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Original Research Paper

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ROLE OF INTRAVENOUS MIDAZOLAM, ESMOLOL AND THEIR COMBINATION IN ATTENUATION OF CARDIOVASCULAR STRESS RESPONSE TO LARYNGOSCOPY AND INTUBATION - A COMPARATIVE CLINICAL STUDY

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ABSTRACT

BACKGROUND AND AIM: Laryngoscopy & intubation are associated with tachycardia & hypertension. These hemodynamic changes are temporary & do not cause any complication in healthy person. But these changes can be detrimental to the patient with history of coronary artery disease and can facilitate and accelerate the development of myocardial ischemia, arrhythmias, infraction and also heart failure. The present study was designed to evaluate and study the efficiency of intravenous midazolam, esmolol and their combination in the attenuation of cardiovascular response to laryngoscopy and intubation in normotensive individuals.

METHOD: This randomized prospective double-blind study was performed on 90 patients of ASA physical status I and II undergoing various elective abdominal surgeries under general anaesthesia with endotracheal intubation. Patients were randomized in three groups, Group M (midazolam) 0.05mg/kg I.V, Group E (esmolol) 2mg/kg I.V and Group M/E (midazolam 0.05mg/kg + Esmolol 2mg/kg I.V) with 30 patients in each group. Hemodynamic parameters were recorded before the study drug and at specified intervals.

RESULT:- All three groups showed less rise in heart rate and blood pressure during laryngoscopy and intubation. Haemodynamic parameters were significantly less in Group-M/E than Group M and E alone just after intubation and 1 and 2 minutes intervals.

CONCLUSION:

Combination of both midazolam and esmolol effectively attenuated the cardiovascular stress response associated with laryngoscopy & intubation than single drug therapy with esmolol or midazolam.

KEYWORDS : Midazolam, Esmolol Laryngoscopy, Intubation

INTRODUCTION:-

The basic components of general anaesthesia are:-amnesia, analgesia & muscle relaxation. Laryngoscopy and tracheal intubation has to be done after giving muscle relaxation. Laryngoscopy is a procedure which is carried out to facilitate tracheal intubation during general anaesthesia. Both laryngoscopy and intubation are associated with various physiological changes including stimulation of sympathetic and parasympathetic nerves which is observed by the rise in heart rate and blood pressure[1, 2]. There are also rise in serum catecholamine levels by the stimulation of sympathetic nerve ending. Hemodynamic changes are generally temporary and without any complication in healthy individuals. However, these changes can be detrimental to the patient with history of coronary artery disease and can facilitate and accelerate the development of myocardial ischemia, arrhythmias, infraction and also heart failure. It can also produce cerebral haemorrhage in a patient with hypertension and cerebrovascular disease[3,4]

Various method are tried to blunt the hemodynamic responses like :- adequate depth of anaesthesia by using proper dose of intravenous or inhalational anaesthetic agents.[5], short acting intravenous opioids like fentanyl, ramifentanyl 2-3 minutes prior to intubation.[6], intravenous administration of 2% preservative free lignocaine 2-3 minutes prior to endotracheal intubation.[7], local xylocaine spray at vocal cords before intubation, intravenous short acting beta blocker prior to induction.[5], use of calcium channel blockers like nicardipine or diltiazem.[8], use of directly acting vasodilator like nitroprusside, use of clonidine and other alpha 2 agonist.[9]

However, no single method has gained wide spread acceptance since each method has its own merits and demerits. We have carried out this study to evaluate whether intravenous Midazolam or Esmolol or combination of both can modify cardiovascular responses to direct laryngoscopy and intubation.

METHODS:

This prospective, randomized, double-blind comparative study was conducted at a tertiary care hospital in Eastern India over a period of one year and three months (January 2016- March 2017). We included 90 patients belonging to American Society of Anaesthesiologists (ASA) physical status (PS) I and II, of either sex, aged 20–50 years, weighing between 40 and 70 kg, scheduled for various elective upper abdominal surgeries under general anaesthesia with endotracheal intubation. Patients were explained about the procedure during the pre-anaesthetic visit. Each patient received a written and verbal description of the research protocol and written informed consent was taken from all the patients in their language for inclusion in the study. Exclusion criteria for the study were patient's refusal, h/o allergy to either esmolol or midazolam, patients with known cardiac disorders, other systemic disorders of lungs and liver, pregnant patients, patients for emergency procedures, BMI>30kg/m2, ASA grades III-IV, patients on antihypertensive drugs and patients with anticipated difficult airway. After obtaining Institutional ethical committee approval, eligible patients were randomly allocated using computer generated -randomized test to one of three equal (30 in each group) groups:-

