



Case Report

ATTENUATION OF CARDIO-VASCULAR RESPONSE TO LARYNGOSCOPY AND INTUBATION  
WITH 10% XYLOCAINE SPRAY DURING GENERAL ANESTHESIA

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ABSTRACT

**Aims/ Background:** Cardiovascular response was increase by direct laryngoscopy and endotracheal intubation. To study the hemodynamic changes associated with induction of general anesthesia and evaluate the efficacy of 100mg of 10% topical lidocaine spray for attenuating stress response during laryngoscopy and endotracheal intubation in normotensive patients undergoing plan routine surgeries.

**Materials and Methods:** This study was conducted during the period from June 2017 to May 2019, in the Department of Anesthesiology and Critical Care, Rama Medical College, Hospital and Research Centre, NH-9, Pilakhuwa, Hapur after approval by the hospital ethics committee on normotensive ASA Grade I & II. All patients had enrolled our study are between the age of 20 years to 60 years and are scheduled for various elective surgical procedures. This study was a prospective, randomized, and clinical comparison study in rural tertiary referral health center. The Sample size for the study was 40 generated using a sample size calculator. The study participants were divided into two groups of 20 each lidocaine and control group. A study patient (Group B) who was received 100 mg of 10% topical lidocaine sprays, (each puff of which delivers 10 mg of the drug). Patients received a total dose of 100 mg. half of which i.e. 50 mg. (5 puffs) was sprayed over laryngotracheal mucosa 10-15 minutes before induction by using tongue depressor, and the rest (5 puffs containing 50 mg. of drug) was given while doing laryngoscopy and intubation. In Group A, who was received only prescribed premedication and listed in control group (Group-A). All patients were monitored heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) with respect to time. All patients were kept unaware of the drug injected to enable double-blinding.

**Results:** In Group A (control group) the maximum increase in PR (**P. Value**-<0.001), blood pressure and MAP occurred at 1 min. post intubation and this gradually returned to baseline over the next 5-10 minutes. Group B (10% Lidocaine Spray) was very effective in obtunding the hypertension as well as tachycardia in response to laryngoscopy and intubation as compared with control group.

**Conclusion:** In present study show the maximum increases in parameters occur at 1 minute post intubation with values returning to baseline at 10 min post intubation in case of pulse rate and at 5 minutes post intubation in case of systolic, diastolic and mean arterial pressure. 10% Lidocaine spray provided consistent and reliable protection from increases in pulse rate, blood pressure, & mean arterial pressure and is most reliable drug for attenuation of cardiovascular response to laryngoscopy and intubation under G.A. without any complication when used in proper doses and time.

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INTRODUCTION

The procedure of laryngoscopy and intubation is an integral part of modern day balanced anesthesia. It is also the most delicate phase in general anesthesia. It is performed for most of the major and some minor surgical procedures. The procedure of direct laryngoscopy and intubation is associated with significant hemodynamic changes such as increase in

heart rate, arterial pressure and dysarrhythmias in up to 90% of the patient (REID LC et al 1940). Unfortunately these are often overlooked during clinical anesthesia as the anesthesiologist may be so engaged in the technical aspects of intubation that he has little opportunity to note any abnormal circulatory reaction unless it is severe or prolonged.

This increase in pulse rate and blood pressure are usually transitory, variable and unpredictable. Transient hypertension and tachycardia are probably of no consequence in healthy individuals but some patients unquestionably require careful

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hemodynamic control during anesthesia and intubation of the trachea. Mostly these are patient with known or suspected ischemic heart disease, recent myocardial infarction and those with hypertension. The complications that may occur because of this sudden rise in blood pressure include left ventricular failure (Masson 1946), myocardial ischemia (Editorial BJA 1969), cerebral hemorrhage (Davidson 1986) and even sudden death.

These cardiovascular changes had initially been ascribed to be due to vago-vagal reflex or due to stimulation of cardiac response. Subsequently it has been postulated that these reflexes are mediated by increased sympathetic nervous system activity. This is reflected by an increase in the level of circulating catecholamines especially noradrenalin. The stimulation of the sympathetic system occurs due to laryngoscope pressing the base of the tongue or lifting the epiglottis thus stimulating the mechanoreceptors in the proximal part of the trachea. Over the period of time various approaches have been advocated ranging from minimizing the duration of laryngoscopy (to less than 15 second) and the use of various pharmacological agents to reduce the extent of these potentially harmful responses.

