Original Research Article

Effect of haemodynamic response to laryngoscopy and endotracheal intubation with intravenous lornoxicam - A double blinded control

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Abstract

Aim: The aim of present study is to evaluate the efficacy of Lornoxicam in attenuating haemodynamic response to laryngoscopy and intubation in a placebo controlled double blinded study. **Materials and Methods:** A clinical comparative study of attenuation of sympathetic response to laryngoscopy and intubation was done in 60 patients posted for elective surgery. 60 cases are divided in to two groups 30 in each group. Group-1 was control group. Group-2 was lornoxicam group. **Results:** In group-1, a maximum increase in heart rate of 32.5%, increase in systolic and diastolic blood pressure of 41% and 34.6% respectively, increase in mean arterial pressure of 38.5%, rate pressure product of 87% was observed after 1 min of laryngoscopy and intubation. In group-2, a maximum increase in heart rate of 9.3%, increase in systolic and diastolic blood pressure of 13.5% and 7.6% respectively, increase in mean arterial pressure of 11.8%, rate pressure product of 22.4% was observed after 1 min of laryngoscopy and intubation. Which is statistically significant in all hemodynamic parameters. **Conclusion:** This study concludes that in patients with no drugs to attenuate the sympathetic response to laryngoscopy and intubation the maximum raise in heart rate, systolic, diastolic and mean arterial blood pressures were statistically and clinically very highly significant and can be detrimental in high risk patients.

Key Words: laryngoscopy, endotracheal.

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INTRODUCTION

Endotracheal intubation has become an integral part of anaesthetic management and critical care since its description in 1921 by Rowbotham and Magill[1]. In 1940 Reid and Brace first described haemodynamic response to laryngoscopy and intubation due to noxious stimuli[2] Evidence from laboratory data demonstrates that epipharyngeal and laryngopharyngeal stimulation augments cervical sympathetic activity in efferent fibres of the heart[3]. Even though the elevation in blood pressure and heart rate due to laryngoscopy and intubation are brief, they may have detrimental effects in high risk patients including myocardial infarction, cardiac failure, intracranial hemorrhage and increases in intracranial pressure. Laryngoscopy and tracheal intubation induces changes in circulating catecholamine levels significantly. Norepinephrine, epinephrine and dopamine levels rise, but the raise in norepinephrine levels is consistently associated with elevation of blood pressure and heart rate. Some authors infact consider the intubation period as one of the greatest risk phase in the surgical patients with coronary artery disease and patients with intracranial aneurysms. Although the response may be transient, it is invariable, significant, often persistant and of great concern. The techniques of laryngoscopy and tracheal intubation are not confined only to the operating room, but are also employed for non anaesthetic purposes. Few instances are diagnostic laryngoscopy, fibreoptic

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bronchoscopy, intubation may be required for prevention of aspiration and protection of airway and during mechanical ventilation. All these procedures can also produce sympathetic responses and one should keep in mind that many of these patients are critically ill and at increased risk. Hence it is important to find an effective means of attenuating sympathetic responses to laryngoscopy and tracheal intubation. Many strategies have been advocated to minimise these hemodynamic adverse responses and aimed at different levels of the reflex arc[4]. Block of the peripheral sensory receptors and afferent input i.e. topical application and infiltration of local anaesthetic to superior laryngeal nerve. Block of central mechanism of integration and sensory input – fentanyl, morphine etc. Block of efferent pathway and effector sites i.v. lignocaine, b blockers, calcium channel blockers, hydralazine etc. No single drug or technique is satisfactory[4] Recommendations for attenuating the reflex hypertension and tachycardia are therefore manifold. The technique besides minimising the cardiovascular responses to anaesthesia for patients at risk must also satisfy the following requirements. It must be applicable regardless of patient's collaboration. It should prevent impairment of cerebral blood flow and avoid arousal of the patient. It should neither be time consuming nor affect the duration or modality of ensuing anaesthesia. The present study is to evaluate the efficacy of Lornoxicam in attenuation of pressor response to laryngoscopy and intubation with minimal side effects and better pharmacological profile.

