A STUDY OF INTRAVENOUS CLONIDINE AND DEXMEDETOMIDINE COMPARED WITH INTRAVENOUS MIDAZOLAM AS AN ACTIVE CONTROL FOR SUPPRESSION OF HAEMODYNAMIC RESPONSE ASSOCIATED WITH LARYNGOSCOPY & ENDOTRACHEAL INTUBATION IN PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY UNDER GENERAL ANAESTHESIA

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ABSTRACT

BACKGROUND

Laryngoscopy and endotracheal intubation violate the patient's protective airway reflexes and invariably cause haemodynamic changes associated with increased heart rate, increased blood pressure and occasional disturbance in cardiac rhythm. Haemodynamic changes are due to sympathoadrenal discharge caused by release of norepinephrine and, to a lesser extent, of epinephrine. Effective attenuation of the sympathoadrenal stress response is an important goal in anaesthesiology.

Aims & Objectives- An attempt has been made to observe, assess, and compare the efficacy of preoperative clonidine and dexmedetomidine infusions in attenuating the haemodynamic response following laryngoscopy and endotracheal intubation in three groups of adult patients of either sex undergoing elective laparoscopic cholecystectomies under general anaesthesia. Injection Midazolam has been taken as a control in this study.

MATERIALS AND METHODS

The 90 patients undergoing elective laparoscopic cholecystectomy under general anaesthesia were randomly allocated preoperatively into three equal groups (n = 30): Group-C (Clonidine), Group - D (Dexmedetomidine), and Group-M (Midazolam or control). Group - C: Received 100 mL infusion containing inj. clonidine 3 µg kg⁻¹ in normal saline. Group - D: Received 100 mL infusion containing inj. dexmedetomidine 1 µg kg⁻¹ in normal saline. Group-M: Received 100 mL infusion containing inj. Midazolam. Haemodynamic parameters (HR, SBP, DBP and MAP) were recorded in different point of time.

RESULTS

All the three groups were statistically comparable with respect to sex, age, body weight, height, ASA grading and preoperative base line HR, SBP, DBP & MAP. After induction of anaesthesia, a significant reduction in HR, SBP, DBP and MAP were noted in Group D (p value 0.032). The increases in HR, SBP, DBP, MAP during laryngoscopy and intubation, at 1, 2, 3 and 5 minutes after intubation were highly significant in Group M compared to Group C and Group D (p value < 0.01). Both the α₂-agonists are devoid of any serious adverse effect and found safe in this study.

CONCLUSION

Both clonidine and dexmedetomidine administered intravenously just before laryngoscopy and endotracheal intubation effectively attenuate the haemodynamic response. Dexmedetomidine has been found to provide better haemodynamic stability than clonidine.

KEYWORDS

Haemodynamic Response, Clonidine, Dexmedetomidine, Midazolam, Infusion, Adverse Effects.

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BACKGROUND

Endotracheal intubation is the translaryngeal placement of a tube into the trachea via the nose or mouth. The influence of airway manipulation on heart rate and blood pressure was

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recognised more than 50 years ago and the magnitude of the changes was observed to depend on the depth of anaesthesia.¹ It is now well established that laryngoscopy and endotracheal intubation violate the patient's protective airway reflexes and invariably cause haemodynamic changes associated with increased heart rate, increased blood pressure and occasional disturbance in cardiac rhythm.^{2,3} These haemodynamic changes resulting from airway instrumentation are due to sympathoadrenal discharge caused by release of norepinephrine and, to a lesser extent, of epinephrine.⁴ In normotensive subjects, these haemodynamic changes are short-lived⁵ and probably of little significance. However, these haemodynamic alterations are hazardous to

the patients with hypertension, myocardial insufficiency or cerebrovascular disease.⁶

The magnitude of response is greater with increasing force and duration of laryngoscopy. Elevation of blood pressure and heart rate typically starts within 5 seconds of laryngoscopy, peaks in 1 to 2 minutes and return to baseline level within 5 - 10 minutes. So, effective attenuation of the sympathoadrenal stress response is an important goal in anaesthesiology. Various pharmacologic and non-pharmacologic methods have been tried to limit the pressor response following the insertion of endotracheal tube.⁷ The success rate is variable with different methods because each method has its own merits and demerits. In several clinical trials drugs like opioids, β -blockers, lidocaine, nitrate calcium channel blockers or magnesium have already been used orally or parenterally to obtund this sympathoadrenal response. Recently, there is considerable interest in the use of α_2 -adrenergic agonists to provide haemodynamic stability during laryngoscopy and endotracheal intubation.

