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COMPARATIVE STUDY OF EFFICACY OF LABETALOL AND DEXMEDETOMIDINE FOR ATTENUATION OF HEMODYNAMIC STRESS RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION: RANDOMIZED CONTROLLED STUDY

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Introduction

Tracheal intubation using a laryngoscope is considered to be the gold standard of airway management during administration of general anesthesia because of its several advantages including delivery of anesthetic gases and oxygen via positive pressure ventilation without inflation of stomach, minimal risk of aspiration, access to tracheobronchial tree for pulmonary hygiene and drug administration (e.g., inhaled bronchodilators), improved surgical access to head and neck.[1,2]

Direct laryngoscopy and tracheal intubation during general anesthesia leads to sympathetic stimulation and release of plasma catecholamines concentration which manifests clinically as tachycardia, hypertension along with raised intraocular and intracerebral pressure.[3]

Normally these hemodynamic responses have its peak effect within 1 -2 minutes after intubation and are normalized within five minutes post intubation, but the response may be unpredictable in duration as it also depends upon co-morbid conditions of the individual patients. Sometimes the abrupt increase in heart rate and systolic blood pressure may lead to adverse effects in patients of cardiovascular and cerebrovascular diseases, compromising myocardial contractility and oxygen supply.[4-6] Variety of pretreatments ranging from topical anesthesia of larynx to administration of several classes of drugs like nitroglycerine, B blockers and opioids have been made. Each technique has its own disadvantages, so many times multi modal therapy rather than single intervention has been in practice to attenuate this response.[7]

Dexmedetomidine is a potent and highly selective α2-adrenoceptor agonist with sedative, anxiolytic, sympatholytic, analgesic-sparing effects, and minimal depression of respiratory function.[8] It exerts actions through activation of central pre and postsynaptic α2-receptors in the locus coeruleus. Dexmedetomidine is rapidly distributed and hepatically metabolized into inactive metabolites by glucuronidation and hydroxylation. After intravenous injection, it has an

onset of action after approximately 10 minutes. Peak concentrations are usually achieved within 1 hour after continuous infusion. It has a rapid distribution half-life of 6 minutes and a terminal elimination half-life of between 2 and 2.5 hrs. In blood vessels, α2 receptors cause vasoconstriction and in the sympathetic terminals they inhibit the release of norepinephrine[9]. This drug causes cardiovascular stability during anesthesia, reduces the need for anesthetic and narcotic drugs. Its common side effects are hypotension and bradycardia. Bradycardia can be resolved either spontaneously or with anticholinergics without any complications.

Labetalol is a α1 and non-selective β-adrenergic blocking drug. Through a mixture of its alpha- and beta-blocking effect, it can produce dose related fall in blood pressure without causing tachycardia or bradycardia. Elevated plasma renins are reduced It is used mainly for perioperative control of blood pressure and hemodynamic stability. It has better safety profile and hemodynamic stability. Onset time after intravenous (IV) administration is 5 minutes; peak effect is seen at 5-15 minutes, with a half-life of 4-6 hrs.[10]

Many studies have been done using opioids, lignocaine, Nitroglycerin, other Beta blockers to attenuate hemodynamic response. A number of clinical researches have been done stating that dexmedetomidine decreases the hemodynamic responses to laryngoscopy and intubation but few studies are available comparing dexmedetomidine with labetalol for the same purpose.

Since the use of opioids during surgery is a risk factor for nausea and vomiting, and respiratory depression, reducing the need for such drugs can reduce the risk of resultant complications.[11,12]

In this study, comparing intravenous Labetalol and Dexmedetomidine in attenuating hemodynamic stress response (Heart Rate and Blood Pressure) to laryngoscopy and intubation and find out which drug is better.

Materials and method

The research study was approved by the Institutional ethical committee. Written informed consent was obtained from all the patients. All the information collected was strictly used for the study purpose only and confidentiality was strictly maintained.

The type of the study design was prospective, randomized, controlled, double blinded. The study was conducted at ENT and Surgery operation theatre at GMERS Medical College and Civil Hospital, Gandhinagar, Gujarat, India.