GROUP M (MIDAZOLAM GROUP):-

received 0.05mg /kg of body weight of midazolam I.V two minutes before laryngoscopy and intubation

GROUP E (ESMOLOL GROUP):-

received 2mg /kg of body weight of esmolol I.V two minutes before laryngoscopy and intubation

GROUP M/E (MIDAZOLAM + ESMOLOL GROUP):-

received 0.05mg /kg of body weight of midazolam and 2mg /kg of body weight of esmolol I.V two minutes before laryngoscopy and intubation

ANAESTHETIC TECHNIQUE

All the patients were subjected to pre-anaesthetic assessment

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including medical history and physical examination with relevant investigations. X-ray chest and ECG was also reviewed. On the day before surgery, all patients included in the study were reexamined and advised for 8 hours fasting state preoperatively. All patients were given tablet alprazolam 0.25mg orally at bedtime on the previous night of surgery.

On the day of surgery after confirmation of NPO status, patients were shifted to the operating room & connected to multiparameter monitor. Basal systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), ECG, oxygen saturation (SpO_2) were recorded. Continuous monitoring of the vital parameters were done. An intravenous line was secured with an appropriate sized cannula. Preloading with 500ml of ringer lactate over 30mins was done to maintain adequate hydration.

Inj. Fentanyl 2 mcg/kg body weight i.v. were given as premedication before surgery and patients were preoxygenated for 3 minutes with 100% O_2. Anaesthesia was induced with propofol 2mg/kg, followed by inj. vecuronium bromide 0.1mg/kg, to facilitate the direct laryngoscopy and intubation. . All the study drugs were prepared at the room temperature and the anaesthesiologist was unaware of its content. All patients received study drugs according to allocated group one minute after induction. Direct laryngoscopy and endotracheal intubation was done two minutes after administering the study drug. All intubations were done by an experienced anaesthesiologist. Any patient requiring more than 20 seconds or more than 1 attempt for intubation was excluded from the study. Anaesthesia was maintained by isoflurane, nitrous oxide 60% in oxygen and followed by intermittent dose of Inj. vecuronium, analgesics and intravenous fluids based on requirements. Intermittent positive pressure ventilation (IPPV) was continued by mechanical ventilator with tidal volume and respiratory rate adjusted to maintain an EtCO2 between 35-40 mm of Hg. Haemodynamic parameters (HR, SBP, DBP and MAP) were recorded by a blinded observer in the following specific time intervals-before the study drug injection (baseline value) and 1,2,3,4 minutes after intubation. No surgical stimulus was allowed during the study period and haemodynamic changes beyond the study period were not taken into account. At the end of surgery, the patients were adequately reversed with Inj.neostigmine 0.05 mg/ kg and Inj.glycopyrrolate 0.01 mg /kg intravenously as required. After oxygenation for about 5 minutes postoperatively patients were sent to the recovery room. The patients were monitored in the postoperative period for any complications and appropriately treated if required.

STATISTICAL ANALYSIS:

Sample size was decided in consultation with statisticians and based on previous studies which indicated that approximately 25-27 patients should be included in each group in order to ensure power of 80% and -error of 0.05 for detecting clinically meaningful reduction by 20% in heart rate and mean arterial blood pressure during laryngoscopy and endotracheal intubation. Assuming a 5% drop out rate and for equal distribution of patients in all the four groups, a total of 90 patients were incorporated for the present study. The results of the observations were tabulated, compiled and statistically analyzed using Statistica version 6 [Tulsa, Oklahoma: Stat Soft Inc., 2001] and SPSS Statistics version 17 [Illinois, Chicago: SPSS Inc., 2008]. Qualitative data (sex, ASA grade, postoperative complications) were compared between groups with Chi-Square (2) test. Quantitative data (age, body weight, height, HR, SBP, DBP, MAP) were compared between groups with ANOVA. A p value < 0.05 was considered as statistically significant and < 0.01 was considered as highly significant.

RESULTS:

DEMOGRAPHIC DATA

All the three groups were statistically comparable with respect to sex, age, body weight, height and ASA grading. No significant differences were observed between the groups (p value > 0.05) [Table 1].