Dexmedetomidine is eight times more selective than clonidine for the α_2 -adrenergic receptors. The ratio of $\alpha_2:\alpha_1$ activity of dexmedetomidine is 1620:1 as compared with 220:1 for clonidine.^{8,9,10} Therefore, it is assumed that high α_2 selectivity of dexmedetomidine may result in more potent haemodynamic stabilising effects than clonidine. Both clonidine¹¹ & Dexmedetomidine have been used for preventing haemodynamic responses associated with laryngoscopy & endotracheal intubation, but there are only a very few studies comparing clonidine & dexmedetomidine as an attenuating agent for pressor response.

Clonidine has both central action on brain & peripheral action on arteries. It causes fall of blood pressure & associated with bradycardia & a fall in cardiac output. It is said to produce analgesic effect to some extent & provides opioid sparing effect. It may also produce preoperative sedation due to its effect on α_2 receptors centrally.

Midazolam is a short-acting Benzodiazepine acting through modulating the CNS GABA-A receptor, most commonly used premedication to prevent anxiety. It is used as an active control in this study.

Laparoscopic cholecystectomy is one of the most commonly undertaken procedures in general surgery, with overall complication rate being less than 1.5%, and the mortality being less than 0.1%.¹²

In this controlled, randomised, single-blind, unicentric, prospective study, an attempt has been made to observe, assess, and compare the efficacy of preoperative clonidine and dexmedetomidine infusions in attenuating the haemodynamic response following laryngoscopy and endotracheal intubation in three groups of adult patients of either sex undergoing elective laparoscopic cholecystectomies under general anaesthesia and to note any adverse effects of these two study drugs. Injection Midazolam has been taken as a control in this study.

MATERIALS AND METHODS

This prospective, randomised, single-blind, controlled study was done after approval of the Ethical-cum-Screening Committee. In the preanaesthetic check-up clinic, a detailed history was taken from each patient. A thorough general survey (Including body weight and height) was performed along with examinations of the cardiovascular and respiratory, genitourinary, gastrointestinal and central

nervous system. The airway of each patient was assessed according to Mallampati classification. Routine preoperative investigations for complete haemogram, coagulation profiles, blood sugar, serum urea, creatinine, chest x-ray and 12-lead resting electrocardiogram, were performed and evaluated.

Randomly selected, ninety patients in the age group between 25 and 50 years, of either sex, belonging to ASA physical status I and II, Mallampati class I-II undergoing elective laparoscopic cholecystectomy under general anaesthesia were selected for this study. Before performing the study, we hypothesised that the beneficial effect of Dexmedetomidine and clonidine alone will be evident in at least 25% of the patients, after reviewing related articles. Considering an absolute improvement in the primary outcome by 40% in the study group can be considered as clinically relevant and based on a Type I error level of 0.05, Type II error level 0.2 and a two-sided test, we needed 25 patients in each group. Therefore, to account for probable dropouts, a number of 30 patients in each group was proposed. Patients with history of cardiovascular, respiratory, hepatic or renal diseases and those on antihypertensive drugs (e.g. α_2 -agonists, methyldopa, β -blockers, calcium channel blockers, ACE inhibitors), benzodiazepines and tricyclic antidepressants were excluded from the study. Patients with history of drug abuse and having serious adverse reaction or allergy to trial drug were not included in the study. Anticipated difficult intubation (Mallampati class III and IV) and pregnancy were also considered for exclusion criteria.

On the day before surgery, all patients included in the study were re-examined and advised for 8 hours fasting state preoperatively. Written informed consent was taken from all patients after explaining to them about the nature of the study and the risks involved in their own language. All patients were given tablet Alprazolam 0.5 mg at bedtime, in the previous night before the surgery.