- **Sample size:**

The confidence interval (two sided) was 95%, Power was 80%, Ratio of sample size [Group B/ Group A] was 1, Mean[2] of Group A and Group B was 85 and 90 respectively and Standard Deviation of both Groups was 6. These details were entered in open-sourced statistical website – open epi for calculation of sample size. Sample size of Group A was 30 and Group B was 30. Total sample size was 60. Sampling technique of this study was Purposive sampling method, which is a non-probability sampling technique, was used considering the patient inflow rate in this hospital during study period was fixed. All indoor patients for ENT surgeries and General surgeries under general anaesthesia, in GMERS

Medical College and Research Hospital, Gandhinagar were chosen for the study. Inclusion criteria were patients undergoing surgical procedures under general anaesthesia, aged 18-60 years of either gender, weighing between 40-80kg, ASA physical status I, II. Exclusion criteria were patients with pre-existing severe bradycardia (heart block) or ventricular dysfunction (ejection fraction <30 %) including decompensated congestive heart failure, allergic to any drug, pregnant patients, poorly controlled hypertension, uncontrolled respiratory diseases, neuromuscular diseases, haematological disorders and severe hepatic or renal insufficiency.

Patients scheduled for elective surgeries undergoing above mentioned inclusion and exclusion criteria were chosen for the study. Preanesthetic check-up was done one day prior to the surgery. Patients were evaluated for any systemic diseases and laboratory investigations like CBC, LFT, RFT, ECG, CXR were evaluated and only if they are within normal limit, that patients were included in this study. The anaesthetic machine was examined. Before beginning the procedure, the appropriate size endotracheal tubes, a working laryngoscope with medium and large size blades, a stylet, and a functional suction apparatus were ready. A crash cart was kept ready.

Procedure

After taking informed and written consent, patients were randomly allocated by a coin toss into two groups-Group A (n = 30) and Group B (n = 30).

In operation theatre, preoperative base line parameters like HR, ECG, RR, SpO2, noninvasive SBP, DBP, and MAP were recorded.

The study drug was prepared by qualified personnel not directly involved in the study (anesthesia faculty or fellow anesthesia residents. Intravenous (IV) access was secured with a 20G cannula and infusion of Ringer's lactate was started. The prepared study drug, either Inj. Dexmedetomidine or Inj. Labetalol had been given as follows:

Group-A (N=30): Intravenous Dexmedetomidine 1.0 mcg/kg in 10 ml Normal Saline was given as a loading dose over 10 minutes, started 20 minutes prior to induction.

Group-B (N=30): Intravenous Labetalol 0.5 mg/kg in 10 ml Normal Saline was given as a loading dose over 10 minutes, started 20 minutes prior to induction.

Baseline parameters HR, SBP, DBP, MAP and SpO2 were monitored and recorded 20 minutes before induction.

Once the infusion of Inj. Dexmedetomidine or Inj. Labetalol was started, the parameters ECG, HR, SBP, DBP, MAP and SpO2 were monitored continuously and recorded 10 minutes after completion of infusion of study drug. After loading dose of study drug, all patient was pre-medicated with inj. Glycopyrrolate 0.2 mg I.V., Inj. Midazolam 1 mg I.V, Inj. ondansetron 4 mg I.V. Induction was started 10 minute after completion of loading dose. Pre oxygenation was done with 100% oxygen for 3 minutes, Inj. Propofol 2mg/kg I.V was injected, neuromuscular

