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International Journal of Current Research
Vol. 10, Issue, 01, pp.64149-64154, January, 2018

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

A COMPARATIVE STUDY TO EVALUATE EFFECT OF IV ESMOLOL AND DILTIAZEM TO ATTENUATE HAEMODYNAMIC RESPONSE TO LARNGOSCOPY AND INTUBATION

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ARTICLE INFO

Article History:
Received 16th October, 2017
Received in revised form
08th November, 2017
Accepted 21st December, 2017
Published online 19th January, 2018

Key words:
Yalova,
City Square,
Multi-purpose use,
Environmental Design.

ABSTRACT

Laryngoscopy and endotracheal intubation is integral part of anaesthesia, which is associated with sudden rise in heart rate, blood pressure, intracranial tension which is harmful in patients with poor cardiac reserve. We conducted study in 150 normotensive patients of ASA 1, 2 who are divided in three equal group of 50 each.Group C, Group E, Group D received normal saline, inj esmolol 2mg/kg, and inj diltiazem. 2mg/kg respectively 3 minutes before laryngoscopy. We measured heart rate, systolic blood pressure, diastolic blood pressure, and mean blood pressure as baseline before induction of anaesthesia,then after induction and 1,3,5, and 10 minutes after laryngoscopy and intubation. We observed for rise or fall in all parameters. Our results are calculated by paired, unpaired 't' test and 'chi square' test. Result showed that there is maximum attenuation of all parameters in esmolol group followed by diltiazem group, control group demonstrated maximum rise in all parameters. Thus we can conclude that esmolol offers better attenuation of haemodynamic response to laryngoscopy and intubation than diltiazem without any side effect

Citation: Rashmee Chavan, Sandeep Kadam and Girish, I. R. 2018. "A comparative study to evaluate effect of iv esmolol and diltiazem to attenuate haemodynamic response to larngoscopy and intubation", *International Journal of Current Research*, 10, (01), 64149-64154.

INTRODUCTION

Even in the recent era of supraglottic airway devices, rigid laryngoscopy and endotracheal intubation is a very essential tool in the hands of anaesthesiologists to provide better ventilation and airway control while providing general anaesthesia. It is extensively studied and proved that laryngoscopy and endotracheal intubation is associated with reflex sympathetic stimulation (Miller Forbs and Dally, 1970; Derbyshire and Smith, 1984) caused by pharyngeal and perilaryngeal stimulation which leads to increased catecholamine levels (Shribman *et al.,* 1987; Derbyshire *et al.,* 1983). With this there is sudden increase in heart rate, blood pressure, intraocular pressure and intracranial pressure and developments of arrhythmias (Miller Forbs and Dally, 1970; Bustein *et al.,* 1950). Although these effects are short lived they may have detrimental effect on high risk patients such as patients with coronary artery disease, uncontrolled hypertension, poor cardiac reserve, IHD intracranial aneurysms (Low *et al.,* 1986). From time to time many attempts have been made to find ideal technique or drug to attenuate this pressor response; to name the few: use of topical anaesthesia using lignocaine, iv lignocaine (Stoelting Robert, 1978), deep general anaesthesia (Miller Forbs, 1970), iv beta blockers like propranolol, esmolol (Siedlecki, 1975; Singh Onkar *et al.,* 1993), antihypertensive agents like pentolamine (Devault *et al.,* 1960), peripheral vasodilators like na nitroprusside (Stoelting Robert, 1979) and nitroglycerine (Fassoulaki and Kaniasis, 1983; Hood *et al.,* 2012), clonidine (Richard *et al.,* 1994), magnesium sulphate (Santosh Kumar *et al.,* 2003), narcotics like fentanyl alfentanyl (Black *et al.,* 1984). But not a single drug proved ideal, main disadvantages are there effect outlasts the purpose and short acting drugs required to be given as iv infusion by syringe pump and direct arterial pressure monitoring required e.g. iv nitroglycerine, na nitroprusside. Many authors have used iv esmolol a cardioselective beta blocker, with quick onset of action within 2-3 min and ultra short acting duration of action lasting for 9 min (Gorczynski, 1985; Allan *et al.,* 1985; Donald Weist, 1995) as a iv bolus and in infusion with variable results, (Singh *et al.,* 2012; Sharma *et al.,* 1996; Feng *et al.,* 1996; Liu *et al.,* 1986) they used lower doses like 0.5 mg/kg. Diltiazem is calcium channel blocker with potent peripheral and coronary vasodilation actions. It has onset of action within 2-5 mins and unlike other ca^{++} channel blockers it can be given as bolus (Chaffman and Broden, 1985; Henry, 1980). Our study is undertaken to determine the efficacy of iv esmolol bolus 2mg/kg a higher dose and iv diltiazem 0.2mg/kg bolus in attenuating the sympathetic response. The duration of action of Esmolols is 9 minutes which coincides with pressor response of laryngoscopy which also lasts for 10 minutes (Gorczynski, 1985; Miller Forbs, 1970). Also beta blockers are found to prevent perioperative cardiovascular events which is additional advantage.