MATERIALS AND METHODS

A clinical comparative study of attenuation of sympathetic response to laryngoscopy and intubation was done in 60 patients posted for elective surgery. Study was conducted in Gandhi Hospital, Secunderabad after obtaining approval of the hospital ethical committee and written informed consent from the patients. General anaesthesia was provided with endotracheal intubation in all patients. Patients undergoing various orthopaedic, ENT, gynaecological, general, surgical, neurosurgical and laparoscopic procedures were selected.

Inclusion Criteria: Patients scheduled for elective surgeries, age between 20 to 50 years of both the sexes, patients with ASA grade I and II, mallampati airway assessment of grade I and II.

Exclusion Criteria: Those who had taken drugs that could influence haemodynamic and autonomic function, patients with risk of pulmonary aspiration, predictably difficult airways, successful intubation after more than one attempt, obesity (BMI>30) and patients with known allergy to NSAIDS, patients with renal or hepatic dysfunction. Patients were selected after thorough preanaesthetic assessment and investigations. An informed consent was taken in all the patients. 60 cases are divided in to two groups 30 in each group. Group-1 was CONTROL group. In this group placebo i.e. (Normal saline-4ml) was administered 30 min before intubation. Group-2 was LORNOXICAM group. In this group patients received lornoxicam, 16mg intravenous 30 min before intubation to attenuate pressor response to laryngoscopy and intubation.

Anaesthetic Technique: All the patients were preoxygenated with 100% oxygen for 3 minutes before induction. Induction was achieved with Inj. Thiopentone sodium 5mg/kg IV given in 2.5% solution. Inj. Glycopyrrolate 0.2mg IV was given along with Thiopentone. After induction of anaesthesia (loss of eyelash reflex), heart rate, systolic and diastolic blood pressures were recorded. Succinylcholine was administered at a dose of 2 mg/kg IV. Laryngoscopy was done using rigid laryngoscope with standard Macintosh blade. Intubation was done with appropriate sized, disposable, high volume low pressure cuffed endotracheal tube. Oral intubation was done for all surgical procedures. Laryngoscopy and intubation was done within 15 to 20 seconds. Heart rate, systolic and diastolic blood pressure were recorded at 1,3,5,10and15 minute intervals from the onset of laryngoscopy. In Group-1 Placebo (normal saline-4ml)was administered 30 min before intubation. In Group-2 Lornoxicam 16 mg was administered through intravenous route 30 min before intubation. Patients were connected to Bain's circuit and anaesthesia was maintained with oxygen (33%), N2O (67%), halothane 0.5% and non depolarising muscle relaxant vecuronium bromide at a dose of 0.05 mg/kg IV and IPPV. Adequacy of ventilation was monitored clinically and SPO2 was maintained at 99-100%. Positioning, epinephrine infiltration throat packing and surgery were withheld till the completion of recording. At the end of the surgery reversal was done with inj. Neostigmine 0.05 mg/kg and inj.Glycopyrrolate 0.01mg/kg IV. An observation was made related to adverse effects of drugs and anaesthesia related problems and were attended to appropriately. Descriptive data presented as mean ± SD and in percentage. Pair wise comparison between the groups was done by unpaired 't' test. For all values a 'P' value of <0.05 was considered as significant.

RESULTS

Table 1: Shows age distribution

Age	Control	Lornoxicam
Minimum	18	18
Maximum	50	50
Mean	31	28
Std. Deviation	8	8

The age range was 20-50 years for control and study groups. The mean values of age with standard deviation are 31±8 and 28±8 in control and Lornoxicam group respectively. There was no significant difference between two groups(p value>0.05).

Table 2: Shows sex distribution

Age	Control (Percentage)	Lornoxicam (Percentage)
Male	14 (46.6%)	14 (46.6%)
Female	16 (53.3%)	16 (53.3%)
Total	**30 (100%)**	**30 (%)**

In control group 46.6% were males and 53.3% were females. In Lornoxicam group also 46.6% were males and 53.3% were females. No significant difference was observed in sex wise distribution of the cases between the two groups (p>0.05). Mean ±SD of weight in control group is 59±7 when compared to 58±6 in Lornoxicam group. There is no much significant difference of weight distribution in two groups.