On the day of surgery after confirmation of NPO status, patients were shifted to the operating room and connected to multipara monitor, heart rate (HR), noninvasive systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP), continuous lead II electrocardiography (ECG) and oxygen saturation (SpO₂) & EtCO₂ were recorded in every patient with the aid of multiparameter monitor (PHILIPS, IntelliVue, MP20 Anaesthesia). The readings obtained acted as preoperative baseline values. Continuous monitoring of the vital parameters was done. Peripheral vein cannulation with three-way stopcock device was done for fluid infusion and administration of study drug. The 90 patients were randomly allocated into three equal groups (n=30): Group-C (clonidine), Group-D (Dexmedetomidine), and Group M (Midazolam or control). Randomisation was achieved by closed envelopes chosen by patients prior to the procedure, and block randomisation using computer assignment. Group C (n = 30)- Received 100 mL infusion containing inj. clonidine 3 $\mu\text{g kg}^{-1}$ in normal saline. Group D (n = 30)- Received 100 mL infusion containing inj. dexmedetomidine 1 $\mu\text{g kg}^{-1}$ in normal saline. Group M (n = 30)- Received 100 mL infusion containing inj. Midazolam.

The trial drugs were prepared in volumetric infusion sets and given to the investigator (Junior Resident, Department of Anaesthesiology) who was blinded to the identity of drugs.

The infusions were given approximately 20 minutes before induction and infused over 15 minutes through infusion pumps.

After study drug infusion, all patients were given Inj. ondansetron (0.1 mg/kg), Inj. fentanyl (2 mcg/kg) intravenously and preoxygenated for 3 minutes with 100% O₂ through Mapleson A breathing system.

Induction of anaesthesia was done by Inj. Propofol (2 mg/kg) slow intravenously till the loss of verbal response. After successful trial ventilation, muscle relaxation was done by Inj. vecuronium (0.1 mg/kg). Patients were then ventilated with 100% oxygen for about 3 minutes after injection of vecuronium. Subsequently, tracheal intubation with an appropriate size endotracheal tube was performed using a Macintosh laryngoscope in less than 15 seconds. Confirmation of endotracheal placement of tube was done by bilateral chest auscultation and end-tidal carbon dioxide (EtCO₂) monitoring. Maintenance of anaesthesia was done by using N₂O:O₂ at the ratio of 60:40, intermittent dose of Inj. vecuronium, Inj. propofol, analgesics and intravenous fluids based on requirements. Controlled ventilation was carried out with Bain coaxial breathing system adjusting the ventilation to maintain an EtCO₂ level between 35-40 mmHg.

Haemodynamic Parameters (HR, SBP, DBP and MAP) were recorded in the following Specific Time Intervals-

- Before study drug infusion (Baseline Value).
- After study drug infusion.
- After induction of anaesthesia.
- During laryngoscopy and intubation.
- 1 minute after intubation.
- 2 minutes after intubation.
- 3 minutes after intubation.
- 5 minutes after intubation.
- 10 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 neostigmine 50 µg kg⁻¹ and glycopyrrolate 10 µg kg⁻¹ 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.

All the parameters were presented as mean ± SD (Standard Deviation), Demographic data were analysed by student's t-test. Qualitative data (Sex, ASA grade, and postoperative complications) were compared between groups with Chi-Square (χ²) test. Quantitative data (Age, body weight, height, HR, SBP, DBP and MAP) were compared between groups with ANOVA. Haemodynamic parameters within group at different time intervals were compared with baseline value with repeated measures ANOVA. A p value < 0.05 was considered as statistically significant and < 0.01 was considered as highly significant. The results of the observations thus obtained in each group of patients were tabulated, compiled and statistically analysed using statistical software SPSS version 16.0, and Microsoft Word & Excel have been used to generate Tables.

RESULTS

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].

When the preoperative baseline HR was compared between three groups, no statistically significant difference was found (p value 0.9213). HR was also similar in all groups after study drug infusion (p value 0.0953). After induction of anaesthesia, a significant reduction in HR was noted in Group D (p value 0.032). The increases in HR during laryngoscopy and intubation at 1, 2, 3 and 5 minutes after intubation were highly significant in Group M compared to Group C and Group D (p value < 0.01). After 10 minutes of intubation, it was also significant in Group M (p value 0.02) [Table 2].

When the preoperative baseline SBP was compared between three groups, no statistically significant difference was found (p value 0.8433). After study drug infusion, a significant reduction in SBP was noted in Group D (p value 0.0104). After induction of anaesthesia, this reduction in SBP became highly significant in Group D (p value < 0.01). The increases in SBP during laryngoscopy and intubation, at 1, 2, 3 and 5 minutes after intubation were highly significant in Group M compared to Group C and Group D (p value < 0.01). After 10 minutes of intubation, it was also significant in Group M (p value 0.0363) [Table 3].