Table 1. Comparison of demographic variables between three study groups

DEMOGRAPHIC VARIABLES	**Group-M** n=30 (Mean±SD)	**Group-E** n=30 (Mean±SD)	**Group-M/E** N=30 (Mean±SD)	*P value*
SEX (M:F)	6:24	7:23	8:22	> 0.05
AGE (YEARS)	40.07 ± 8.461	42.03 ± 7.902	41.20 ± 8.290	0.835
BODY WEIGHT (KG)	56.90 ± 9.935	56.07 ± 9.684	55.37 ± 9.197	0.826
HEIGHT (CM)	160.03± 10.361	158.63± 9.419	159.6 ± 9.568	0.705
ASA GRADE (I:II)	24:6	24:6	23:7	0.936

SD : standard deviation

COMPARISON OF HEART RATE (HR) (BEATS/MIN) BETWEEN GROUPS

When the preoperative baseline HR was compared between three groups, no statistically significant difference was found (p value 0.125). 1 minute after intubation, significant reduction in HR is noted in Group-M/E compared to Group M and E (p value <0.005). HR was also significantly lower in Group-M/E compared to Group M and E (p value < 0.001) 2 min after intubation. The increases in HR at 3,4 minutes after intubation were significant in Group M and E compared to Group-M/E (p value < 0.05) [Table 2].

Table-2. Comparison of heart rates between the study groups at different points of time

TIME INTERVAL	**Group M** (n =30) (Mean ± SD)	**Group E** (n =30) (Mean ± SD)	**Group M/E** (n =30) (Mean ± SD)	***p value***
Before study drug injection (baseline) (T1)	81.43±10.28	83.13±8.52	80.53±11.14	0.125
1 minute after intubation (T2)	74.03±12.44	76.07±11.25	66.20±11.99	<0.005
2 minute after intubation(T3)	90.77±15.34	88.67±14.67	66.47±11.27	<0.001
3 minute after intubation (T4)	89.27±14.82	85.20±13.74	75.30±15.37	<0.05
4 minutes after intubation (T5)	87.03±14.48	83.27±13.28	73.43±14.48	<0.05

COMPARISON OF SYSTOLIC BLOOD PRESSURES (SBP) (MMHG) BETWEEN GROUPS

When the preoperative baseline SBP was compared between three groups, no statistically significant difference was found (*p* value 0.091).1 minute after intubation, significant reduction in SBP is noted in Group-M/E compared to Group M and E (*p* value <0.025).SBP was also significantly lower in Group-M/E compared to Group M and E (*p* value < 0.011) 2 min after intubation. The increases in SBP at 3,4 minutes after intubation were significant in Group M and E compared to Group-M/E (*p* value < 0.05) [Table 3].

Table 3. Comparison of SBP between the study groups at different points of time

TIME INTERVAL	**Group M** (n =30) (Mean ± SD)	**Group E** (n =30) (Mean ± SD)	**Group M/E** (n =30) (Mean ± SD)	***p value***
Before study drug injection (baseline) (T1)	125.07±9.34	126.53±11.70	127.83±13.71	0.091
1 minute after intubation (T2)	115.00±10.37	117.37±13.38	110.43±15.30	<0.025
2 minute after intubation(T3)	149.30±17.41	145.23±20.18	134.53±18.79	<0.011
3 minute after intubation (T4)	146.20±17.01	142.07±18.63	133.60±18.45	<0.05
4 minutes after intubation (T5)	143.27±16.52	139.13±18.27	131.60±17.83	<0.05

COMPARISON OF DIASTOLIC BLOOD PRESSURES (DBP) (MM HG) BETWEEN GROUPS

When the preoperative baseline DBP was compared between three groups, no statistically significant difference was found (*p* value 0.650).1 minute after intubation, significant reduction in DBP is noted in Group-M/E compared to Group M and E (*p* value <0.001).DBP was also significantly lower in Group-M/E compared to Group M and E (*p* value < 0.001) 2 min after intubation. The increases in DBP at 3,4 minutes after intubation were significant in Group M and E compared to Group-M/E (*p* value < 0.05) [Table 4].