blockade was achieved with Inj. succinylcholine 2 mg/kg I.V. The parameters, HR, SBP, DBP, MAP and SpO2 were recorded after injection of induction drugs. Induction was followed by laryngoscopy and endotracheal intubation. Once endotracheal tube position is confirmed, positive pressure ventilation was started with tidal volume 6-8 ml/kg and respiratory rate 12-14/minute. The same parameters were recorded during laryngoscopy and immediately after endotracheal intubation and 5,10 and 15 minutes after endotracheal intubation. Closed circuit breathing system with soda lime was used. Anaesthesia was maintained with sevoflurane and O2: Nitrous oxide (40:60) along with Inj. Atracurium 0.5 mg/kg loading dose and 0.1 mg/kg for maintenance for neuromuscular blockade. Intraoperatively the parameters like HR, SBP, DBP, MAP, SpO2 were continuously monitored. Adverse effects like bradycardia, tachycardia, hypotension, hypertension, nausea, vomiting, if any, noted during intra operative or post operative period and were treated as follows: Bradycardia - (HR<60/min): Inj. Atropine 0.3-0.6 mg I. V; Tachycardia – (HR >30% above baseline value): inj. Propofol 20 mg I. V; Hypotension – (SBP<20% of baseline value) Inj. Mephentermine Sulphate 6 mg I.V and Inj. Ringer Lactate; Hypertension – (SBP> 140 mmHg): Inj. Propofol 20mg I.V and increasing concentration of sevoflurane. Post operative nausea and vomiting: Inj. Metoclopramide 10mg I.V.

Statistical analysis:

Data was cleaned, Validated and Analysed by Epi. Info 7.2 software. Descriptive Statistical analysis for continuous variable range, mean and standard deviation were calculated and for categorical variables proportion and percentage were obtained. Bi-Variate analysis to know the association between dependent and independent variable chi-square and student t - test applied accordingly. P value <0.05 was considered as significant.

Results:

Table 1 shows demographic and ASA status of the study participants. There was no statistically significant difference between two groups with regards to Age, Sex, Body mass index (BMI) and ASA grade (P >0.05).

Table-1: Demographic characteristics and ASA Status

		Group A	**Group B**	**P value**	**Remarks**
No. of patient		30	30		NS
Age (years) (mean ± SD)		48.6 ± 10.9	46.4 ± 11.5	0.45	
BMI (kg/m^2) (mean ± SD)		23.9 ± 1.7	24.3 ± 1.5	0.13	
Sex (M: F)		12:18	9:21	0.41	
ASA	Grade-I	13	14	0.79	
	Grade- II	17	16		

P value: >0.05 for all parameters, using chi-square test

NS: Not significant

Table 2: comparison of heart rate (per min) at various intervals

Time (minutes)	Group A		Group B		P value	Remark
	Mean	**SD**	**Mean**	**SD**		
Baseline 20 minutes before induction	80.3	7.8	76.8	9.7	0.32	NS
10 minutes after infusion study drug and before induction	74.6	6.4	77.6	9.3	**0.01***	**HS**
After Induction	70.8	6.4	76.6	8.8	**0.001***	**HS**
During Laryngoscopy	68.1	6.4	77.2	9.8	**0.001***	**HS**
Immediately after Endotracheal Intubation	72.2	5.7	80.9	10.5	**0.002***	**HS**
5 minutes after intubation	71.4	5.6	82.4	9.4	**0.001***	**HS**
10 minutes after intubation	71.2	5.9	83.4	11.0	**0.001***	**HS**
15 minutes after intubation	70.1	7.7	82.8	10.0	**0.004***	**HS**
NS = Not Significant, HS = Highly Significant						

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TABLE 3: comparison of systolic blood pressure (mmHg) at various intervals

Timeline (mins)	Group A		Group B		P value	Remark
	Mean	SD	Mean	SD		
Baseline 20 minutes before induction	129.1	14.1	128.3	15.3	0.75	NS
10 minutes after infusion of study drug and before induction	122.3	12.2	126.2	6.8	**0.03***	**HS**
After induction	114.8	13.7	122.1	8.7	**0.002***	**HS**
During Laryngoscopy	111.1	11.5	120.5	6.7	**0.001***	**HS**
Immediately after Endotracheal Intubation	114.0	14.3	125.5	8.9	**0.001***	**HS**
5 minutes after intubation	112.1	13.2	123.6	10.4	**0.001***	**HS**
10 mins after intubation	110.5	9.6	122.3	9.3	**0.001***	**HS**
15 mins after intubation	111.5	9.3	121.6	9.8	**0.001***	**HS**
NS= Not significant, HS = highly significant						