When the preoperative baseline DBP was compared between three groups, no statistically significant difference was found (p value 0.8082). Significant reductions in DBP were noted in Group D after study drug infusion (p value 0.0374) and after induction of anaesthesia (p value 0.0307). The increases in DBP during laryngoscopy and intubation, at 1, 2, and 3 minutes after intubation were highly significant in Group M compared to Group C and Group D (p value < 0.01). After 5 minutes of intubation, it was also significant in Group M (p value 0.0129). DBP became similar in all groups after 10 minutes of intubation (p value 0.6217) [Table 4].

When the preoperative baseline MAP was compared between three groups, no statistically significant difference was found (p value 0.8923). After study drug infusion, a significant reduction in MAP was noted in Group D (p value 0.0246). After induction of anaesthesia, this reduction in MAP became highly significant in Group D (p value < 0.0069). The increases in MAP during laryngoscopy and intubation at 1, 2, 3 and 5 minutes after intubation were highly significant in Group M compared to Group C and Group D (p value < 0.01). MAP became similar in all groups after 10 minutes of intubation (p value 0.2971) [Table 5].

Postoperative Complications

The HR in the postoperative period less than 60 bpm was considered as bradycardia. Three patients in Group C and two patients in Group D had HR below 60 bpm in the early postoperative period. Postoperative SBP less than 90 mmHg, or DBP less than 60 mmHg, or both were considered as hypotension. It was seen in three patients in Group C, two patients in Group D and two patients in Group M. Hypoxaemia was adjudged by any drop in SpO₂ below 90% and it was seen in six patients (Two in each group) in the early postoperative period. Two patients in each group complained of shivering in the recovery room. Postoperative

nausea was complained by two patients in Group C, two patients in Group D and six patients in Group M.

When these complications were compared between three groups with Chi- Square (χ^2) test, no statistically significant difference was found (p value 0.6688) [Table 6]. Postoperative nausea was complained by two patients in Group C, two patients in Group D and six patients in Group M.

Demographic Variables	Group - C n = 30	Group - D n = 30	Group - M n = 30	P value
Sex (M: F)	12: 18	10:20	10:20	0.8237
Age (Years)	38.03 ± 8.16	39.07 ± 8.39	39.13 ± 8.37	0.8487
Body Weight (KG)	56.07 ± 9.68	56.90 ± 9.94	55.83 ± 8.91	0.9029
Height (Cm)	161.63 ± 9.39	160.03 ± 10.39	159.63 ± 9.57	0.7043
ASA Grade (I : II)	24:6	24:6	23:7	0.9355

Table 1. Comparison of Demographic Variables between Three Study Groups

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].

Heart Rates (Beats per minutes)

Time Interval	Group - C n = 30 Mean ± SD	Group - D n = 30 Mean ± SD	Group - M n = 30 Mean ± SD	P Value
Before Study Drug Infusion (Baseline) T 1	83.13 ± 9.24	84.03 ± 9.14	83.27 ± 9.49	0.9213
After Study Drug Infusion T 2	80.60 ± 8.52	79.17 ± 8.66*	83.93 ± 8.79	0.0953
After Induction of Anaesthesia (T 3)	78.03 ± 8.51*	76.10 ± 8.18**	81.80 ± 8.57	0.0320
During Laryngoscopy & Intubation (T 4)	87.90 ± 6.98*	83.63 ± 6.74	98.47 ± 7.77**	<0.0001
1 Minute After Intubation	93.63 ± 7.06*	87.63 ± 7.55	107.67 ± 6.38**	<0.0001
2 Minutes After Intubation	91.43 ± 7.09**	86.07 ± 7.32	103.13 ± 6.76**	<0.0001
3 Minutes After Intubation	84.50 ± 7.29	81.83 ± 6.72	94.70 ± 8.41**	<0.0001
4 Minutes After Intubation	80.27 ± 6.48	78.00 ± 6.95**	86.63 ± 6.63	<0.0001
5 Minutes After Intubation	77.17 ± 6.69**	76.83 ± 7.03**	81.50 ± 7.48	<0.0001

Table 2. Intergroup Comparison of Mean Heart Rate at Different Points of Time

SD: Standard Deviation

* Statistically significant (p<0.05) [when compared with baseline value within group]

