

A COMPARATIVE STUDY OF IV LIGNOCAINE VS ORAL CLONIDINE FOR ATTENUATION OF HAEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION

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ABSTRACT

Background: Laryngoscopy and tracheal intubation induce potentially harmful hemodynamic response. None of the advocated methods had been accepted as the most effective option. Ease of use and economical advantages of the suggested methods are also important considerations. This study was designed to address this concern by using two common drugs (intravenous lignocaine vs. oral clonidine).

Material and Method: A randomized, controlled, prospective, single blind study was planned involving 70 patients divided equally into two groups – Group C (patients received oral Clonidine 4 mcg/kg 90 minutes prior to intubation) and Group L (Patients received intravenous Lignocaine 2 mg/kg 3 minutes prior to intubation).

Observations: Focus was on hemodynamic parameters - Heart rate, Systolic, Diastolic, Mean blood pressures and Rate pressure product, however, sedation and anxiety score was also compared.

Results: Demographic profile and time taken for intubation was same in both the groups. Post intubation rise (>25 % from base line) in heart rate was observed more in Gr.L (54.28 %) as compared to 5.71 % in Gr.C. Systolic, diastolic and mean arterial blood pressure variations were observed more in Gr L (42.85 %, 25.71 % and 22.85%) as compared to Gr. C (2.85 %, 5.71 % and 2.85 %). Difference for all the above parameters was statistical significant (p -value < 0.05). However 40 % of patients were drowsy, 82.85 % of patients had dryness of mouth, two patients (5.71 %) had bradycardia and hypotension in Clonidine group, whereas such observations were not made in Lignocaine group.

Conclusion: Oral Clonidine at a dose of 4 mcg/kg body weight (up to a maximum limit of 200 mcg) therefore can be considered as better option than time tested intravenous Lignocaine

Key Words: Anaesthesia, Intubation response, Effective attenuation of laryngoscopic response, Lignocaine, Clonidine

INTRODUCTION

Haemodynamic fluctuations, higher myocardial oxygen demand and cardiac arrhythmia are undesirable but inevitable side effects of laryngoscopy and endotracheal intubation. This is a concern in all patients especially in patients with coronary artery disease, valvular heart disease, elevated intracranial pressure and cerebrovascular disease.

In 1951, King et al ¹ highlighted this and since then, numerous pharmacological agents (nitroglycerine ² fentanyl³ esmolol³

calcium channel blockers⁴ Magnesium⁵ lidocaine⁶ gabapentin⁷ have been tried to attenuate ill desired haemodynamic response. Clonidine, had also been used as simpler and cost effective alternative but failed to gain popularity despite ease of administration through oral route^{7,8}. This present study was designed to address the issue of attenuating effect of oral clonidine versus time tested intravenous Lignocaine on the haemodynamic response.

MATERIAL & METHOD

After taking approval from hospital's ethics committee, a randomized, prospective, single blind study was conducted in department of Anaesthesiology and Critical Care, Tata main hospital, Jamshedpur to compare the attenuating effects of oral Clonidine Vs intravenous Lignocaine on hemodynamic response to laryngoscopy and endotracheal intubation. Study was conducted between October 2010 and April 2013.

Inclusion Criteria: Patients (age range 20 to 60 years, ASA Grade 1 or 2, Body Mass Index ≤ 30 kg/m²) admitted in the hospital for elective surgery under general anaesthesia requiring endotracheal intubation were included

Exclusion Criteria: Anticipated difficult intubation, Hypertensive patients on alpha and or beta adrenergic receptor blockers, Patients with bronchospastic and major Cardiac diseases, pregnant patients, Patients with intracranial space occupying lesions, Patients requiring more than one attempt or more than 15 seconds for intubation

Randomization: was done by sealed envelope method.

Sample size calculation: A pilot study was done (with 5 patients in each group) and then assuming the power of study of 80 % with an α - error of 5 % and anticipated dropout rate of 2%, sample size of 32 patients in each group was advised and therefore, we included 35 patients in each group.

Anaesthesia technique: Standard 8 hour overnight fasting for solid foods and water per orally was allowed till 2 hours prior to the stipulated time of anaesthesia and surgery. All the study cases were kept first in the list so that administration of Clonidine (90 min. prior to intubation) would be convenient.