Lidocaine is the oldest and most widely used drug for the purpose of attenuating pharyngeal and laryngeal reflexes. It is particularly suitable for this purpose because of its rapid onset and short duration of action which is compatible with the duration of this pressor response. It is used topically as laryngotracheal spray or by intravenous route.

Other drugs that have been postulated for attenuation of these pressor responses include intravenous narcotics like Fentanyl, Alfentanil (KAY B 1985 ) and various antihypertensive agents such as beta blockers (PYRS PROBERS C.et al 1973), ganglion blockers (SEIDLECKI 1975 ), central sympatholytics like clonidine (ORKO ct al 1987 ), calcium channel blockers, ACE inhibitors and peripheral vasodilators like nitroprusside and hydralazine (CURREN 1980 KAMRAS 1986 ).None of these pharmacological approaches has proved entirely satisfactory because the response may not be completely blocked or the method itself carries some additional risk. The agent used may have too long action or have unfeasible side effects.

Therefore, there exists an ongoing search for ideal agents for attenuating cardiovascular response to laryngoscopy and intubation. The aim of the present study was to compare the hemodynamic effects of sublingual Nifedipine in healthy normotensive patients during general anesthesia and to study the hemodynamic and electrocardiographic changes of these patients during laryngoscopy and tracheal intubation.

### **Aims and Objectives**

To study the hemodynamic changes associated with induction of general anesthesia and evaluate the efficacy of 100mg of 10% topical lidocaine spray for attenuating stress response during laryngoscopy and endotracheal intubation.

## **MATERIAL AND METHOD**

This is a prospective, randomized control study was conducted during the period from June 2017 to May 2019, In the Department of Anesthesiology and Critical Care, Rama Medical College, Hospital and Research Centre, NH-9, Pilkhuwa, Hapur after approval by the hospital ethics committee on 40 normotensive ASA Grade I & II .They were

randomly divided into two groups of 20each(Lidocaine and Control group) and Cardio-Vascular response like pulse rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure monitoring and analysis after laryngoscopy and intubation.

### **Criteria for Selection of Patients**

All patients underwent a thorough pre anesthetic checkup comprising of general physical examination, systemic examination and routine investigations. Other investigations were conducted whenever required,

Following investigations were routinely performed.

- |               |                          |
|---------------|--------------------------|
| -Hemoglobin % | -Blood Sugar Random      |
| - TLC, DLC    | -Blood Urea.             |
| - ESR         | - E.C.G                  |
| - BT/CT       | -Chest X-Ray- P. A. View |
| - Urine R/M   |                          |
| - LFT         |                          |

Selected patients were of both sexes, 20-60 years old and of ASA Grade I & II only.

### **Exclusion Criteria**

Following patients were not included in the study:-

1. Patients not willing for research
2. Patient suffering from renal, hepatic or psychiatric illness.
3. Patients with a history of hypertension, diabetes mellitus, bronchial asthma.
4. Patient on medication with any cardio –vascular diseases.
5. Patient with addiction to any drugs particularly narcotics.

## **METHODOLOGY**

After obtaining informed consent patients were randomly divided into 2 groups (A & B) of 20 each.

### **Pre-medication**

Uniform premedication was done in both groups with tablet diazepam 5 mg on the night before surgery and with Inj pethidine 1 mg /kg, Inj Phenergan 0.5 mg / kg I.M. 45 min. before induction of general anesthesia.

### **Group A**

Patient in this group only received the premedication and formed the control group.

### **Group B**

Patients in this group were given 100 mg. topical 10% Lidocaine Spray, (each puff of which delivers 10 mg of the drug). Patients received a total dose of 100 mg. half of which i.e. 50 mg. (5 puffs) was sprayed over laryngotracheal mucosa 10-15 minutes before induction by using tongue depressor, and the rest (5 puffs containing 50 mg. of drug) was given while doing laryngoscopy and intubation.