**Statistically highly significant (p<0.01) [when compared with baseline value within group]

Time Interval	Group C n = 30 Mean ± SD	Group D n = 30 Mean ± SD	Group M n = 30 Mean ± SD	P value
Before Study Drug Infusion (Baseline) T 1	121.60 ± 11.76	122.47 ± 12.22	120.63 ± 12.37	0.8433
After Study Drug Infusion T 2	115.77 ± 10.93	119.70 ± 11.97**	118.57 ± 11.12	0.0104
After Induction of Anaesthesia (T 3)	101.87 ± 10.76**	101.33 ± 10.96**	112.83 ± 11.37*	<0.0001
During Laryngoscopy & Intubation (T 4)	123.33 ± 9.69	118.77 ± 8.15	137.60 ± 8.05**	<0.0001
1 Minute After Intubation	130.77 ± 8.11**	123.50 ± 9.10	148.00 ± 7.60**	<0.0001
2 Minutes After Intubation	127.47 ± 8.69*	122.53 ± 8.02	142.47 ± 7.52**	<0.0001
3 Minutes After Intubation	117.67 ± 9.66	113.73 ± 8.51**	130.23 ± 7.97**	<0.0001
4 Minutes After Intubation	110.53 ± 9.84**	110.30 ± 8.66**	119.97 ± 7.87	<0.0001
5 Minutes After Intubation	107.73 ± 9.36**	109.07 ± 8.85**	113.47 ± 8.44*	0.0363

SD- Standard Deviation. *Statistically significant (p <0.05) [When compared with baseline value within group].

**Statistically highly significant (p<0.01) [When compared with baseline value within group].

Time Interval	Group C n = 30 Mean ± SD	Group D n = 30 Mean ± SD	Group M n = 30 Mean ± SD	P value
Before Study Drug Infusion-Baseline (T 1)	80.83 ± 9.44	79.73 ± 9.47	79.27 ± 9.67	0.8082
After Study Drug Infusion (T 2)	75.67 ± 9.09*	72.10 ± 8.25**	78.00 ± 9.17	0.0374
After Induction of Anaesthesia (T 3)	69.97 ± 8.36**	67.67 ± 7.69**	75.53 ± 9.46**	0.0307
During Laryngoscopy & Intubation (T 4)	82.60 ± 9.07	78.37 ± 7.42	87.83 ± 6.65**	< 0.0001
1 Minute After Intubation (T 5)	86.37 ± 9.21*	81.83 ± 7.55	95.87 ± 7.21**	< 0.0001
2 Minutes After Intubation (T 6)	85.00 ± 8.88	80.47 ± 7.15	92.33 ± 6.79**	< 0.0001
3 Minutes After Intubation (T 7)	78.67 ± 9.30	75.93 ± 7.58	83.47 ± 7.21	0.0019
4 Minutes After Intubation (T 8)	74.17 ± 9.24**	73.13 ± 7.41**	78.83 ± 6.52	0.0129
5 Minutes After Intubation (T 9)	71.20 ± 9.08**	72.37 ± 7.88**	73.23 ± 7.27**	0.6217

Table 4. Intergroup Comparison of Diastolic Blood Pressure at Different Points of Time

SD- Standard Deviation

* Statistically significant ($p < 0.05$) [When compared with baseline value within group]

**Statistically highly significant ($p < 0.01$) [When compared with baseline value within group]

Mean Arterial Blood Pressure

Time Interval	Group C n = 30 Mean $\pm$ SD	Group D n = 30 Mean $\pm$ SD	Group M n = 30 Mean $\pm$ SD	P value
Before Study Drug Infusion- Baseline (T 1)	94.33 $\pm$ 10.19	93.90 $\pm$ 10.33	93.07 $\pm$ 10.57	0.8923
After Study Drug Infusion (T 2)	89.07 $\pm$ 9.59*	84.70 $\pm$ 9.41**	91.43 $\pm$ 9.66	0.0246
After Induction of Anaesthesia (T 3)	82.03 $\pm$ 9.14**	78.90 $\pm$ 8.68**	86.67 $\pm$ 10.09*	0.0069
During Laryngoscopy & Intubation (T 4)	96.10 $\pm$ 9.11	91.83 $\pm$ 7.49	104.47 $\pm$ 6.88**	<0.0001
1 Minute After Intubation (T 5)	101.13 $\pm$ 8.51**	95.80 $\pm$ 7.91	113.20 $\pm$ 7.18**	<0.0001
2 Minutes After Intubation (T 6)	99.23 $\pm$ 8.63*	94.50 $\pm$ 7.33	109.07 $\pm$ 6.81**	0.0001
3 Minutes After Intubation (T 7)	91.73 $\pm$ 9.25	88.57 $\pm$ 7.61*	99.00 $\pm$ 7.33*	<0.0001
4 Minutes After Intubation (T 8)	86.30 $\pm$ 9.21**	85.50 $\pm$ 7.51**	92.50 $\pm$ 6.80	0.0014
5 Minutes after Intubation (T 9)	83.37 $\pm$ 8.98**	84.60 $\pm$ 7.93**	86.63 $\pm$ 7.58**	0.2971
Table 5. Intergroup Comparison of Mean Arterial Pressure at Different Points of Time				