Table 3: Shows comparison of heart rate (in bpm) in between two groups

	Heart Rate				T-Test	
	Control		Lornoxicam			
	Mean±Sd	(%)Diff	Mean±Sd	(%)Diff	P Value	T Value
Baseline	83±8	-	86±12	-	0.2592	1.1393
15min Preinduction	86±7	3.61%	88±7.7	2.3%	0.2969	1.0527
30min Preinduction	87±7	4.8%	89±7.4	3.5%	0.2866	1.0754
Postinduction	89+8.2	7.22%	94±7.7	9.3%	0.0180	0.0180
1min	110±7.5	32.5%	94±7.5	9.3%	<0.0001*	8.2624
3min	102±8.2	22.8%	91±8.9	5.8%	<0.0001*	4.9786
5min	96±7	15.6%	89±7.1	3.5%	0.0003*	3.8454
10min	90±7	8.4%	85±7.1	1.2%	0.008*	2.7467
15min	82±7	1.2%	83±5	3.5%	0.5268	0.6367

The difference in the heart rate between control and lornoxicam groups remain significant at immediately after laryngoscopy and intubation and at 1min,3min and 5 min with p value being(<0.0001) and not much significant at 10 and 15 min post intubation. Maximum increase in heart rate is 32.5% in control group and 9.3% in lornoxicam group. It is statistically very significant with p value being(<0.001). These differences in heart rate between control group and lornoxicam group remains statistically very significant at all times except at 10th minute where it is statistically insignificant. At 1and 3 minutes post laryngoscopy the difference is very highly significant (p <0.001).

Comparison of Systolic pressure (mm of Hg) in two groups: At 5min,10 min and 15 min there is further fall in systolic blood pressure to 7.6%,3.4% and 1.7% of baseline. In comparison to control group and lignocaine group attenuation of systolic blood pressure is significant in Lornoxicam group. A rise in systolic blood pressure of 11.2% is observed in Lornoxicam group when compared to 41% increase in control group.

Comparison of Diastolic pressure (mm of Hg) in two groups: Immediately after induction there was 6.3% increase in diastolic blood pressure with mean of 84±12. After 1 min there was 7.6% increase from baseline. It came down to 3.8% at 3min with mean value of 82±7.1. It further came down to 1.3% and 3.8% at 5min and 10min with mean values being 78±6.6 and 76±9.4. At the end of 15min the mean values were 75±8.8 which is near to baseline. A maximum rise of 7.6% is observed in Lornoxicam group when compared to 34.6% increase in control group.

Table 4: Shows comparison of mean arterial pressure (in mm of Hg) in two groups

	Mean Arterial Pressure				T –Test	
	Control		Lornoxicam			
	Mean±Sd	(%)Diff	Mean±Sd	(%)Diff	P Value	T Value
Baseline	92±8	_	93±8.9	_	0.6489	0.4577
15min Preinduction	94±8	2.2%	92.8±7.5	0.2%	0.5513	0.5994
30min Preinduction	95±6	3.3%	94±7.3	1.1%	0.5644	0.5796
Postinduction	93±7	1.1%	103±10	10.8%	<0.001	4.4871
1min	127±8.5	38%	104±11	11.8%	<0.0001	9.0621
3min	117±7.1	27.2%	98±5.7	5.4%	<0.0001	11.4298
5min	109±8.1	18.5%	94±5.5	1.07%	<0.0001	8.4395
10min	95±6.8	3.3%	91±8.8	2.15%	0.0536	1.9700
15min	91±6.8	1.1%	89±8.2	4.3%	0.3081	1.0283

In lornoxicam group, 30 min pre-induction mean arterial pressures in this group was 93±8.9. At 15min and 30min after giving drug there was 0.2% and 1.1% change when compared to baseline. Immediately after intubation there was 10.8% increase from baseline with mean value being 103±10. At 1min after intubation there was 11.8% increase from baseline with mean value of 104±11. It decreased to 5.4% of baseline at 3min after intubation. It further decreased to 1.07% and 2.15% at 5min and 10 min after intubation respectively. At the end of 15min the mean arterial pressure mean being 89±8.2. Maximum increase in mean arterial pressure in Lornoxicam group is 11.8% compared to 38% increase in control group.