Table 4: comparison of diastolic blood pressure (mmHg) at various intervals

Timeline (mins)	Group A		Group B		P value	Remark
	Mean	SD	Mean	SD		
Baseline 20 minutes before induction	82.7	8.6	81.4	7.2	0.89	NS
10 minutes after infusion of study drug and before Induction	78.5	8.6	80.9	8.3	**0.03***	**HS**
After induction	75.6	8.8	78.9	7.1	**0.01***	**HS**
During Laryngoscopy	73.7	10.3	78.0	6.8	**0.001***	**HS**
Immediately after endotracheal Intubation	72.9	13.3	79.9	10.5	**0.04***	**HS**
5 minutes after intubation	69.3	12.0	77.3	9.6	**0.001***	**HS**
10 mins after intubation	67.8	9.9	76.8	8.9	**0.001***	**HS**
15 mins after intubation	65.7	8.3	75.3	9.0	**0.001***	**HS**
NS = Not significant, HS = highly significant						

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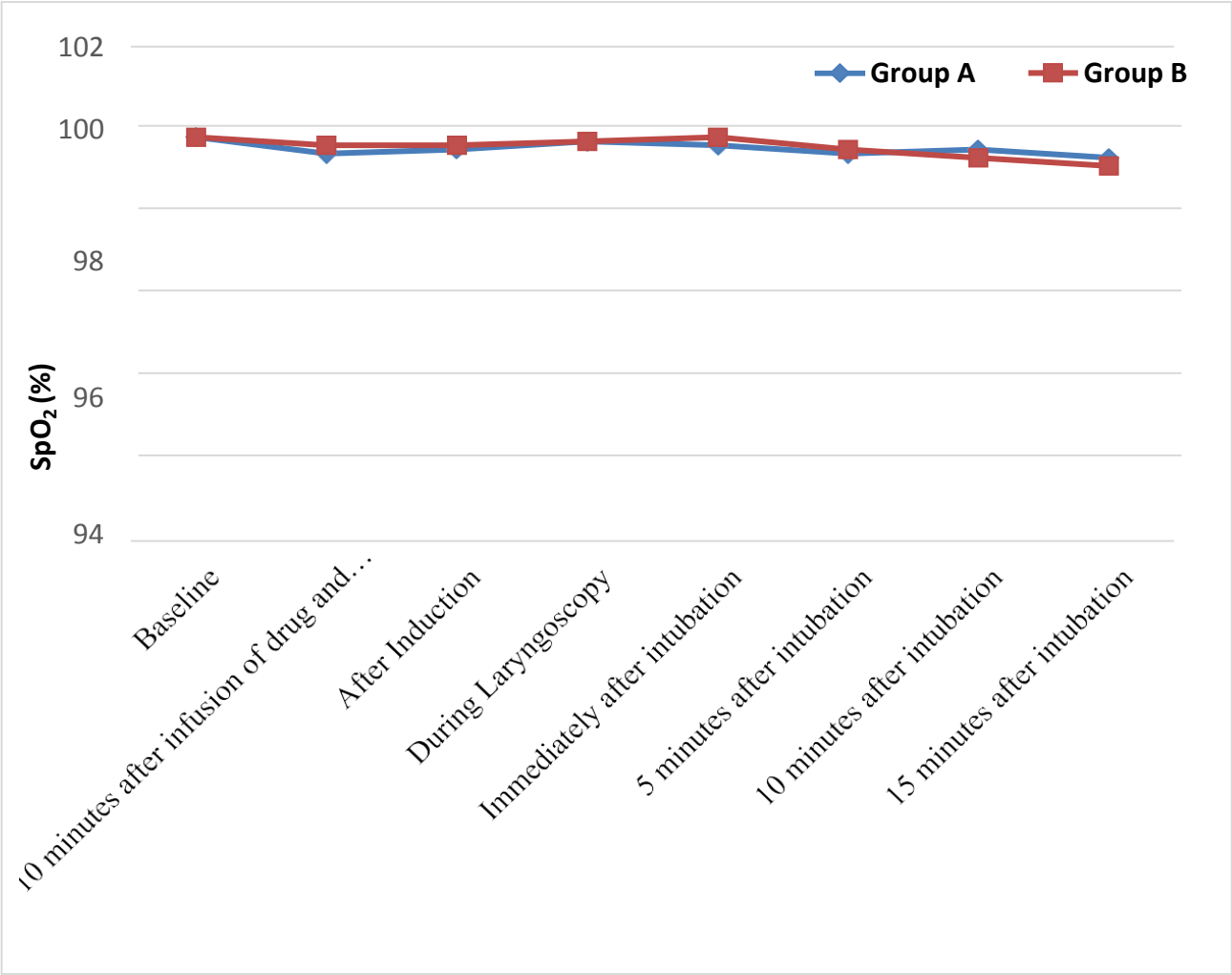
Table 5: comparison of mean arterial pressure (mmHg) at various intervals