### **Induction and maintenance of anesthesia**

Baseline parameters were recorded in operation room. The patient was pre oxygenated for 3 minutes with 100% oxygen. Induction was done with injection thiopentone sodium (5 mg/kg) I/V followed by injection succinylcholine (1.5 mg / kg) I/V. Endotracheal intubation was carried out with optimal size

endotracheal tube and maintained with oxygen, nitrous oxide and injection vecuronium (0.1 mg /kg) I/V with Bain's or closed circuit. At the end of surgery reversal was done with injection atropine 0.02mg /kg and injection neostigmine 0.05mg / kg I/V.

**Following Parameters Were Observed For the Study**

1. Pulse rate (PR)
2. Blood Pressure – Systolic(SBP) and Diastolic (DBP)
3. Mean Arterial Pressure (MAP)
4. SPO<sub>2</sub> %
5. E.C.G

The readings were recorded at the following intervals:-

- Just before giving drugs ( baseline values, B.V)
- After giving drugs (before induction, B.I )
- After induction, (A.I)
- Just after laryngoscopy and intubation, (L&I)
- Post intubation at 1<sup>st</sup> (I<sub>1</sub>), 3<sup>rd</sup> (I<sub>3</sub>), 5<sup>th</sup> (I<sub>5</sub>), 10<sup>th</sup> (I<sub>10</sub>), 15<sup>th</sup> (I<sub>15</sub>) and 30<sup>th</sup> (I<sub>30</sub>) Minute intervals.

Adverse effects if any were recorded. All the above information was recorded in a Performa.

**Analysis of Data**

After completion of the study observations were tabulated qualitatively and quantitatively and analyzed using proper statistical methods.

**OBSERVATIONS AND RESULTS**

The present study was conducted in 40 patients of both sexes, age group 20-60 yrs., scheduled for elective surgery under general anesthesia at Rama Medical College Hospital & Research Centre, NH-24, Pilkhuwa, Hapur. Demographic data are shown in table 1, 2 and 3.

**Table No 1** Distribution of Patients

S. No.	Group	No. Of patient	Dose of drug
1	A	20	Control group
2	B	20	10% topical Lidocaine spray

**Table no 2** Age Distribution

S. No	AGE GROUP	GROUP A	GROUP B	TOTAL
1	20-30	10	6	16
2	31-40	8	9	17
3	41-50	1	4	5
4	51-60	1	1	2
	TOTAL	20	20	40

**Table no 3** sex distribution

S. NO.	GROUP	NO. OF PAT.	SEX	
			MALE	FEMALE
1	A	20	4	16
2	B	20	1	19
	TOTAL	40	5	35

**Table no 4** Weight Distribution

S. No	WEIGHT	GROUP A	GROUP B	TOTAL
1	30-40	3	3	6
2	41-50	8	4	12
3	51-60	5	6	11
4	> 61	4	7	11
	TOTAL	20	20	40

The majority of the patients were in the range of 20-40 years in both the groups and weight of the patients was between 40 to 60 kg in control and study group.

**Table No 5** Mean Pulse Rate in two Groups at Relevant Recording Time

Group	B.V.	V.I.	A.I.	L&I	I <sub>1</sub>	I <sub>3</sub>	I <sub>5</sub>	I <sub>10</sub>	I <sub>15</sub>	I <sub>30</sub>	
A (Control)	Mean	87.05	87.05	99.95	103.65	119.65	109.05	100.40	98.85	89.75	87.55
	S.D	7.69	7.69	5.51	5.82	9.03	9.81	5.91	5.40	5.50	5.61
B (10% topical Lidocaine spray)	Mean	103.80	103.30	102.40	102.65	110.35	103.25	101.00	101.05	100.55	101.05
	S.D	9.09	8.01	9.14	9.12	5.75	6.57	5.55	4.42	4.35	4.15

**Table No 6** Statistical Analysis of Mean Pulse Rate In Two Groups At Relevant Recoding Time And Their Comparison With Baseline Value

Group	P. Value	B.V- B.I	B.V- A.I	B.V- L&I	B.V- I <sub>1</sub>	B.V- I <sub>3</sub>	B.V- I <sub>5</sub>	B.V- I <sub>10</sub>	B.V- I <sub>15</sub>	B.V- I <sub>30</sub>
A (Control)	--	<0.001	<0.001	<0.001	<0.001	<0.05	<0.05	>0.05	>0.05	>0.05
B (10% topical Lidocaine spray)	--	H.S.	H.S.	H.S.	H.S.	S.	S.	N.S.	N.S.	N.S.
	P. Value	>0.05	>0.05	>0.05	<0.05	>0.05	>0.05	>0.05	>0.05	>0.05
	Significance	N.S.	N.S.	N.S.	S.	N.S.	N.S.	N.S.	N.S.	N.S.