Table 5: Shows comparison of rate pressure product (mm of Hg) in two groups

	Rate Pressure Product				T-Test	
	Control		Lornoxicam			
	Mean±Sd	(%)Diff	Mean±Sd	(%)Diff	P Value	T Value
Baseline	10047±1432	_	10429±1532	_	0.3226	0.9977
15min Preinduction	10579±1297	5.3%	10674±1332	2.34%	0.7806	0.2799
30min Preinduction	10966±1122	9.14%	11016±1316	5.6%	0.8772	0.1553
Postinduction	10983±1348	9.3%	12564±1517	20.5%	<0.001	4.2671
1min	18870±1943	87%	12761±1381	22.4%	<0.0001	14.0367
3min	16355±1570	62.7%	11735±1289	12.5%	<0.0001	12.4571
5min	14189±1655	41.2%	11314±970.6	8.5%	<0.0001	8.2075
10min	11564±1619	15%	10357±984.4	0.7%	0.0009	3.4891
15min	10052±1088	0.05%	10026±847.3	3.9%	0.9181	0.1033

In lornoxicam group, Baseline rate pressure product before induction was 10429±1532 in this group. There was 2.34% and 5.6% change at 15min and 30min before induction. Immediately after intubation there was 20.5% increase with mean value being 12564±1517. After 1min following intubation the rate pressure product was 12761±1381 which was 22.4% from baseline. At 3min after intubation the value is 11735±1289 which was 12.5% from baseline. At 5min and 10min the values were 8.5% and 0.7% from baseline. At the end of 10min the rate pressure product is 10026±847.3 which is 3.9% from baseline. The maximum increase in rate pressure product of 22.4% in Lornoxicam group is compared to 87% increase in control group.

DISCUSSION

The sequence of induction anaesthesia, laryngoscopy and tracheal intubation are associated with marked haemodynamic changes and autonomic reflex activity which may be a cause of concern in many high risk patients. Laryngoscopy and intubation is associated with rise in heart rate, blood pressure and incidence of cardiac arrhythmias. These potentially dangerous changes disappear within 5 minutes of onset of laryngoscopy[5]. Although these responses of blood pressure and heart rate are transient and short lived they may prove to be detrimental in high risk patients especially in those with cardiovascular disease, increased intracranial pressure or anomalies of the cerebral blood vessels. An average rise in mean arterial pressure of 25mm Hg and 47.7 mmHg have been documented. An increase in mean arterial pressure of 26.5 mm Hg and 20 to 40 torr when compared with awake control levels and 35 to 60 torr when compared with preintubation values have been reported after placement of an endotracheal tube. A rise in mean heart rate of 29.9 beats/min has also been noted. Many factors influence the cardiovascular changes associated with laryngoscopy and intubation. Age, drugs, type and duration of procedures, depth of anaesthesia, hypoxia, hypercarbia etc., influence the pressor response. Variations of heart rate changes decrease with increasing age. Young patients show more extreme changes. Marked fluctuations in haemodynamic responses are often seen in geriatric patients. In our study we selected the optimal age range of 18 to 50 years. The hypothesis made before study is, Laryngoscopy and Intubation causes marked stress response caused because of release of catecholamines which is the cause of morbidity and mortality in patients who are chronically hypertensives or the patients with compromised cardiorespiratory reserve. Hence to attenuate this response many drugs have been studied and in use. Lornoxicam is one such drug which has minimal side effects and wide margin of safety which is found to attenuate the pressor response to laryngoscopy and intubation. Basal heart rates were measured in both he groups. Then heart rate was measured at 15min and 30 min before induction and then immediately after intubation and 1,3,5,10,15min there after. The values are compared in both the groups statistically the amount of significance was measured using(P- value). Maximum increase in heart rate in two groups: Group-1(control)-An increase of 32.5% was observed at 1min after laryngoscopy and intubation. Group-2 (Lornoxicam)-An increase of 9.3% was observed after 1min after