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MATERIALS AND METHODS

This study was carried out in Dr. D. Y. Patil Medical College, within a two yrs period (May 2012-April 2014), after approval from institutional ethical committee. Study population consisted of nonhypertensive ASA grade 1 and 2, male and female patients within age of 20- 50 yrs, posted for various elective surgeries under general anaesthesia requiring endotracheal intubation. Patients with anticipated intubation difficulty, obese patients, patients with known allergies, patients with deranged hepatic and renal function were not included. If during procedure laryngoscopy and intubation happens to take >20 secs plan was to exclude these patients too. Written informed consent was obtained from all selected patients.

Study design

Randomised prospective double blind placebo controlled study. Sample size of 150 was generated by sample size calculator. Patients were randomly divided in three group by computer generated random numbers as follows:

Group C (Control) N=50: received normal saline (NS). Group E (Esmolol) N=50: received iv esmolol 2mg /kg. Group D (Diltiazem) N=50: received iv diltiazem 0.2mg/kg. All patients were clinically examined and investigated properly in preanaesthetic checkup. All patients received Tab Diazepam 10 mg orally at night before surgery. On the day of surgery iv line was secured on left dorsum of hand with 20 no. intravenous cannula and multipara monitor of HR, SPO2, NIBP, $ETCO_2$, 5 Lead ECG was attached and baseline parameters were recorded. Patients were given intravenous premedication in the form of inj glycopyrrolate 0.004 mg/kg, inj midazolam 0.04mg/kg, inj pentazocin 0.6 mg/kg. All three study drugs were diluted in 10 cc normal saline and kept ready. Drugs were coded to enhance blinding. 15 min after sedation preinduction data was recorded for HR, SBP, DBP, MAP. All patients were preoxygenated with 100% oxygen for three minutes and were induced in following manner. Group C received 10cc normal saline, Group E received esmolol 2mg/kg, Group D received diltiazem 0.2mg/kg. Induction achieved with inj propofol 2 mg /kg, after loss of eyelash reflex and confirming bag mask ventilation succinylcholine was given to facilitate enditracheal intubation in dose of 2mg/kg. After fasciculation were over i. e. 3 min after giving the study drug laryngoscopy and endotracheal intubation was done with appropriate sized Macintosh blade and proper sized cuffed oral ETT. All intubations were done by co author in < 20 secs. HR, SBP, DBP, MAP were recorded at 1, 3, 5, 10 min interval after intubation. After intubation patients were connected to circuit and anaesthesia was maintained with oxygen (33%), N_2O (65%) and sevoflurane 2%. Nondepolarising muscel relaxant vecuronium bromide was used. Surgery was started after 10 min from laryngoscopy. Also observations made related to adverse effects of drugs like bradycardia, hypotension, arrhythmias.

Observations and results

All descriptive statistics and master chart is prepared by using MS Exel 2007. All quantitative variables are measured by using unpaired 't' test. Qualitative variables are compared by using 'Z test' for proportions. Statistical analysis was done using 'Graphpad Quickcal software'. Mean and standard deviation were used to calculate average value. Chi square test and unpaired t tests applied to compare two groups. P value < 0.001 considered as statistically highly significant, P<0.05 as statistically significant. P >0.05 considered as not significant. All three groups were comparable with respect to age, sex distribution and weight, as P value is >0.05. (Table 1, 2, 3)

Table 1. Age distribution (age in years)

	Control	Esmolol	Diltiazem
Minimum age	20	20	20
Maximum age	50	50	50
Mean age	34.7	35.9	35.4
Std. Deviation	9.6	9.1	10.2

P value not significant

Table 2. Sex distribution (in numbers)