Timeline (mins)	Group A		Group B		P value	Remark
	Mean	SD	Mean	SD		
Baseline 20 minutes before induction	98.2	7.5	97.0	7.0	0.22	NS
10 minutes after infusion of study drug and before induction	93.1	8.8	96.0	6.5	**0.01***	**HS**
After induction	88.7	9.0	93.3	7.7	**0.02***	**HS**
During Laryngoscopy	86.2	9.9	92.2	5.7	**0.01***	**HS**
Immediately after Endotracheal Intubation	86.6	13.1	95.1	8.5	**0.01***	**HS**
5 minutes after intubation	83.6	11.7	92.7	9.7	**0.001***	**HS**
10 mins after intubation	82.0	9.3	92.0	11.2	**0.001***	**HS**
15 mins after intubation	81.0	8.7	90.7	7.4	**0.001***	**HS**
NS = Not significant, HS = highly significant						

Comparison of SpO2 (%) at various intervals



Baseline SpO2 (%) was comparable in both the study groups. In our study there was no difference in SpO2(%) after injecting the drug as well as after intubation in group A and B. It was observed that there was no significant change in SpO2 at any time in both the groups.

The results of this study demonstrated that dexmedetomidine is an effective agent for blunting the hemodynamic response to laryngoscopy and endotracheal intubation. There was significant decreased in hemodynamic parameter like HR, SBP, DBP and MAP from baseline after laryngoscopy and tracheal intubation in dexmedetomidine group as compared to labetalol group. The difference was statistically significant and without any side effect.

Discussion

Laryngoscopy and endotracheal intubation frequently induce a cardiovascular stress response characterized by hypertension and tachycardia[3]. This sympathoadrenal stress response to laryngoscopy results in an increase in myocardial O2 demand leading to ischemia and acute heart failure in susceptible individuals[4-6]. This reflex sympathetic response may be diminished or modified locally, centrally and peripherally. In an attempt to blunt these potentially adverse hemodynamic responses, different techniques and agents are used with varying success and many studies had been done for the same[7].

There are various studies which compared the hemodynamic variations with dexmedetomidine and labetalol following laryngoscopy and endotracheal intubation. A number of clinical research has been done stating that dexmedetomidine decreases the hemodynamic responses to laryngoscopy and intubation.[13-15] Dexmedetomidine has been used in doses ranging from 1-2 mcg/kg to prevent the hypertensive and tachycardia response associated with laryngoscopy and intubation. Labetalol has been used mainly for perioperative control of blood pressure and hemodynamic stability.

Raval et al[4] found 1mcg/kg dexmedetomidine to be more effective than 0.5mcg/kg in attenuating hemodynamic responses with no side effects.

In our study inj. Dexmedetomidine 1mcg/kg to be more effective than inj. Labetalol 0.5mg/kg to prevent the hemodynamic response associated with laryngoscopy and intubation without any side effects like bradycardia, hypertension and hypotension.

