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Comparison of efficacy between clonidine and Dexmedetomidine in attenuating the cardiovascular response to laryngoscopy & intubation in laparoscopic cholecystectomy

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Abstract

Laryngoscopy and tracheal intubation are nearly always associated with an increase in the blood pressure and an increase in heart rate due to reflex sympathetic discharge which is caused by epipharyngeal and laryngopharyngeal stimulation. In recent years the laparoscopic surgery which once upon a time were considered to cause least trauma are reported to have hemodynamic instability. Conclusively during general anesthesia, it is desirable to have a stable intraoperative hemodynamic status. Hence in this study, it has been attempted to compare the beneficial effect and also side effect of the two α_2 -agonist clonidine and Dexmedetomidine in maintaining the perioperative parameters like MAP, heart rate.

Keywords: General anesthesia, clonidine, Dexmedetomidine, heart rate, mean arterial pressure

Introduction

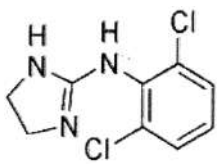
Laryngoscopy and tracheal intubation are nearly always associated with an increase in the blood pressure and an increase in heart rate due to reflex sympathetic discharge which is caused by epipharyngeal and laryngopharyngeal stimulation. This increased sympathoadrenal activity may result in hypertension, tachycardia and arrhythmia. Thus hemodynamic stability during perioperative period is of paramount importance as there are many patients who have a compromised cardiovascular and are on medication. Critical event during perioperative period especially during induction, intubation and surgical stimulus initiate metabolic response to trauma that need to be considered and attended. In recent years the laparoscopic surgery which once upon a time were considered to cause least trauma are reported to have hemodynamic instability^[1]. The anesthesiologists traditional approach to anesthesia for laparoscopic cholecystectomy has been the emphasis on the maintaining hemodynamic stability by avoiding hypertension, hypotension and tachycardia. The problem has been more complex than has been originally thought and most of the hemodynamic instability is persistent during the duration of pneumoperitoneum. Numerous agent and combination of agents has been used in an effort to minimize the hemodynamic instability during this period. Alpha 2-adrenergic agonists decrease sympathetic tone and preoperative use of clonidine has been shown to blunt the hemodynamic response to noxious stimulation and to prevent the overall hemodynamic variability^[2-4]. It has also sedative and anesthetic sparing effects. Dexmedetomidine is a highly selective alpha 2-receptor agonist having 8 times high affinity and alpha 2 selectivity compared to clonidine and has a shorter duration of action than clonidine. It provides anesthetic sparing effect, anxiolysis, co-operative sedation and analgesia without respiratory depression. The mechanism of action of Dexmedetomidine differ from clonidine as it possesses selective alpha 2-adrenoceptor agonist, especially for the 2A subtype of this receptor, which causes it to be a much more effective sedative and analgesic agent than clonidine^[5].

Objective: To compare the efficacy of Dexmedetomidine with clonidine in attenuating the cardiovascular response to laryngoscopy & intubation.

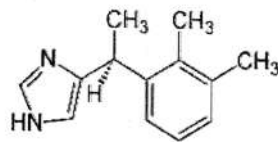
Basic Pharmacology-physiology: The alpha-2 adrenoceptor is a transmembrane receptor. This is an excitable protein which traverses the cell membrane and reacts selectively with extracellular ligands (endogenous hormones or exogenous molecules such as drugs)

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to initiate a cascade of events leading to a physiological effect. The three alpha-2 receptor subtypes are 72-75% identical to each other with respect to amino acid sequence in the membrane-spanning domains. Pre synaptic alpha-2 adrenoceptors are present in sympathetic nerve endings and noradrenergic neurons in the central nervous system where they inhibit the release of noradrenaline. Postsynaptic alpha-2 adrenoceptors exist in a number of tissues where they have a distinct physiological function. These include the liver, pancreas, platelets, kidney, adipose tissue and the eye [6, 7]. The medullary dorsal motor complex in the brain has a high density of alpha-2 adrenoceptors and activation of these may be responsible for the hypertensive and bradycardic effects of alpha-2 adrenoceptor agonists. The locus coeruleus is an important modulator of wakefulness and may be the major site for the hypnotic action of alpha-2 adrenoceptor agonists mediated by alpha-2a adrenoceptors located there.



Dexmedetomidine



Clonidine

Clonidine is an imidazole and is the only alpha-2 adrenoceptor agonist. It is a partial agonist with an alpha-2a-to -alpha-1 selectivity ratio of 39. The alpha-2a-to-imidazoline selectivity ratio is 16. Dexmedetomidine, a more specific and shorter-acting alpha-2 adrenoceptor agonist with an alpha-2 a-to-alpha-1 ratio of 1300 and alpha-2a-to-imidazoline selectivity ratio of 32.