Gender	Control	Esmolol	Diltiazem
Male	25	26	21
Female	25	24	29
Total	50	50	50

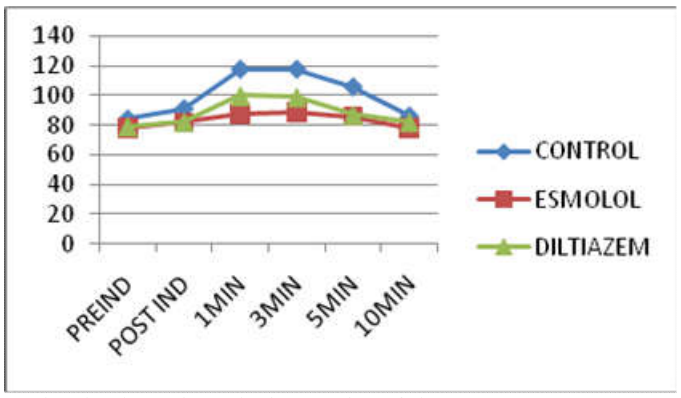
P value not significant

Table 3. Weight Distribution (weight in kilograms)

	Control	Esmolol	Diltiazem
Minimum wt.	39	39	38
Maximum wt.	74	75	74
Mean wt.	54.62	55.44	54.42
Std. Deviation	7.7	7.4	8.8

P value>.05, not significant for above table)

Table 4 shows changes in mean heart rate (mean $\pm$ SD) in all three groups compared to their basal values at different time intervals. It demonstrates preinduction values in all groups were comparable. In control group HR rose to 40-41% of preinducton value at 1 min, and it took more than 5 min to returns to baseline. This is statistically highly significant compared to group E and D (P<. 001). In E group rise was maximum 13% at 3 min and it came down to baseline at 5 min. In D group HR rose to maximum 26% at 1 min and remained elevated for more than 5 mins. On comparing E and D groups the rise in HR was statistically significant in D group at 1, 3 min. (P<. 001). Graph 1 shows analysis of HR changes in graphical manner in all groups with respect to time.



X axis—time interval, Y axis –heart ate beats /min

Graph 1. Analysis of heart rate

Table 5 is analysis of changes in SBP with time. It demonstrates preinduction values in all groups were comparable. At 1, 3 and 5 min there was significant rise in SBP in C group i.e. 18-19%, this is statistically significant as compared to group E and D (P<. 001).

Table 4. Analysis of heart rate

	Control		Esmolol		diltiazem		Differences between the groups** C-E		E-D		C-D	
	Mean+SD	% diff	Mean+ SD	% diff	Mean+SD	% diff	t value	P value	t value	P value	t value	P value
preind	84.2+8.2	-	78.4+6.6	-	79.3+6.8	-	3.88		0.66	>0.05NS	3.26	<0.01S
postind	91.5+10.7	8.7	82.8+6.7	5.6	82.8+6.7	4.4	4.99	<0.001	0.05	>0.05NS	4.85	<0.001
1 min	118.8+10.1	41.1	88.4+6.5	12.8	100.1+8.2	26.2	17.9	<0.001	7.9	<0.001	10.15	<0.001
3 min	118.5+11.8	40.7	89.1+6.0	13.6	99.0+9.5	24.8	15.73	<0.001	6.22	<0/001	9.13	<0.001
5 min	106.7+13.4	26.7	86.2+13.3	9.9	87.3+4.1	10.1	7.75	<0.001	0.54	>0.05NS	9.96	<0.001
10 min	86.2+8.4	2.4	78.0+4.2	-0.5	82.7+5.4	4.3	6.18	<0.001	4.48	<0.01 S	2.49	<0.05

-ve sign indicates decreases, **unpaired 't' test, P<.05,.01 are significant, P<0.001 is highly significant and P>0.05 is not significant

Table 5. Analysis of systolic blood pressure

	Control		Esmolol		Diltiazem		Differences between the groups** C-E		E-D		C-D	
	Mean+SD	% diff	Mean+SD	% diff	Mean+SD	% diff	t value	P value	t value	P value	t value	P value
preind	130.5+10.9	-	128.9+11.7	-	131.9+11.5	-	0.71	0.48NS	1.33	0.19NS	0.66	.51NS
postind	129.2+12.0	-1.0	125.5+11.0	-2.6	131.0+11.3	-0.7	1.61	0.11NS	2.44	<0.05	0.77	NS
1min	156.4+11.4	19.8	133.8+10.6	3.8	144.1+11.8	9.2	10.2	<0.001	4.59	<0.001	5.31	<.001
3min	155.1+11.6	18.9	134.2+10.1	4.1	142.2+10.9	7.8	9.6	<0.001	3.80	<0.01	5.72	<.001
5min	143.8+13.2	10.2	133.0+9.7	3.2	136.1+10.4	3.2	4.67	<0.001	1.55	<0.05	3.24	<.01
10min	130.1+10.1	-3.0	128.2+9.5	-0.5	129.6+11.0	-1.7	0.84	0.40NS	0.69	0.51NS	0.12	.9NS