Scheinin B et al[16]used a dose of 0.6 mcg/kg in healthy individuals and found it to be effective in reducing cardiovascular response to laryngoscopy and intubation, without significant bradycardia or hypotension.

In our current study, we used a dose of 1mcq/kg to be effective in reducing cardiovascular response to laryngoscopy without significant bradycardia and hypotension.

Radwan TA et al[17] showed that both dexmedetomidine in a dose of 1 mcg/kg/hour and labetalol 0.5 mg/kg/hour starting at Dural closure had a significant effect in reducing HR, SBP, DBP, MAP during emergence from anesthesia. The number of patients needing nitroglycerin was significantly lower in dexmedetomidine group and labetalol group in comparison with the control group. SBP, DBP and MAP were lower in dexmedetomidine group during emergence from anesthesia.

In this study, we used inj. Dexmedetomidine 1mcg/kg and inj. Labetalol 0.5mg/kg to reduce hemodynamic response associated with laryngoscopy and intubation without any significant bradycardia and hypotension. HR, SBP, DBP,

MAP was significantly lower in dexmedetomidine group. We didn't compare hemodynamic response during emergence from anesthesia similar to this study. None of the patient had hypertension in our study.

Guler et al[18] also found that there was less significant increase in HR, SBP and DBP at extubation with dexmedetomidine with no difference in the time for tracheal extubation or for emergence from anesthesia.

In our study, we didn't compare hemodynamic response during tracheal extubation or emergence from anesthesia similar to this study.

In a study done by **Kewalramani A et al**[19], although labetalol had maintained the blood pressure, tachycardia was still prominent during laryngoscopy and intubation. It had partial effect on attenuation of heart rate. This finding is similar to the observations of this study and which is statistically significant.

The results of study conducted by **Hatami M et al**[20] indicated that dexmedetomidine had higher efficacy, compared to labetalol, in reducing HR, SBP, DBP, MAP following micro laryngoscopy.

The result of our study is similar to this study as dexmedetomidine has higher efficacy to attenuate the hemodynamic response associated with laryngoscopy and intubation as compared to labetalol. Labetalol has been used mainly for perioperative control of blood pressure and hemodynamic stability. The result of our study is statistically significant.

The efficacy of labetalol in blunting the pressure response and its comparison to dexmedetomidine was evaluated by **El-Shmaa NS et al**[21]. They found that there was significant decrease in HR, MBP, and rate pressure product in group dexmedetomidine in comparison with group labetalol.

This finding is similar to the results of this study.

In study by **Singla D et al**[22], they found that both dexmedetomidine and labetalol given intravenously are effective in preventing significant fluctuations in blood pressure and heart rate when used in individuals predisposed to such events. However, Dexmedetomidine appears to be slightly more effective in reducing the hemodynamic stress response, as patients in Dexmedetomidine group showed significantly lower blood pressure values immediately after intubation and after extubation. These findings are comparable to the present study.

Bradycardia was reported after single dose of 0.5mcg/kg inj. Dexmedetomidine by **Basar et al**[15]. However, this may due to combination with fentanyl as it also causes bradycardia and dexmedetomidine, administered along with fentanyl has synergistic effect to cause fall in heart rate.

We did not use fentanyl along with dexmedetomidine in our study, and no significant bradycardia was observed after administration of dexmedetomidine.

The study done by **Kumari et al**[23] showed attenuation of hemodynamic responses with a single pre-induction intravenous dose of dexmedetomidine of 0.5mcg/kg.

In our study, we used a pre-induction intravenous dose of dexmedetomidine 1mcq/kg given over 10 minutes to prevent hemodynamic response attenuation during laryngoscopy and intubation compared with dose of labetalol 0.5 mg/kg given over 10 minutes. It is more effective and statistically significant.

Tanskanen et al[24] pointed out that infusion of dexmedetomidine (0.4 mcg/kg/hour) resulted in heart rate and blood pressure reduction compared to placebo infusion in 53 patients undergoing elective surgery. In our study, we compared the efficacy of dexmedetomidine (1 mcg/kg over 10 minute) versus labetalol (0.5mg/ kg over 10 min) in reducing hemodynamic stress during laryngoscopy and endotracheal intubation. We didn't use infusion in our study, but with loading dose in both groups decrease in HR, SBP, DBP and MAP but statistically significant between two groups.