S=Significant, N.S. = Non Significant, H.S. = Highly Significant

In GROUP A (control) the rise in mean pulse rate was statistically highly significant after induction, at laryngoscopy & intubation and at 1 & 3 minutes post intubation and it was significant at 5 & 10 minutes post intubation.

In GROUP B (10% Lidocaine spray) the statistically non-significant changes from basal value were observed at all recording interval except at 1 minute post intubation when a significant an increase in the mean pulse rate was observed.

**Table No. 7** Mean Systolic Blood Pressure In Two Group At Relevant Recording Time

Group	B.V.	B.I.	A.I.	L & I	I <sub>1</sub>	I <sub>3</sub>	I <sub>5</sub>	I <sub>10</sub>	I <sub>15</sub>	I <sub>30</sub>	
A (Control)	Mean	128.80	128.80	127.30	139.40	165.40	145.00	134.30	130.30	129.10	127.70
	S.D	10.29	10.29	13.30	11.46	16.44	8.17	9.61	8.74	8.32	9.59
B (10% topical Lidocaine spray)	Mean	132.70	128.00	118.10	131.50	137.90	130.90	128.00	127.10	128.70	131.40
	S.D	11.11	8.31	11.65	12.22	12.18	7.35	8.31	7.72	8.16	7.76

**Mean systolic blood pressure**

In GROUP A (control) the rise in mean systolic blood pressure was statistically highly significant after laryngoscopy and intubation at 1min. post intubation and significant at 3 & 5 min. post intubation.

In GROUP B (10% Lidocaine spray) statistically significant fall in mean systolic blood pressure was seen after induction while the change in the rest of the values was non-insignificant when compared with the basal value.

**Table No. 8** Mean Diastolic Blood Pressure in Two Groups At Relevant Recording Time

Group	B.V.	B.I.	A.I.	L & I	I <sub>1</sub>	I <sub>3</sub>	I <sub>5</sub>	I <sub>10</sub>	I <sub>15</sub>	I <sub>30</sub>	
A (Control)	Mean	77.50	77.50	76.50	81.95	96.40	87.50	81.70	79.40	76.30	75.30
	S.D	6.39	6.39	5.91	9.62	8.62	3.78	6.03	5.73	4.91	4.65
B (10% topical Lidocaine spray)	Mean	78.20	77.20	75.80	81.60	84.50	78.20	76.20	79.10	79.80	79.40
	S.D	7.08	6.47	7.97	8.52	7.05	6.71	5.84	6.44	5.69	5.88

**Mean Diastolic Blood Pressure**

In GROUP A (control) there was a statistically highly significant increase in the mean diastolic blood pressure at 1 & 3 minutes post intubation and significant increase subsequent to laryngoscopy and intubation and at 5 minutes post intubation.

In GROUP B (10% xylocaine spray) statistically significant increase in mean diastolic blood pressure was observed only at 1 minute post intubation.

**Table No 9** Mean of Arterial Blood Pressure in Two Groups at Relevant Recording Time

Group		B.V.	B.I.	A.I.	L&I	I <sub>1</sub>	I <sub>3</sub>	I <sub>5</sub>	I <sub>10</sub>	I <sub>15</sub>	I <sub>30</sub>
A (Control)	Mean	94.70	94.70	93.50	101.10	119.50	106.60	99.25	96.45	93.95	92.75
	S.D	6.83	6.83	7.19	9.54	10.25	4.03	5.73	5.38	5.16	5.77
B(10% topical Lidocaine spray)	Mean	96.35	94.05	89.90	98.30	102.20	95.80	93.40	95.00	96.15	96.75
	S.D	7.19	5.78	8.32	9.14	7.93	6.41	6.42	5.53	5.63	5.90

In GROUP A an increase in mean arterial pressure from basal was observed which was statistically significant at laryngoscopy & intubation, 5 min post intubation and highly significant at 1 & 3 min post intubation.