Premedication: No sedative was given at bed time the day before surgery.

Group L: Patients in this group were given, 10 mg oral Diazepam (to allay anxiety as Lignocaine doesn't have any anxiolytic effect) as per the body weight (0.20 mg/kg body weight and all patients were between 50 to 65 kgs), 90 min. before intubation. Intravenous Lignocaine at a dose of 2mg/kg body weight (diluted to 10 ml with distilled water) was administered 3 min. prior to intubation.

Group C: Patients were given Oral Clonidine 4 mcg/kg body weight (up to a max. of 200 mcg) 90 min. before intubation. Intravenous normal saline (10ml) was injected 3 min prior to intubation.

Monitoring: Electrocardiography, Noninvasive blood pressure (NIBP) monitor, Pulse oximetry, Capnography were attached and baseline parameters were noted. NIBP monitoring was done using Philips v24e bedside monitor.

Induction & Maintenance: All patients were preoxygenated. Intravenous Pethidine (1.5 mg/kg body weight) was administered followed by intravenous Thiopentone 2.5% (5 mg/kg body weight) and Suxamethonium hydrochloride (1.5 mg/kg body weight). Once the fasciculation disappeared, all patients were placed in sniffing position and then laryngoscopy was done with Macintosh laryngoscope blade of appropriate size followed by endotracheal intubation. Intubation was done by experienced anaesthesiologist who had atleast 5 years of experience after passing M.D or D.N.B and had done at least 50 consecutive successful laryngoscopies and endotracheal intubations. Anaesthesia was maintained as per hospital protocol. Hemodynamic parameters specifically for the study were monitored till 15 minutes after the intubation as per the protocol given below. No surgical stimulus was allowed during the study period. Beyond this time frame, routine monitoring and maintenance of anaesthesia were continued as per the need by the same anaesthesiologist but the data captured were not used for comparison of result.

Observation : Base line Heart rate, Systolic blood pressure, Diastolic blood pressure and Mean blood pressure were recorded after attaching the above mentioned monitors and

designated as B.L. Above mentioned parameters were again recorded after giving induction agents (designated as P.I), every minute for first 5 minutes after intubation (designated as T1 to T5 where the numbers 1,2,3,4,5 denotes readings at 1,2,3,4,5 minutes after intubation respectively) .This was followed by two more readings at 5 minutes interval till next 10 minutes (designated as T6 and T7). Rate pressure product was calculated by multiplying heart rate with systolic blood pressure and were noted at all point of times as mentioned above from BL to T7.

Intubation response: Defined as > 25 % increase in the hemodynamic parameter immediately after intubation from their baseline values. ¹¹

Statistical tools applied: All data were compiled and analyzed using SPSS version 14.0

- 1) Arithmetic mean
- 2) Standard deviation
- 3) Mann Whitney U test for comparison of demographic profile and duration of intubation (non-parametric data)
- 4) Chi square test with Yate's correction (χ^2 value) to compare inter- group hemodynamic parameters.
- 5) p-value- p- value of < 0.05 is considered as significant and p-value of < 0.01 is considered as highly significant.

With a degree of freedom of 1, χ^2 value of > 3.841 and > 6.635 corresponds to p-value of < 0.05 and < 0.01 respectively.

OBSERVATIONS & RESULT

Table 1: Comparison of demographic profile
(age, weight, height and B.M.I) in both groups (mean \pm std.dev)

	GROUP - L (mean \pm s.d)	GROUP - C (mean \pm s.d)	Mann Whitney U	p - value
AGE (in years)	40.40 \pm 18.38	42.88 \pm 16.97	537.00	0.37
WEIGHT (kg)	55.06 \pm 4.24	57.26 \pm 7.78	576.00	0.66
HEIGHT (cm)	157.23 \pm 3.54	155.60 \pm 0.71	550.00	0.46
B.M.I (kg/m ²)	22.25 \pm 2.87	23.43 \pm 3.46	456.00	0.06

After statistical analysis using Mann - Whitney U test, it was found that there was no significant difference (p value > 0.050) and the two groups were comparable in demography characteristics like age, sex, weight, height and body mass index (B.M.I)