Roelofse JA et al[25] assessed the effect of labetalol 1mg/kg as an IV bolus 1 minute before laryngoscopy, and it was not effective in the attenuation of HR. The negative result of that study is probably explained by the different time of administration of the study drug because labetalol has onset at 5 minute and peak effect after 5-10minutes. In our present study we used inj. labetalol 0.5mg/kg over 10 minutes, started 20 minutes prior to induction. There is decrease in HR, SBP, DB and MAP which is statistically significant.

Pipanmekaporn T et al [26] used 0.5-1 mcg/kg of dexmedetomidine to attenuate stress response to intubation and found that there was reduction in both HR and MAP.

In our study, we used 1 mcg/kg of dexmedetomidine to attenuate stress response to laryngoscopy and endotracheal intubation over 10 minutes, started 20 minutes prior to induction and there is

Significantly decrease in HR, SBP, DBP and MAP.

In a study by **Lawrence CJ et al**[27] a single dose of 2.0 mcg/kg dexmedetomidine before induction was found to be effective in attenuating hemodynamic response. However, the incidence of bradycardia and hypotension was found to be higher. All these observations can be explained on the basis of decreased central nervous system sympathetic activity by mechanism of dexmedetomidine and labetalol. Dexmedetomidine has property of analgesia, sympatholytic and flexibility to titrate sedation without causing major respiratory depression. Labetalol is a competitive beta-adrenergic blockade may produce fall in blood pressure associated reduction in the heart rate. Cardiac output may not be affected much. Peripheral vascular resistance may be reduced. Labetalol is very useful in blunting heart rate and blood pressure response to exercise

There was no difference in SpO_2 (%) after injecting the drug as well as after intubation in

group A and B. It was observed that there was no significant change in SpO_2 at any time in both the groups.
No any respiratory depression with dexmedetomidine and labetalol.

Extubation is equally important as it can be detrimental for high-risk patients. Dexmedetomidine as well as labetalol enabled a smooth change over during reversal till post-extubation phase. Due to analgesic and sympatholytic property, dexmedetomidine had led to stable hemodynamics with good control of heart rate and blood pressure when compared to labetalol at the time of extubation as well as postoperatively.[28]
Benefit of this study is that beneficial effects on attenuation of hemodynamic response with both of the study drugs, with dose and duration which we have used, without any major side effects. So, these drugs are recommended to avoid deleterious effects of hemodynamic responses to laryngoscopy and intubation. Although Dexmedetomidine is more efficacious than Labetalol for attenuation of heart rate and blood pressure whereas Labetalol attenuates the blood pressure but reflex tachycardia was noted.

Limitations of this study are, further studies will be required using these dose regimes on hypertensive patients and with more sample size. Use of Dexmedetomidine and Labetalol may be individualized and titrated to higher MAP in hypertensive patients. Further studies need to be done to establish the superiority of any one drug over the other by taking into consideration their adverse effects and overall outcome of patients. Secondly, the study did not look at extubation outcome. Third limitation is, this study did not measure the sparing effect of study drugs on induction agents and analgesics.

Conclusion

This study evaluated the efficacy between Dexmedetomidine 1.0 mcg/kg versus Labetalol 0.5 mg/kg on hemodynamic response to patients undergoing laryngoscopy and endotracheal intubation.

The results of this study demonstrated that dexmedetomidine is an effective agent for blunting the hemodynamic response to laryngoscopy and tracheal intubation. There was significant decreased in hemodynamic parameter like HR, SBP, DBP and MAP from baseline after laryngoscopy and tracheal intubation in dexmedetomidine group as compared to labetalol. The difference was statistically significant and without any side effect.

However further studies need to be done to establish the superiority of any one drug over the other by taking into consideration their adverse effects and also the age group, clinical condition and the overall outcome of patients.

Conflicts of interest: None declared.

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