SD- Standard Deviation. *Statistically significant ($p < 0.05$) [When compared with baseline value within group].

**Statistically highly significant ($p < 0.01$) [When compared with baseline value within group].

Postoperative Complications	Group – C n = 30	Group – D n = 30	Group – M n = 30
Bradycardia	3	2	0
Hypotension	3	2	2
Hypoxaemia	2	2	2
Shivering	2	2	6
Post-Operative Nausea Vomiting	2	2	2
Table 6. Comparison of Postoperative Complications between Three Study Groups			

Statistical Analysis- Chi Square Test value 5.8070, p value 0.6688.

DISCUSSION

Laryngoscopy and endotracheal intubation are associated with rise in heart rate, blood pressure and occasional disturbance in cardiac rhythm.^{1,3} Although in normotensive subjects these responses of blood pressure and heart rate are transient and short lived,⁵ they may prove to be detrimental in high risk patients especially in those with cardiovascular disease, increased intracranial pressure and anomalies of the cerebral blood vessels.⁶ So, effective attenuation of haemodynamic response to laryngoscopy and tracheal intubation is of great importance in prevention of perioperative morbidity and mortality.

In this controlled, randomised, single-blind, unicentric, prospective study, an attempt has been made to observe, assess, and compare the efficacy of preoperative clonidine and dexmedetomidine infusions in attenuating the haemodynamic response following laryngoscopy and endotracheal intubation in three groups of adult patients of either sex undergoing elective laparoscopic cholecystectomies under general anaesthesia. Injection Midazolam has been taken as a control in this study.

The factors influencing the cardiovascular changes associated with laryngoscopy and intubation are age, drugs, type and duration of procedures, depth of anaesthesia, hypoxia and hypercarbia. Variations in heart rate to stressful events decrease with increasing age. Young patients show more extreme changes.¹³ Marked fluctuations in haemodynamic response have been also reported in geriatric patients.^{14,15} Therefore, patients with an optimal age range of 25 to 50 years were selected for this study. Difficult intubation takes longer time and is invariably associated with marked haemodynamic change even in well premedicated patients. So, patients with higher Mallampati class (III and IV) were excluded from this study. Patients on antihypertensive drugs were also excluded as they might exhibit a decrease in pressor response to laryngoscopy and intubation. α_2 -agonists are extensively metabolised in liver and excreted in urine. Therefore, patients with altered liver functions and renal functions were not included in this study. The safety of α_2 -agonists in pregnancy is not well established till now. So, we excluded the women of reproductive age group with a history of amenorrhoea and a positive urine test for pregnancy. Ideally, dexmedetomidine should be used as continuous infusion after a loading dose to achieve a sustained clinical effect as it has a short distribution half-life ($t_{1/2 \alpha}$) of 6 minutes. This multiple dosing is not recommended for clonidine. Here we used only loading dose of dexmedetomidine to blind our study easily. This is a short clinical study and main focus was on the first few minutes following laryngoscopy and intubation. This is another reason for using single dose of dexmedetomidine.

After study drug infusion, a significant fall in HR (p value<0.05) and highly significant fall in NIBP (SBP, DBP and MAP) (p value<0.01) were noted in Group D. Though a decreasing trend in haemodynamic parameters was observed in Group C after study drug infusion, but only DBP and MAP became significant (p value<0.05). This is most probably due to the difference between the onsets of action of two study drugs. Dexmedetomidine has rapid onset of action (15 minutes) after its administration while clonidine exhibits its clinical effects 30 minutes after the initial dose.