intubation. There was significant attenuation of increase in heart rate with Lornoxicam with P- value(<0.0001). Basal systolic and diastolic blood pressures, mean arterial blood pressure and rate pressure product were measured in both the groups. Then systolic and diastolic, mean arterial blood pressure and rate pressure product was measured at 15min and 30 min before induction and then immediately after induction and 1,3,5,10,15min after laryngoscopy and intubation there after. The values are compared in both the groups statistically the amount of significance was measured using(P-value). Maximum increase in systolic blood pressure in two groups: GROUP-1(control): A maximum increase of 41% from baseline was observed after 1min of laryngoscopy and intubation. GROUP-2(Lornoxicam): A maximum increase of 13.5% was observed 1min after intubation. Maximum increase in diastolic blood pressure in two groups: GROUP-1(control): A maximum increase of 34.6% from baseline was observed after 1min of laryngoscopy and intubation. GROUP-2(Lornoxicam): A maximum increase of 7.6% was observed 1min after intubation. Maximum increase in mean arterial blood pressure in two groups: GROUP-2(control): A maximum increase of 38.5% from baseline was observed after 1min of laryngoscopy and intubation. GROUP-2(Lornoxicam): A maximum increase of 11.8% was observed 1min after intubation. Maximum increase in rate pressure product in two groups: GROUP-1(control): A maximum increase of 87%% from baseline was observed after 1min of laryngoscopy and intubation. GROUP-2(Lornoxicam): A maximum increase of 22.4% was observed 1min after intubation. Raid W, Moussa A *et al*, [6] conducted a study in elderly individuals to evaluate the efficacy of lornoxicam in attenuation of intubation response. Fifty patients aged between 65 and 75 yr were randomly recruited to this randomized, double-blind, placebo-controlled study. They were divided into two groups to receive either Lornoxicam 8 mg or placebo half an hour before surgery. Systolic and diastolic blood pressure, mean arterial pressure, and heart rate were recorded before and after administration of the intravenous anaesthetic, also at 1, 3, 5 and 10 min after tracheal intubation found that this drug effectively suppresses pressor response when administered perioperatively. Daabiss M, Hashish M *et al* [7] conducted a study in 50 adult patients enrolled in to two groups. One group received 16mg of Lornoxicam intravenously and other group received placebo. Heart rate and mean arterial pressures were measured at 1min and every minute there after and measured catecholamine levels in blood at 1min and concluded that there was significant variation of haemodynamics in control group when compared to Lornoxicam group. Soliman W.R; Moussa A. *et al*[8] have done a study entitled "preoperative lornoxicam attenuates haemodynamic response to laryngoscopy and intubation". 50 elderly patients aged between 65-75 year, ASA class I and II enrolled in this study. All patients received no premedication. Patients randomly assigned intotwo groups using sealed enveloped technique, to received either Lornoxicam 8 mg or placebo in 5 ml covered syringe half hour before surgery. Anaesthesia was induced with fentanyl, propofol and atracurium to facilitate tracheal intubation. Systolic, diastolic, mean arterial blood pressure and heart rate were recorded before and after administration of the intravenous anaesthetic, also at 1, 3, 5 and 10 min after intubation. Abdel Ghaffar HS *et al* [9] have done a study to evaluate pre-incisional peritonsillar lornoxicam in paediatric post-tonsillectomy pain. A total of 68 patients (7-15 years), ASA I-II, scheduled for tonsillectomy divided into two groups (n = 34) to receive bilateral peritonsillar saline infiltration (placebo group) or peritonsillar saline infiltration in one tonsil (placebo side) and 8 mg lornoxicam in the other tonsil (intervention side; study group). Drugs were administered after induction of anaesthesia and before start of surgery. Concluded that the lack of significant complications suggests that pre-incisional peritonsillar lornoxicam followed by intravenous paracetamol rescue analgesia may be safe for tonsillectomy in children. Tsakiridis k *et al* [10] have conducted a study to evaluate the effect of lornoxicam in lung inflammatory response syndrome after operations for cardiac surgery with cardio-pulmonary bypass. 14 volunteers patients with ischemic coronary disease undergoing coronary artery bypass grafting were taken. In seven of them 16 mg lornoxicam was administered IV before the anesthesia induction and before the connection in heart-lung machine. In control group (7 patients) same amount of normal saline administered. Concluded that haemodynamics and respiratory parameters improved when compared to control group. Khan FA and Mahboobi SK[11], studied the effects of laryngoscopy and tracheal intubation on pulse pressure and the influence of age on this response. Two groups of 40 ASA I and II patients were included as young (18-25 years) and middle aged (45-55years) groups. Systolic, diastolic, mean arterial blood pressure and heart rate were measured pre-induction, 1,2, and 3 minutes after induction and every minute for 5minutes post intubation. No pulse pressure changes occurred in young group despite a significant increase in both systolic and diastolic blood pressure. The middle aged group showed an average rise of +18mm Hg of pulse pressure. These changes in pulse pressure during anaesthesia may indicate an additional pulsatile stress in vulnerable patients.

