Minutes.

ministration of a remifentanil bolus of 1 mcg/kg, and the risk of hypotension after intubation could be reduced.

With the same dosage bolus of remifentanil (1 mcg/kg), it has been reported in other studies that an increase in IOP and HR could be effectively suppressed after intubation (14,15).

In a study by Drenger et al. of a pediatric patient group, IOP in both eyes was measured 5 min after induction with inhalation anesthesia and was recorded as the basal value. IOP was then measured and recorded at 1 and 2 min after the administration of iv lidocaine, and at 1, 2, 3, and 4 min after intubation. The IOP values recorded at 2 min after the lidocaine injection were observed to be significantly low compared to those of the control group. The IOP values measured at 1 min after intubation in the control group were found to be significantly higher than those of the lidocaine group (16).

Sator-Katzenschlager et al. compared the effects on IOP of remifentanil and fentanyl in anesthesia maintenance and in recovery from anesthesia in patients operated on for non-ophthalmological reasons. There was concluded to be no significant difference between remifentanil and fentanyl in respect of IOP and hemodynamic changes during maintenance and recovery (10).

In a similar study that used succinylcholine, the effects were compared of remifentanil and fentanyl on increased IOP developing in intubation, and no significant difference

was determined between remifentanil and fentanyl in the effects on IOP (17).

Kashani and Moein Vaziri compared the effects of lidocaine and fentanyl on increased IOP developing as a response to intubation. Patients in the control group were not administered any drugs, in the second group, 5 mcg/kg iv fentanyl was administered 5 min before intubation; and in the third group, 1.5 mg/kg iv lidocaine was administered 3 min before intubation. Both fentanyl and lidocaine were observed to prevent an increase in IOP developing as a response to intubation (18).

Moeini et al. (19) examined the effects of the use of lidocaine, sufentanil, and succinylcholine in the prevention of increased IOP developing after intubation. As a result of the study, it was reported that the use of lidocaine and sufentanil premedication prevented increased IOP and even lowered it, and provided better conditions for the operation.

In the current study, a statistically significant increase was determined in IOP at 1 min after intubation in the lidocaine group. This suggested that lidocaine was less effective than fentanyl and remifentanil in the prevention of increased IOP developing as a response to intubation.

The results of the current study also showed a correlation between hemodynamic parameters and IOP. The sympathetic activity developing associated with laryngoscopy

and intubation significantly increases IOP (at least 10–20 mmHg). The associated increase in venous pressure that develops increases the intraocular episcleral venous pressure and this causes an increase in the aqueous humor, resulting in increased IOP. An increase in arterial pressure is known to be one of the factors increasing IOP (9).

This view was supported by the observation in the current study that lidocaine was inadequate compared to the other two groups in the suppression of the hemodynamic response and IOP.

### **Limitation**

IOP measurements were taken by only one observer. Subgroup analysis for different ages was not evaluated. These were among our study limitations.

### **Conclusion**

From the results of this study, it was concluded that remifentanil and fentanyl were more effective drugs than lidocaine in the prevention of increased IOP and hemodynamic response to intubation, and there was no significant difference between these two drugs.

### **Disclosures**

**Ethics Committee Approval:** Approval for this study was granted by the Local Ethics Committee (Decision no: HNEAH-KAEK 2015/36, Dated: 25.05.2015). Written informed consent was obtained from all the patients.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** The authors declare no conflicts of interest.

**Authorship Contributions:** Concept – A.C.S., O.D., F.D.S., S.I., O.E.; Design – A.C.S., O.D., F.D.S., S.I., O.E.; Supervision – A.C.S., O.D., F.D.S., S.I., O.E.; Materials – A.C.S., O.D., F.D.S., S.I., O.E.; Data collection and/or processing – A.C.S., O.D., F.D.S., S.I., O.E.; Analysis and/or interpretation – A.C.S., O.D., F.D.S., S.I., O.E.; Literature search – A.C.S., O.D., F.D.S., S.I., O.E.; Writing – A.C.S., O.D., F.D.S., S.I., O.E.; Critical review – A.C.S., O.D., F.D.S., S.I., O.E.

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