Table 2: Duration of Intubation
(mean \pm std.dev) in both groups

	GROUP - L (mean \pm s.d)	GROUP - C (mean \pm s.d)	Mann whitney U	Z - value	p- value
DURATION OF INTUBATION (in seconds)	11.70 \pm 3.00	10.74 \pm 3.36	449.500	- 1.915	0.066

On statistical analysis using Mann Whitney U test , both the groups are found to be comparable and there is no statistical significant difference (p - value > 0.05)

Table 3 – Comparison of two groups in respect to all observed parameters (mean \pm std.dev) at nine points of time

		BL	PI	T1	T2	T3	T4	T5	T6	T7
HEART RATE	GR C	70.77 \pm 9.19	77.97 \pm 16.26	80.14 \pm 8.49	80.74 \pm 4.24	77.11 \pm 4.24	74.86 \pm 7.78	74.83 \pm 3.54	78.91 \pm 14.14	78.94 \pm 14.14
	GR L	89.14 \pm 11.31	99.14 \pm 17.68	114.74 \pm 12.73	109.97 \pm 14.14	105.37 \pm 11.31	96.14 \pm 8.49	94.03 \pm 10.61	91.69 \pm 16.97	90.83 \pm 12.02
SYSTOLIC BLOOD PRESSURE	GR C	118.14 \pm 2.83	109.29 \pm 2.12	122.20 \pm 1.41	120.86 \pm 3.54	116.17 \pm 7.78	110.94 \pm 16.97	108.46 \pm 12.02	108.57 \pm 0.71	117.77 \pm 7.78
	GR L	134.03 \pm 13.44	120.31 \pm 15.56	161.91 \pm 19.09	157.26 \pm 22.63	147.34 \pm 24.04	140.49 \pm 27.58	141.54 \pm 22.63	132.46 \pm 25.46	132.77 \pm 23.33
DIASTOLIC BLOOD PRESSURE	GR C	74.66 \pm 5.66	68.40 \pm 4.95	76.49 \pm 3.54	76.60 \pm 6.36	71.46 \pm 7.07	67.74 \pm 2.83	67.03 \pm 7.07	69.57 \pm 16.97	77.14 \pm 12.73
	GR L	81.54 \pm 7.78	74.31 \pm 8.49	97.86 \pm 8.49	95.23 \pm 18.38	88.94 \pm 18.38	84.63 \pm 14.85	82.66 \pm 19.09	80.57 \pm 11.31	82.29 \pm 5.66
MEAN BLOOD PRESSURE	GR C	89.15 \pm 2.83	82.03 \pm 2.59	91.72 \pm 1.89	91.35 \pm 3.06	86.36 \pm 2.12	82.14 \pm 3.77	80.84 \pm 0.71	82.57 \pm 11.55	90.69 \pm 11.08
	GR L	99.06 \pm 11.31	89.24 \pm 10.14	116.61 \pm 15.32	113.67 \pm 28.76	106.56 \pm 26.63	101.49 \pm 21.45	100.61 \pm 25.69	96.70 \pm 15.56	98.90 \pm 11.55
RATE PRESSURE PRODUCT	GR C	8380.94 \pm 1004.09	8525.31 \pm 1749.38	9885.03 \pm 1395.83	9825.29 \pm 1347.04	9010.34 \pm 633.57	8353.60 \pm 305.47	8208.71 \pm 263.04	8650.74 \pm 1909.19	9330.37 \pm 1873.13
	GR L	11952.69 \pm 67.88	11918.31 \pm 335.88	18573.09 \pm 687.31	17208.74 \pm 1714.03	15479.20 \pm 1815.85	13441.29 \pm 1623.52	13295.31 \pm 1693.52	12125.91 \pm 738.22	12068.74 \pm 511.95

Table 4: Comparison of effectiveness of both the agents in attenuating the haemodynamic response in respect to all observed parameters

		Intubation Response attenuated		χ^2 value after Yate's correction	p-value
		n	%		
HEART RATE	Gr. C	33	94.28	17.4	<0.01
	Gr. L	16	45.71		
SYSTOLIC BLOOD PRESSURE	Gr. C	34	97.14	13.70	< 0.01
	Gr. L	20	57.14		
DIASTOLIC BLOOD PRESSURE	Gr. C	33	94.28	3.86	< 0.05
	Gr. L	26	74.28		
MEAN BLOOD PRESSURE	Gr. C	34	97.14	4.58	< 0.05
	Gr. L	27	77.14		
RATE PRESSURE PRODUCT	Gr. C	25	71.42	23.53	< 0.01
	Gr. L	04	11.42		