Table 4. Comparison of DBP between the study groups at different points of time

TIME INTERVAL	**Group M** (n =30) (Mean ± SD)	**Group E** (n =30) (Mean ± SD)	**Group M/E** (n =30) (Mean ± SD)	***p value***
Before study drug injection (baseline) (T1)	75.03±7.44	75.87±9.34	76.33±11.60	0.650
1 minute after intubation (T2)	69.87±6.39	71.93±8.64	70.37±12.20	<0.001
2 minute after intubation(T3)	88.30±9.11	85.03±12.02	81.93±12.96	<0.001
3 minute after intubation (T4)	85.07±9.04	82.43±12.01	80.17±12.32	<0.05
4 minutes after intubation (T5)	82.27±8.67	81.27±12.33	79.53±12.03	<0.05

COMPARISON OF MAP (MMHG) BETWEEN GROUPS

When the preoperative baseline MAP was compared between three groups, no statistically significant difference was found (*p* value 0.891). 1minute after intubation, significant reduction in MAP was noted in Group-M/E compared to Group M and E (*p* value <0.01). MAP was also significantly lower in Group-M/E compared to Group M and E (*p* value < 0.01) 2 minute after intubation. The increases in MAP at 3,4minutes after intubation were highly significant in Group M and E compared to Group-M/E (*p* value < 0.01) [Table 5]

Table 5. Comparison of mean arterial pressures between three study groups at different points of time

TIME INTERVAL	**Group M** (n =30) (Mean ± SD)	**Group E** (n =30) (Mean ± SD)	**Group M/E** (n =30) (Mean ± SD)	***p value***
Before study drug injection (baseline) (T1)	93.90±10.330	94.33±10.186	93.07±10.570	0.891
1 minute after intubation (T2)	113.20±7.488	101.13±8.513	91.83±7.184	<0.01
2 minute after intubation(T3)	110.89±7.593	99.61±7.972	90.17±6.8	<0.01
3 minute after intubation (T4)	109.07±7.610	99.23±8.625	88.57±6.807	<0.01
4 minutes after intubation (T5)	103.28±7.436	94.82±8.596	86.51±6.875	<0.01

POST-OPERATIVE COMPLICATIONS

The HR in the postoperative period less than 60 bpm was considered as bradycardia. Two patients in Group-M, three patients in Group-E and one patient in Group-M/E had HR below 60 bpm in the early postoperative period. Postoperative SBP less than 90mmHg, or DBP less than 60 mmHg, or both were considered as hypotension. It was seen in two patients in Group-M, three patients in Group-E and two patients in Group-M/E. Two patients in each group complained of shivering in the recovery room. Postoperative nausea was complained by two patients in Group-M, two patients in Group-E and one patient in Group-M/E. When these complications were compared between three groups with Chi-Square (2) test, no statistically significant difference was found (*p* value 0.6688) [Table 6].

Table 6. Comparison of post-operative complications between three study groups

Post-operative complications	Group M (n =30)	Group E (n =30)	Group M/E (n =30)	Statistical Analysis
Bradycardia	2	3	1	Chi-Square (2) value 5.8070 p value 0.6688
Hypotension	2	3	2	
Shivering	2	2	2	
PONV	2	2	1	

PONV : postoperative nausea and vomiting

DISCUSSION :-

Most of the general anaesthetic procedures in the modern anaesthetic practice are carried out with endotracheal intubation. Laryngoscopy and tracheal intubation are considered as the most critical events during administration of general anaesthesia, as they provoke transient but marked sympathoadrenal responses[1] manifesting as hypertension and tachycardia. As these responses are transient and variable, so they do not make any significant impact in otherwise normal individuals. But it can precipitate potentially harmful effect like left ventricular failure, pulmonary oedema, ventricular dysrrhymias and cerebral haemorrhage in patients with cardiovascular compromised like hypertension, ischemic heart disease, cerebrovascular disease and in patients with intracranial aneurysms.[10] . Heart rate is an important determinant of myocardial oxygen demand, and tachycardia in patients with ischaemic heart disease is a risk factor for the development of perioperative myocardial ischemia and infarction by increasing myocardial oxygen demand.

Hence, the need to attenuate this sympathetic response to laryngoscopy and endotracheal intubation is important in patients with coronary artery disease undergoing coronary revascularisation. Direct laryngoscopy involves stretching the oropharyngeal tissues and direct pressure on the tongue, this stretch can cause pain and trigger a stress response. Since tracheal intubation is unavoidable for major surgical procedures like cardiac surgery, the attempt to reduce the sympathetic stimulation is now directed towards minimising the stretching of tissues in the epipharynx and laryngo-pharynx& minimising the time required for intubation. Both laryngoscopy and intubation separately result in sympathetic stimulation, but the catecholamine rise with intubation exceeds that with laryngoscopy alone. This is by far the most important indication for attenuation of hyperdynamic cardiovascular responses to laryngoscopy and tracheal intubation.