In GROUP B there was a statistically significant decrease in mean arterial blood pressure after induction and significant increase at 1 min post intubation.

### ECG Changes

Sinus tachycardia was seen in all cases and no other abnormality was seen in ECG throughout the study.

### SPO<sub>2</sub> Changes

In all the cases SPO<sub>2</sub> was 98 % or more throughout the study.

### Complication

No adverse effect of any drug and no complication was observed in the study.

## DISCUSSION

The most vital element in providing safe anesthesia is the maintenance of a patent airway. Laryngoscopy and endotracheal intubation is the routinely performed procedure to ensure an intact airway and hence form an integral part of modern day balanced anesthesia.

The procedure of laryngoscopy and intubation is associated with significant hemodynamic changes and attenuation of these has attracted the attention of anesthetists for more than half a decade. Reflex cardiovascular response to laryngoscopy and intubation are tachycardia and hypertension were reported by King (1951). There is a positive increase in sympathoadrenal activity and definite increase in plasma adrenaline, noradrenaline and dopamine levels in patients undergoing endotracheal intubation [20]. The reason for this is an occasional sudden death following intubation, tachycardia, hypertension and arrhythmias. These cardiovascular changes though transient may be potentially dangerous especially in hypertensive patients and develops pulmonary edema, cardiac failure and cerebral vascular insufficiency (Fox et al 1977) [12], abnormal rhythms [4],[18] and myocardial ischemia [6].

Over the period of time various approaches have been advocated, ranging from minimizing the duration of laryngoscopy to less than 15 seconds to the use of various pharmacological agents but none has been found to be ideal alone so far. Therefore the pursuit of an ideal agent for the suppression of cardiovascular response to intubation without altering the normal physiology continues.

Lidocaine is directly effect on myocardial depressant, a central stimulant, a peripheral vasodilating and finally an effect on synaptic transmission [1]. There was no indication that the cardiovascular symptoms during laryngoscopy and intubation are caused by systemic stress. An explanation may be a direct neural impulse via sympathetic efferents to the heart. On the other hand, topical application of lidocaine did prevent coughing and cardiac irritation, and the increase in HR was

attenuated [2] those patients who had received lidocaine prior to endotracheal intubation showed minimal cardiovascular changes [3]. Topical analgesia for tracheal intubation using lignocaine is described based on spraying the pyriform fossae to effect a superior laryngeal nerve block combined with topical analgesia of larynx and trachea which avoids excessive exposure of the lower airway to the local analgesic [5]. The effects of lidocaine on induction haemodynamic variables have varied [14]. Lidocaine, which decreases MAC by 10 to 28 per cent, t7 reduced STP requirements by 13.3 per cent. Hemodynamic values were significantly modified by lidocaine given 4.27 - 0.25 rain (mean +- SD) before intubation [7]. Lidocaine alters the response to laryngoscopy and intubation by obtunding laryngeal reflexes [8]. In younger adults the optimal time to administer IV lidocaine before intubation is approximately three minutes and lidocaine given one, two and five minutes before intubation had no beneficial effect [10]. The complications occurred frequently among the patients given lidocaine with 34 per cent of them having tinnitus. The reported incidence of side effects from similar doses of IV lidocaine varies from 0 to 100 per cent [10], [11]. Prophylactic therapy with diltiazem-lidocaine combination is more effective than diltiazem or lidocaine alone for attenuating the cardiovascular changes associated with tracheal intubation in hypertensive patients [13]. Only esmolol provided consistent and reliable protection against increases in both heart rate and systolic blood pressure accompanying laryngoscopy and intubation [16]. With less-than-optimal anesthetic management, cardiac arrhythmias can be a warning that the patient is in physiologic or pharmacologic distress and that rapid remedial action is necessary [17]. Only the combination of lidocaine and esmolol attenuated both HR and BP responses to tracheal intubation [18]. Inhalation of lidocaine 120 mg prior to induction of anesthesia is an effective, safe, and convenient method to attenuate the circulatory response to laryngoscopy and endotracheal intubation [19].

The aim of the present study was to compare the hemodynamic effects of 10% Lidocaine Spray in healthy normotensive patients during general anesthesia and to study the hemodynamic and electrocardiographic responses to laryngoscopy and tracheal intubation.