COMPLICATIONS

All side effects monitored in this study were significantly more in clonidine group. Two patients had hypotension. One patient had profound hypotension (72/48 mm Hg). Despite initial fluid load and vasopressor support, patient did not show

marked improvement and therefore, according to study protocol, this patient was excluded from the study and was managed in critical care for 24 hours. Patient made uneventful recovery. A new patient was included on random basis in place of excluded patient to keep number of patients 35 in each group.

SIDE EFFECTS	GROUP - C		GROUP - L	
	N	%	n	%
DROWSINESS	14	40.00	0	0
DRYNESS OF MOUTH	29	82.85	0	0
BRADYCARDIA	2	5.71	0	0
HYPOTENSION	2	5.71	0	0

DISCUSSION

Effective attenuation of the sympathoadrenal stress response to laryngoscopy and endotracheal intubation is an important goal, especially in high risk patients. Several methods to attenuate this response had been tried so far, but an ideal and uniformly accepted method is still not available. Moreover certain orally available drugs like Clonidine had not been given due recognition by researchers despite certain obvious advantages and ease of administration. This study attempts to compare this drug with time tested intravenous lignocaine.

Wide variation in dose of lignocaine(1mg -3 mg/kg)^{6,12} and clonidine(2-6 microgram/kg)^{7,8,9} has been found. It was observed that 1- 1.5 mg /kg body weight intravenous lignocaine did not offer desired benefit^{6,12}. Increasing the interval, between lignocaine injection and laryngoscopy, from 1 to 2 and 3 minutes had also proved to be ineffective¹². Contrary to this lignocaine 2 mg/kg in isolated head injury patients had been found to be better alternative for attenuating haemodynamic pressor response⁶. Lignocaine 2 mg/kg body weight with injection - laryngoscopy gap of 3 minutes had also resulted in complete attenuation of pressor response.¹³ Based on these observations 2mg /Kg dose was selected in this study and lignocaine was injected 3 minutes prior to laryngoscopy. Pressor response attenuating dose of clonidine had also been a matter of debate. Various authors had used 2-4mcg/kg body

weight dose of clonidine with upper limit of 200 mcg. Higher dose of 300mcg caused higher incidence of perioperative hypotension¹⁴. Oral administration 90 min prior to induction had been found to be exerting satisfactory effect.^{7,8} Statistical analysis of the demographic parameters like age, sex, weight, height, body mass index showed that both the groups were statistically comparable (Table 1). It only supports that our method of randomization and selection was appropriate. Time needed for intubation despite its influences on hemodynamic response¹⁵ was ignored in the present study because duration of intubation was not significantly different (11.70 ± 3.00 seconds vs. 10.74 ± 3.36 seconds, p-value-0.06) in Lignocaine (Gr L) and Clonidine group (Gr C) respectively. (Table 2)

Variability in heart rate and blood pressures was compared at 9 time intervals ; baseline (B.L), post induction (P.I), post intubation at an interval of 1 minute for first five minutes (T1 to T5) and then at an interval of 5 minutes for next ten minutes (T6 and T7) ^{7,8,9}. More than 25 % rise in heart rate from baseline was considered as post intubation pressor response ¹¹. Baseline heart rate and Systolic blood pressure (SBP) was 70.77 ± 9.19 and 118.14 ± 2.83 respectively in group C. In group L, baseline heart rate and SBP was 89.14 ± 11.31 beats/min and 134.03 ± 13.44 mm Hg (p>0.05). (Table – 3). This difference, in favor of clonidine, could probably be attributed to better sedative and anxiolytic effect. Post intubation pressor response in heart rate

was observed in 5.72% in Gr C as compared to 54.29% in Gr L (p-value of < 0.01) (Table-5). The post intubation pressor response (>25 % increase from base line) was observed in 2.86 % patients in group C and 42.86 % patients in Gr L, which was statistically highly significant. (p<0.01) (Table- 4). In a comparative study, Dipak L Ravel et al⁸ claimed positive response in 6 % cases following Clonidine premedication, which was higher than the observation made in this study. In similar single arm study with Lignocaine, Levitt et al ⁶ had documented 29.82 % rise in the incidence of SBP at T1 interval. The post intubation pressor response got settled to base line value in 3 minutes in Gr C as compared to 10 minutes in Gr L (Table-3) in our study.