Various methods have been used to attenuate this cardiovascular responses like deepening of anaesthesia, use of beta blocker, use of lignocaine, use of calcium channel blocker, nitro glycerine, nitropruside. The most important laryngoscopic factor influencing the cardiovascular response is found to be the duration of laryngoscopy. A linear increase in heart rate and mean arterial pressure during first 45 sec has been observed. Further prolongation has little effect. As the duration of laryngoscopy is normally <30 sec the result of studies in which it takes longer than this have less clinical relevance. The force applied during laryngoscopy has only minor effect. In our study, the duration of laryngoscopy and intubation was limited to 30 sec.

A multicentre trial was conducted in five hundred & forty eight patients to determine the dose-response and side-effects of esmolol when administered as a single i.v bolus prior to induction of anaesthesia for controlling the haemodynamic response to tracheal intubation. it was found that esmolol can able to control heart rate & blood pressure effectively than placebo but it become more effective when narcotics are added with esmolol.[11] Singh H et all shows lidocaine 1.5 mg/kg IV and nitro-glycerine 2 μg/kg IV both were in effective to control the hemodynamic response following laryngoscopy and intubation. Esmolol 1.4 mg/kg IV was more effective than either drugs in controlling the HR response to laryngoscopy and intubation. Esmolol also was significantly more effective than lidocaine in minimizing the increase in MAP[12] N tomoki et all shows that anaesthesia induction with a combination of midazolam-thiopental was effective in reducing hemod ynamic and cardiac autonomic nervous system responses to tracheal intubation in comparison with the conventional induction with thiopental alone.[13]

Result obtained from the present investigation suggest that pre-treatment with a combination of Midazolam@0.05mg/kg and Esmolol@2mg/kg provides safe and effective suppression of the cardiovascular responses to laryngoscopy and intubation in healthy individual. Only two patients receiving this combination had a peck heart rate above 100/min following laryngoscopy and tracheal intubation. This group also evidenced a smaller change from baseline systolic blood pressure and fewer patients with systolic blood pressure >160mmHg than did the groups receiving Esmolol or midazolam along.

Midazolam@ 0.05mg/kg administration along did not constantly provide hemodynamic stability during laryng oscopy and intubation. Patients receiving Midazolam along experienced the highest degree of hemodynamic responses to intubation. Higher dose of Midazolam may able to abolish intubation surge but it may be associated with high sedation and respiratory depression.

Although Esmolol has been used to blunt the hemodynamic responses to intubation but moderate to higher doses of Esmolol often are not given because moderate to high dose of Esmolol causes sinus bradycardia, myocardial depression & varying degree of heart block.

We postulated that Esmolol block the adrenergic receptors & Midazolam decreases sympathetic outflow and catecho lamine release by increasing depth of anaesthesia. So their combination would provide effective blunting of the responses to intubation while minimizing the side effects of larger doses of each agent along. We noted a decreased heart rate prior to induction in esmolol and combination group but such changes are clinically insignificant because in each case the heart rate increased after induction of anaesthesia. But one should be very careful because combination of Midazolam and Esmolol can precipitate severe bradycardia in rare cases.

LIMITATIONS OF THE STUDY

- Serum catecholamines are the most important markers to assess the sympathoadrenal stress response to any stimulus. But, in this study we could not measure its level in every patient due to scarcity of the resources. This was the major limitation of our study.
- Use of non-invasive blood pressure monitoring- Invasive monitoring gives us time to time variability and exact readings while with non-invasive blood pressure, there was a time lag present.
- After reviewing the literatures, it was observed that there is still no consensus on optimal dose and timing of administration of esmolol and midazolam for attenuation

of laryngoscopic pressor responses. More studies are required to determine this.

CONCLUSION:-

From the present study we can conclude that:-Midazolam and esmolol alone are not able to blunt the hemodynamic responses during laryngoscopy and intubation effectively. Combination of both midazolam and esmolol can more effectively blunt cardiovascular responses during laryngoscopy and intubation. Moreover, we can avoid complication associated with using of high dose of midazolam and esmolol. Both the study drugs are devoid of any serious adverse effect and found safe in this study.

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