BP decreased further in all groups after induction of anaesthesia. These decrements were highly significant in Group C and Group D (p value <0.01) and significant in Group M (p value <0.05). This is most likely due to vasodilatation and depression of medullary vasomotor centre caused by propofol. The baseline HR and post-induction HR were similar in Group M (p value >0.05). HR decreased significantly from the baseline value in Group C (p value <0.05) and Group D (p value <0.01) after induction of anaesthesia due to the negative chronotropic effect of the α_2 -agonists.

The most significant factor influencing cardiovascular responses is the duration of laryngoscopy.¹⁶ The force applied during laryngoscopy has only minor effect. In this study, the durations of laryngoscopy and intubation were limited to less than 15 seconds. During laryngoscopy, adequate depth of anaesthesia was maintained avoiding hypoxia and hypercarbia. In all groups, peak haemodynamic surges were observed at 1 minute after intubation. HR increased from the baseline value by 12.6% and 4% in Group C and Group D respectively. In control group M, a rise of 29.3% in HR was noted and this was statistically highly significant (p value <0.01). Similarly, BP increased by 7 to 7.5% in Group C, 1 to 2.5% in Group D and 21 to 23% in Group M (p value <0.01). This one-minute post-intubation peak corroborates with the result of the study by Derbyshire DR et al (1983)¹⁷ and Shribman AJ et al (1987)¹⁸ who concluded that plasma catecholamine concentration increased to their maximum at 1 minute after laryngoscopy.

These altered pressor responses were normalised after 3 minutes in Group C and 5 minutes in Group M. This finding is again in agreement with the study by Shribman AJ et al (1987)¹⁹ which shows that plasma catecholamine concentration comes down by 3 to 5 minutes after laryngoscopy. Haemodynamic parameters in Group D remained around the baseline value in first 2 to 3 minutes after intubation followed by a gradual fall in the next few minutes. Thereafter, no alteration in HR and BP was seen in Group D. Similar findings were documented by Kaya C et al (2006)²⁰ in their study with intramuscular dexmedetomidine.

A few patients in all groups showed certain dysrhythmias during laryngoscopy and intubation on continuous ECG monitoring. These included mostly sinus tachycardia and ventricular premature contractions. However, none of these dysrhythmias reached alarming levels during the study to require treatment and converted to normal sinus rhythms spontaneously. It has been shown by various authors like Shribman AJ et al (1987)¹⁹ and Bedford RF (1988)²¹ that reflex autonomic responses provoked by laryngoscopy and endotracheal intubation could cause various types of dysrhythmias.

Regarding other complications, three patients in Group C and two patients in Group D had bradycardia in the early postoperative period. Intravenous atropine 0.5 mg was prescribed to them to normalise the HR. Postoperative hypotension was seen in three patients in Group C, two patients in Group D and two patients in Group M. They were treated with intravenous colloid infusion. Hypoxaemia was seen in six patients (Two in each group) in the early postoperative period, which was corrected by the administration of oxygen by face mask alone. None of them had to be intubated or required artificial ventilation

postoperatively. Two patients in each group complained of shivering in the recovery room, which was resolved with warm blanket covering and oxygen supplementation. Postoperative nausea was complained by two patients in Group C, two patients in Group D and six patients in Group M. These patients were treated with intravenous ondansetron.