-ve sign indicates decrease,** unpaired 't'test,p<0.01.0.05 is significant p<0.001 is highly significant, p>0.05 is not significant

Table 6. Analysis of diastolic blood pressure

	Control		Esmolol		Diltiazem		Differences between the groups** C-E		E-D		C-D	
	Mean+SD	% diff	Mean+SD	% diff	Mean+SD	% diff	tvalue	Pvalue	tvalue	Pvalue	tvalue	Pvalue
preind	76.3+6.1	-	76.4+5.1	-	76.7+5.8	-	0.11	0.91NS	0.29	0.77NS	0.37	0.71
postind	74.0+6.4	-3.0	74.1+4.4	-3.0	75.8+5.3	-1.2	0.11	0.91NS	1.75	0.08NS	1.55	0.12
1min	89.6+5.4	17.4	80.9+4.4	5.1	84.6+5.0	10.3	8 .89	<0.001	3.89	<0.01	4.85	<0.001
3min	89.4+5.2	17.2	81.3+3.8	6.4	83.1+4.8	8.3	8.90	<0.001	2.09	0.04	6.29	<0.001
5min	84.6+6.1	10.9	80.0+3.9	4.7	79.4+4.1	3.5	4.45	0.001	0.78	0.44NS	4.98	<0.001
10min	76.7+5.5	0.8	77.4+4.4	1.3	76.0+4.5	-0.9	0.7	0.47	1.60	0.11NS	0.71	0.48

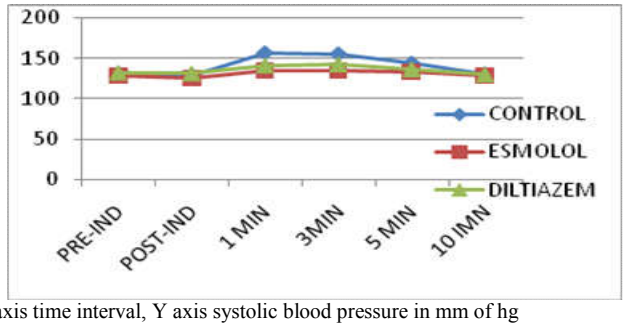
-ve sign indicated decrease, P < 0.05,0.01 is significant, P<.001 is . highly significant,P>0.05 is not significant

Table 7. Analysis of mean arteria pressure

	Control		Esmolol		Diltiazem		Differences between the groups** C-E		E-D		C-D	
	Mean+SD	% diff	Mean+ SD	% diff	Mean+SD	% diff	tvalue	Pvalue	tvalue	Pvalue	tvalue	Pvalue
preind	94.4+6.3	-	93.8+5.0	-	95.1+6.5	-	0.44	0.66NS	1.08	0.28NS	0.59	0.56NS
postind	92.2+6.9	-2.3	92.2+5.2	-2.8	94.2+6.1	-0.9	0.87	0.39NS	2.67	<.05	1.49	0.14
1min	112.1+6.2	18.8	98.5+5.3	5.0	104.4+6.6	9.8	11.8	<.001	4.93	<.001	6.01	<.001
3min	113.3+6.2	17.9	98.9+4.7	5.4	102.8+6.0	8.1	11.3	<.001	3.62	<.01	6.94	<.001
5min	104.1+6.8	10.3	97.7+4.7	4.2	98.3+5.1	3.4	5..51	<.001	0.66	0.51	4.80	<.001
10min	94.4+5.9	0.0	94.7+4.7	1.0	93.8+5.7	-1.4	0.35	0.73NS	0.86	0.39	0.45	0.66

- value indicates decrease,P<.05,P<.01. are significant P<.001 is highly significant,P>.05 is not significan

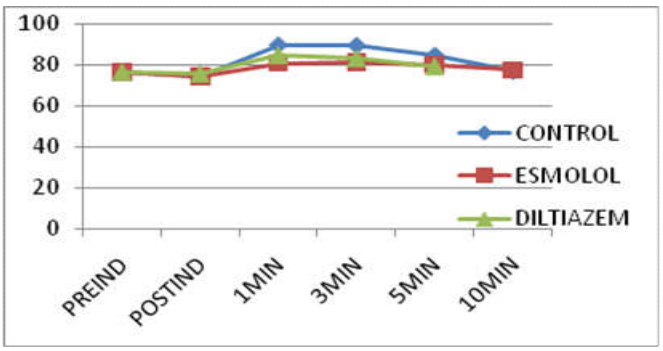
E group showed rise of 3.8-4.1% while D group showed rise of 7.8-9.2%. Thus group D demonstrates significant rise in SBP than group E (P <.001, 01). Graph 2 demonstrates SBP changes with time in all three groups.