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CONCLUSION

This study concludes that in patients with no drugs to attenuate the sympathetic response to laryngoscopy and intubation the maximum raise in heart rate, systolic, diastolic and mean arterial blood pressures were statistically and clinically very highly significant and can be detrimental in high risk patients. Lornoxicam significantly attenuates the sympathetic response to laryngoscopy and tracheal intubation.

REFERENCES

1. Usha Saha, Jayalakshmi. T S. Pressor response and hypertension. Ind J. Anesth 2003; 47 :(6) : 443-449.
2. Karagoz AH, Basgul E, Celiker V, Aypar U. The effect of inhalational anaesthetics on QTc interval. Eur J Anaesthesiol 2005; 22(3): 171-4.
3. Lindgren L, Yli-Hankala A, Randell T, Kirvela M, Scheinin M, and Neuvoven PJ. Hemodynamic and catecholamine responses to induction of anaesthesia and tracheal intubation comparison between propofol and thiopentone. Br J Anaesth 1993; 70: 306-310.
4. Ismail S, Azam SI, Khan FA. Effect of age on hemodynamic response to tracheal intubation. A comparison of young middle aged and elderly patients. Anaesth Intensive Care 2002; 30(5): 608-14.
5. Onkar Singh, Kumar P, Swarn Kaur. Attenuation of the pressure response to laryngoscopy and tracheal intubation: comparison of beta blockers and calcium channel blockers. Ind J Anaesth 1993; 41: 320-324.
6. W Raid ; A Moussa :Lornoxicam attenuates haemodynamic response to laryngoscopy and intubation in elderly.European journal of Anaesthesiology,Vol25,Issue09,Sep 2008,p732-736.
7. Daabiss, M.; Hashish, M.; AlOtabi, et al(2010).Effect of lornoxicam on haemodynamic and catecholamine response to laryngoscopy and intubation.British Journal of Medical Practitioners, Vol. 3 Issue 3,p6-10.5p.
8. Soliman WR; Moussa A.A: Preoperative lornoxicam attenuates haemodynamic response to intubation in elderly, European Journal of Anaesthesiology: June 2007 - Volume 24 - Issue - p 193.
9. Abdel-Ghaffaer HS,Abdel –Azeem HG etal:Safety and efficacy of pre-incisional peritonsillar lornoxicam in paediatric post tonsillectomy pain:A prospective double blind,placebo controlled, split-body clinical study,Clin Otolaryngol.2015 jun :40(3);219-26.doi:10:1111/coa.12351.
10. Kosmas Tsakirdas, Paul zerogoulidis et al: Effect of lornoxicam in lung inflammatory syndrome after operations of cardiac surgeries with cardiopulmonary bypass, J Thorac Dis.2014 Mar;6(Suppl 1):S7-S20.
11. Khan FA and Mahboobi SK. Effect of laryngoscopy and tracheal intubation on pulse pressure and influence of age on this response. Anaesth Intensive Care 2004 Aug; 32(4); 535-41.

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