Post intubation (T1) rise in Diastolic blood pressure (DBP) in Gr. L (20.01 %) was statistically significant (p-< 0.01) in present study (Table – 3). Splinter and Cervenko¹⁶ had similar experience with 1.5 mg/kg i.v. lignocaine. Despite use of higher dose (2mg / kg) of Lignocaine, we failed to demonstrate beneficial impact of lignocaine on DBP which showed that lignocaine is ineffective in dealing with diastolic pressor response. On the contrary, in Clonidine group, DBP rise at T1 interval (2.45 %) was insignificant (p > 0.05) in our study (Table-3), which is consistent with the observation made by Dipak L Ravel et al (9.36 %) ⁸. Drop in DBP from T1 value to the base line value took 5 minutes in Gr L, whereas in Gr C the time taken was only 3 minutes (Table-3). Finding of Dipak L Ravel et al ⁸ in clonidine treated patients matched with our observation. Post intubation pressure response could be attenuated successfully in 94.28% of cases in Gr C and in 74.28% in Gr L with p-value <0.05 (Table-4).

Mean arterial blood pressure is a better parameter than systolic and diastolic blood pressure for monitoring tissue perfusion. The base line mean arterial blood pressure in group C was 89.15± 2.83 mmHg and in group L it was 99.06 ± 11.31mmHg (Table-3). Mean arterial blood pressure in group C returned to normal value in 3 min following intubation whereas it took more than 5 min in group L (p>0.05). Only 1 patient out of 35 (2.86 % of cases) in group C and 8 patients (22.86 % of cases) in group L crossed the post intubation pressor

response limit (>25 % rise from baseline). (Table – 4) This difference between the two groups was statistically significant (p-value<0.05). C.D.Miller¹², in his single arm study with Lignocaine, failed to appreciate effective attenuation of the pressor response in any of the patients. As compared to his study, we observed that in 77.14 % of patients, lignocaine could prevent the pressor response beyond the limit of 25 %. However, C.D.Miller¹² used 1.5 mg/kg lignocaine, which was lower than the dose used in our study (2mg/kg). This explains the difference in observation between the two studies.

Rate pressure product was calculated by multiplying heart rate with systolic blood pressure and it indicates myocardial oxygen demand. In group C, 10 out of 35 patients (28.58 % of cases) had more than 25 % increase in rate pressure product; where as in group L, 31 out of 35 patients (88.58 % of cases) had post intubation pressor response (Table-4). This difference between the two groups was statistically highly significant (p-value < 0.01). C.D.Miller et al ¹² failed to appreciate beneficial effect on rate pressure product following 1.5 mg/kg lignocaine .In comparison; we found that it was effective in 11.42 % patients. Variation in the observation can be explained by higher dose of Lignocaine (2mg/kg) used in our study. Similar comparison was not possible with Clonidine due to lack of any published study addressing this parameter. The rate pressure product decreased to its base line value within 4 min after intubation in group C whereas in group L it remained at a higher level than base line value even 15 min after intubation (Table-3).

CONCLUSION

Based on the results of our study, we suggest that although both the agents have potential to attenuate haemodynamic response to laryngoscopy and endotracheal intubation, oral Clonidine at a dose of 4mcg/kg is a better attenuating agent than intravenous Lignocaine 2mg/kg. Moreover, Clonidine offers other advantages such as ease of administration by oral route, sedative effect, anxiolytic effect and intraoperative haemodynamic stability. However, it was associated with dryness of mouth and

sedation in most of the patients along with bradycardia and hypotension in very few patients.

Oral Clonidine at a dose of 4 mcg/kg body weight (up to a maximum limit of 200 mcg) therefore can be considered as better option than time tested intravenous Lignocaine to attenuate the haemodynamic response to laryngoscopy and endotracheal intubation.

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LIMITATIONS

Oral Clonidine has got variable absorbtion and hence intravenous Clonidine would have been a better option in this study.

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