In 2007, Dogru K et al²² assessed the effectiveness of a single preinduction intramuscular bolus dose of dexmedetomidine 2.5 $\mu\text{g kg}^{-1}$ in attenuating haemodynamic responses to tracheal intubation and rapid-sequence anaesthesia induction in hypertensive patients treated with angiotensin-converting enzyme inhibitors and concluded that intramuscular dexmedetomidine 2.5 $\mu\text{g kg}^{-1}$ administered 45 to 60 minutes before induction attenuated haemodynamic responses to tracheal intubation in patients with essential hypertension. In 2007, İşik B et al also studied the effects of α_2 -adrenergic receptor agonist dexmedetomidine on haemodynamic response in direct laryngoscopy. They used intravenous dexmedetomidine 1 $\mu\text{g kg}^{-1}$ and midazolam 0.05 mg kg^{-1} in two groups of patients. The findings of their study showed that dexmedetomidine controlled hypertension and tachycardia following direct laryngoscopy more efficiently without prolonging the recovery time as compared to midazolam. In 2008, Kaymak Ç et al²³ studied the effects of low (0.45 $\mu\text{g kg}^{-1} \text{ hr}^{-1}$) and moderate (0.6 $\mu\text{g kg}^{-1} \text{ hr}^{-1}$) doses of dexmedetomidine infusions by evaluating haemodynamic and neuroendocrine responses in patients undergoing elective transurethral surgery under desflurane anaesthesia. They suggested that intraoperative low and moderate doses of dexmedetomidine result in similar intubation, recovery and haemodynamic responses. Cardiovascular and neuroendocrine parameters were suppressed more efficiently by moderate dose of dexmedetomidine. In 2008, Smania MC et al²³ also carried out a randomised controlled trial in 26 children undergoing video laparoscopic appendectomy under isoflurane anaesthesia and used dexmedetomidine infusion of 1 $\mu\text{g kg}^{-1}$ over 10 minutes and then maintained with a dose of 0.5 $\mu\text{g kg}^{-1} \text{ hr}^{-1}$. During the strongest nociceptive stimuli (Airway access and abdominal catheter placement), the heart rate and systolic blood pressure increased significantly in the control group as compared to the dexmedetomidine group. Compared to baseline levels, the haemodynamic responses to nociceptive stimuli were less when dexmedetomidine was used in combination with inhaled isoflurane. The need for supplemental doses of fentanyl and the haemodynamic parameters were similar in both groups.

In 2010, Bhattacharjee DP et al²⁵ carried out a randomised clinical trial to evaluate the efficacy of dexmedetomidine infusion (0.2 $\mu\text{g kg}^{-1} \text{ hr}^{-1}$) to provide perioperative haemodynamic stability in patients undergoing elective laparoscopic cholecystectomy. Mean arterial pressure and heart rate in the dexmedetomidine group were significantly less after intubation and pneumoperitoneum than the control group. In 2010, İlhan O et al²⁶ compared the efficacy of dexmedetomidine and fentanyl in patients undergoing intracranial tumour surgery. They found that dexmedetomidine controlled the haemodynamic changes better than fentanyl intraoperatively, after extubation and during the early postoperative period. In 2012, Bhandari D et al²⁷ carried out a prospective randomised double blinded comparative study. They studied efficacy of oral Clonidine

(150 micrograms 90 minutes before induction of anaesthesia) in reducing perioperative haemodynamic instability & to assess the haemodynamic changes during laparoscopic cholecystectomy and to find the effect of oral clonidine premedication in prevention of these haemodynamic responses. When vital parameters were compared significant rise in heart rate, systolic and mean blood pressure was noted in control group following intubation & pneumoperitoneum, whereas in clonidine group the rise if present was not more than 10% of baseline. In 2012, Sukhminder et al also conducted a prospective randomised controlled study to investigate the haemodynamic effect of intravenous dexmedetomidine (1 mcg/kg) as an adjunct to anaesthetic induction to attenuate haemodynamic response to endotracheal intubation & dose sparing of opioid & isoflurane to achieve adequate analgesia & anaesthesia. Authors noted that the pressor response to laryngoscopy, intubation, surgery & extubation were effectively decreased by dexmedetomidine (1 mcg/kg) IV given over 15 min. before induction and were highly significant on comparison ($p < 0.001$). The mean dose of fentanyl & isoflurane also decreased significantly (>50%) by administration of dexmedetomidine.

In 2006, Kaya C et al²⁰ carried out a randomised controlled trial in 57 patients undergoing elective abdominal surgery under desflurane anaesthesia to study the effects of intramuscular dexmedetomidine premedication on haemodynamics, plasma norepinephrine, cortisol and glucose concentrations. They concluded that intramuscular 1 $\mu\text{g kg}^{-1}$ dexmedetomidine decreased opioid requirement at induction and at postoperative period and suppressed the surge of norepinephrine as a response to anaesthetic and surgical stress.

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 is the major limitation of our study.

CONCLUSION

From these observations and analysis of the present study, it can be inferred that both clonidine and dexmedetomidine administered intravenously just before laryngoscopy and endotracheal intubation effectively attenuate the haemodynamic response by limiting the extent of rises in heart rate and blood pressure. Dexmedetomidine has been found to provide better haemodynamic stability than clonidine. Both the α_2 -agonists are devoid of any serious adverse effect and found safe in this study.

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