X axis time interval, Y axis systolic blood pressure in mm of hg

Graph 2. Analysis of systolic blood pressure

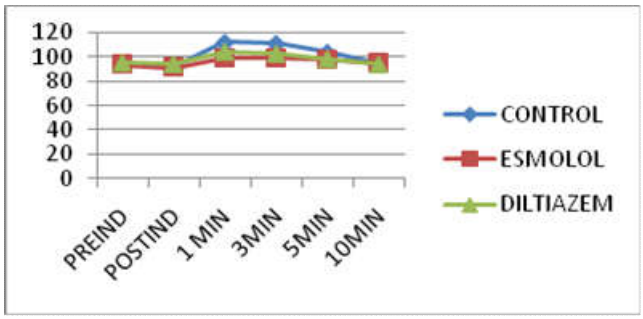
Table 6 is analysis of diastolic blood pressure changes in all 3 groups at different time interval. It shows fall in DBP just after induction which is comparable, but at 1, 3, 5 min interval there is rise in DBP which is- maximum in C group i.e. 17% and it sustained till 5 minutes (P <.001). E and D group also showed rise but to lesser magnitude i.e. 5% and 10% respectively at 1 min, and 6.3% and 8.3% at 3 min. thus E and D both attenuated rise in DBP but esmolol was superior to D group as per statistics as (P <.01) at 1 min. Graph 3 shows DBP changes in graph.



X axis time interval, Y axis diastolic pressure

Graph 3. Analysis of diastolic blood pressure

Table 7 is about analysis of MAP with respect to time in all 3 groups. There was rise in MAP to extent of 18% in C group at 1, 3 min and is statistically significant (P<. 001) as compared to E and D groups. When we compared E and D groups rise in MAP was statistically more in D at 1, 3 min (P<.001). Graph 4 demonstrates same in graphical manner



Xaxis- time interval, Yaxis-mean arterial blood pressure in mm of hg

Graph 4. Analysis of mean arterial pressure

We observed no episodes of bradycardia, arrhythmia or hypotension in any group at any time. After observation period of 10 min surgery and anaesthesia continued in routine manner.