### Group A (Control)

After induction there was a highly significant increase in PR, and a non-significant decrease in the SBP and MAP.

Just after laryngoscopy and intubation there was a highly significant increase in PR, SBP, DBP and MAP. At 1 min post intubation a highly significant increase was observed in all the parameters from the basal value.

At 3 min post intubation there was highly significant increase in PR, DBP and MAP, though a decrease was seen in the SBP. It was still significantly higher than the basal value. At 5 minutes post intubation a gradual decline was seen in all the parameters with SBP, DBP and MAP reaching the basal value by 10 minutes post intubation and PR by 15 minutes post intubation.

### Group B (10% Xylocaine Spray)

In the present study after pre-treatment with 10% Xylocaine Spray 100 mg. a statistically non significant fall was observed in PR, SBP, DBP and MAP.

After induction there was a statistically significant fall in SBP, MAP while there was a decrease in PR and DBP from the baseline value though it was statistically non-significant.

Just after laryngoscopy and intubation statistically non significant rise was observed in DBP and MAP when compared with the baseline. At 1 minute after laryngoscopy and intubation a statistically significant increase in the mean systolic blood pressure which was statistically non significant. There after a steady, statistically non significant fall occurred in all the parameters reaching the baseline value 3 minutes post intubation. There was a non significant change from the baseline in rest of the reading obtained at further recording intervals.

### Summary

The present study is to assess and compare the efficacy of 100 mg. topical 10% Xylocaine Spray for attenuation of cardiovascular stress responses to laryngoscopy and intubation during general anaesthesia. Forty normotensive adult patients of either sex, undergoing elective surgery under general anesthesia with ASA grade 1 & 2 were included. They were randomly divided into two groups.

### Group A

Patient in this group received the premedication only and formed the control group.

### Group B

Patients in this group were given 100 mg. topical 10% Xylocaine Spray, (each puff of which delivers 10 mg of the drug). Patients received a total dose of 100 mg. half of which i.e. 50 mg. (5 puffs) was sprayed over laryngotracheal mucosa 10-15 minutes before induction by using tongue depressor, and the rest (5 puffs containing 50 mg. of drug) was given while doing laryngoscopy and intubation.

All patients received uniform premedication with tablet diazepam 5 mg HS on the night before surgery and Inj Pethidine 1 mg / kg i.v. and Inj Phenergan 0.5 mg / kg i.v., 45 minutes before induction.

In both groups baseline parameters were recorded in operation room. All the patients were pre- oxygenated for 3 minutes with 100% oxygen with a face mask. Induction was done with Thiopentone sodium (3-5 mg/kg) I/V slowly till loss of eyelash reflex followed by injection Succinylcholine (1.5 mg / kg) I/V. Intubation was then carried out with endotracheal tube. General anesthesia was maintained with Oxygen, Nitrous oxide and injection Vecoranium (0.08 to 0.1 mg/ kg) I/V using Bain's or closed circuit under controlled ventilation.

The clinical parameters studied were pulse rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure product, SPO<sub>2</sub> and ECG. The values recorded after premedication and before pretreatment with study drug were taken as basal reading. Then parameters were recorded after pretreatment, after induction, just after laryngoscopy and intubation and at specified intervals of 1,3,5,10,15 and 30 minutes post intubation.

The observations were recorded, tabulated, interpretation and discussed in detail to draw conclusions. On statistical analysis in Group A (control Group) the maximum increase in PR, blood pressure and MAP occurred at 1 min. post intubation and this gradually returned to baseline over the next 5-10 minutes. Group B (10% Xylocaine Spray) was very effective

in obtunding the hypertension as well as tachycardia in response to laryngoscopy and intubation as compared with control group.

### CONCLUSION

Laryngoscopy and intubation are associated with significant increases in pulse rate, blood pressure, mean arterial pressure, and sinus tachycardia. In present study show the maximum increases in parameters occur at 1 minute post intubation with values returning to baseline at 10 min post intubation in case of pulse rate and at 5 minutes post intubation in case of systolic, diastolic and mean arterial pressure. 10% Lidocaine spray provided consistent and reliable protection from increases in pulse rate, blood pressure, & mean arterial pressure and is most reliable drug for attenuation of cardiovascular response to laryngoscopy and intubation under G.A. without any complication when used in proper doses and time.

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