DISCUSSION

The sequence of direct laryngoscopy and intubation is associated with marked haemodynamic changes in the form of rise in HR, BP, arrhythmias due to sympathetic stimulation caused by stretching of oropharyngeal tissue (Stoelting Robert, 1978). Though these effects are short lived they may cause concern in high risk patient like heart disease, COPD, DM, cerebrovascular disease. Average rise of 25-47.7 mm of Hg observed in MAP and similar rise in HR observed when compared to pre-laryngoscopic value (Wycoff, 1960) Many drugs have been tried so far to attenuate this response but not a single drug found satisfactory. Each drug has its advantages and disadvantages. The most obvious being that prevention often outlasts the stimulus. Recently new drug dexmeditomidine is tried with promising results but action is prolonged and monitoring required for extended period (Venkatesh Selvaraj and Kartik Raj Manoharan, 2016). Intravenous diltiazem and esmolol appeared ideal as they have immediate onset of action i.e. within 2-3 mins and no advanced monitoring or gadgets required for administering can be safely given as bolus. Monitoring for extended period post operatively is not required. Esmolol is an ultra short acting cardioselective beta blocker, dose of 2mg/kg was decided by studing previous study material (Sharma *et al.,* 1996; Feng *et al.,* 1996; Liu *et al.,* 1986). Diltiazem is a calcium channel blocker used as antianginal and antiarrhythmic drug. We used in dose of 0.2 mg/kg as we reviewed other studies (Hasegava *et al.,* 1992; Fujii *et al.,* 1995; Mikawa *et al.,* 1990). We decided to compare both the drugs in a quest to find ideal agent to attenuate the pressor response. We selected age group 20-50 yrs as heart rate variability is minimal in this age group. Hypertensive patients on drug therapy were excluded as standardization of drug therapy was technically difficult and result might get altered because of antihypertensive medication. Different drugs are used to control hypertension like ACE inhibitors and beta blockers they have their own effects and may alter the results. Though in our study different drugs like glycopyrrolate, pentazocine, propofol, midazolam are used which have some effect on BP and HR, we used same combination in all three groups to make the groups comparable. We had given both the drugs 3 min prior to intubation so as to have optimum maximum effect of the drug and to enhance blinding. Till now there are various studies where esmolol is used in various doses and is compared to various other drugs like lignocaine, labetolol, nitroglycerine, gabapentine (Chitrangana Gupta *et al.,* 2017; Sarvesh *et al.,* 2010; Singh *et al.,* 1995; Shrestha *et al.,* 2011) and found to be superior to all of them. Also esmolol is more effective in dose of 2mg/kg rather than 0.5-1 mg/kg. In recent sudy where esmolol is compared o dexmeditomidine, dexmeditomidine is found to be superior but required to be given in drip for 10 min prior to intubation and effect to be monitored for 2 hrs for side effects like bradycardia and hypotension (Venkatesh Selvaraj and Kartik Raj Manoharan, 2016). Diltiazem is also studied so far and is compared to various drugs like verapamil, magnesium sulphate, lignocaine (Mikava *et al.,* 1996; Santosh Kumar *et al.,* 2016; Fujii *et al.,* 1999). Our study showed significant rise in HR i.e. 41% in C group as compared to E group where it was 13.6% and in D group was 26.2%. And these findings are comparable to study done by King *et al.* (1951) who showed rise in HR about 25 beats after intubation. HR was better attenuated in E group than in D group. These findings are comparable to that of Menkhaus *et al.* (1985) who found attenuation of HR by esmolol continuous drip, (Menkhaus *et al.* 1985) and to Mikawa et al (1990) who found diltiazem failed to attenuate rise in HR due to sympathoadrenal reflex stimulation (Mikawa *et al.,* 1990). Similar results are seen with studies of Santosh Kumar (2003) and Chitrangana *et al.* (2017).

In our study SBP in control group showed maximum rise of 19% as compared to other two study groups. And when E and D were compared E group was more superior with only 4.1% rise than D where SBP showed rise of 9.1%. These findings were correlating with study by Menkhaus *et al.* (1985) and Vacevic *et al.* (1992). We did not observe fall of SBP as expected with D group. Like in our study recent study by Singh *et al.* (2017) also failed to observe significant fall of SBP with diltiazem even at dose of 0.3 mg/kg (Singh *et al.,* 2017). In our study we found that DBP in C group showed maximum rise i.e. 17.4% than E and D group. And E group was better with 6.4% rise than D group where rise was 10.3%, these results are comparable to results of Parvez *et al.* (2010), and to Gupta *et al.* (2017). Similar to findings of SBP, DBP we found MAP was maximally increased in C group 18.8% followed by D group 9.8% and least by E group 5.4%. Our results are similar to results of study by Shobhana Gupta et al (2011), and that of Santosh kumar *et al.* (2003). Thus from above discussion it is more evident that there was maximum stress response to laryngoscopy and intubation if we don't give any attenuating drug i. e. in C group.. And when compared esmolol to diltiazem, esmolol appears better attenuating agent than diltiazem as HR, BP control was better, quick and short lived, though it failed to prevent rise in HR, SBP, DBP to laryngoscopy and intubation. We also think might be higher doses of Diltiazem are required to get desired effect and one has scope to study it further with high doses. Limitations of study: as we studied in nonhypertensive ASA 1 and 2 population, we don't know the effectiveness in hypertensive patients. Adequate depth o anaesthesia and neuromuscular relaxation was monitored oly by clinical observations. We know that laryngoscopy and intubation separately contribute to pressor response, we did not study it separately.

Conclusion

Intravenous Esmolol 2mg/kg as well as iv Diltiazem 0.2mg/kg both are effective agents in attenuating haemodynamic response to laryngoscopy and endotracheal intubation without any deleterious effect. Esmolol 2mg /kg appears to be superior than diltiazem and should be considered as potential drug of choice for suppressing pressor response of laryngoscopy and intubation.

Future prospect of study

Though we found that esmolol is better choice than diltiazem for attenuation of haemodynamic response to laryngoscopy and intubation, it did not abolished it completely and further research in this area is required to find ideal agent, or proper dose of drugs studied so far.

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