Intravenous alpha-2 adrenoceptor agonist administration leads to a decrease in heart rate and a transient increase in arterial blood pressure and systemic vascular resistance, but a decrease in cardiac output due to the activation of post junctional vascular alpha-2 adrenoceptors. This is followed by a longer lasting decrease in heart rate and blood pressure due to a centrally mediated decrease in sympathetic tone and an increase in vagal activity. Neither the exact location nor the specific receptors responsible for the central hypotensive action of alpha-2 adrenoceptor agonists are yet known. It seems that postsynaptic alpha-2 adrenoceptors and imidazole receptors in the brainstem are involved. The bradycardia commonly seen after administration of alpha-2 adrenoceptor agonists may be due to the central sympatholytic action of these drugs leaving vagal tone unopposed. It may also be due to presynaptic-mediated reduction of noradrenaline release or a direct vagomimetic action.

Physiology of Laparoscopy

Increased TAP affects venous return (VR), SVR and myocardial function. Initially owing to auto transfusion of pooled blood from splanchnic circulation, there is an increase in circulating blood volume, resulting in an increase in VR & cardiac output. The supine position and general anesthesia decreases functional residual capacity (FRC). Pneumoperitoneum and Trendelenburg position cause cephalad shift of the diaphragm, further decreasing FRC, to values less than the closing volume, causing airway collapse, atelectasis, ventilation perfusion (V/Q) [8, 9].

Materials and Methods

This study was conducted during the period of Dec. 2014 to Dec. 2015. The study design was Double Blind Randomized Control Trial. The study population comprised of 90 patients of ASA grade 1 & 2, aged between 20 yr. & 65 yr. written informed consent was taken from each patient. The patient were randomly assigned to one of the three groups, each containing 30 patients.

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Sample size calculation

Based on previous studies the sample size was calculated using the formula as below;

$$2(Z\alpha + Z\beta) 2x 2s^2$$

$$N = (x1 - x2)^2$$

Where, S	=	Variance
S2	=	(S1)2 + (SZ)2
S1 S2	=	Standard Deviations
X1 X2	=	Means
A	=	Error is taken as 5%
Power	=	80%

$$2(Z\alpha + Z\beta)2x 2s^2$$

$$n = (x1 - x2)^2$$

$$S1 = 60$$

$$S1 = 7.8$$

$$X2 = 94$$

$$S2 = 12.4$$

$$2(1.96 + 0.84)2 x \{(94)^2 + (12.4)^2\}$$

$$n = (60 - 7.8)^2$$

The minimum value of n1 is found to be 7

$$2(Z\alpha + Z\beta) 2x0.84)^2 x \{(5)^2 + (7)^2\}$$

$$n = (15 - 28)^2$$

$$X1 = 15$$

$$S1 = 5$$

$$X2 = 28$$

$$S2 = 7$$

The minimum value of n2 is found to be 7.

The n1 and n2 were calculated and among the two the larger value that is, seven was taken as the minimum sample size for each of the three groups. However, it was decided to study 15 cases in each group.

Selection Criteria

Inclusion

1. ASA Grade I and II.
2. Age between 20 to 65 years
3. Patient having cholelithiasis & undergoing laparoscopic cholecystectomy.

Exclusion

1. Patient refusal.
2. Patient with known allergy to drug.
3. Patients with known allergy to drug.
4. Hypertensive patients on treatment with Beta Blockers, Methyl Dopa, MAO inhibitors.
5. Patients with Renal dysfunction.
6. Patients with elevated AST, ALT values.
7. Morbid obesity, diabetes.

- 8. Pregnant & nursing women.
- 9. Patient having difficult airway.

Randomization

Based on the computer generated randomization, patients were randomly allocated to three group as below.

- Group P (Placebo group; n = 30) - Received normal saline (50 ml in 10 mm)
- Group C (Clonidine group; n = 30) - Received 2mcg/kg of Inj Clonidine in 50 ml 0.9% normal saline in 10 min.
- Group D (Dexmedetomidine group; n = 30) - Received 1 mcg/kg of Inj Dexamedetomidine in normal saline in 10 min.

The ethical clearance for the study was obtained from the Institutional Ethics Committee. Patients undergoing elective laparoscopic cholecystectomy, under general anesthesia were screened for the eligibility. Patients fulfilling selection criteria were selected for the study and briefed about the nature of study and explained about anesthetic procedure. A written informed consent was obtained from the patient. The doses of Clonidine and Dexmedetomidine were intended to be equipotent. All prefilling, coding and decoding was done in the Department of Clinical Pharmacy. Two IV line were secured, one 20 G IV cannula in right hand for the infusion and another 18 G IV cannula in left hand for Intravenous fluids and drug administration. 500 ml of crystalloids (Ringer Lactate) was started. HR. MAP and SpO2 using

pulse oximeter were monitored before, during and after the surgery. End tidal Carbon Dioxide was monitored intraoperatively and kept between 25 to 30 mm of Hg. Mean arterial pressure and HR was measured at;

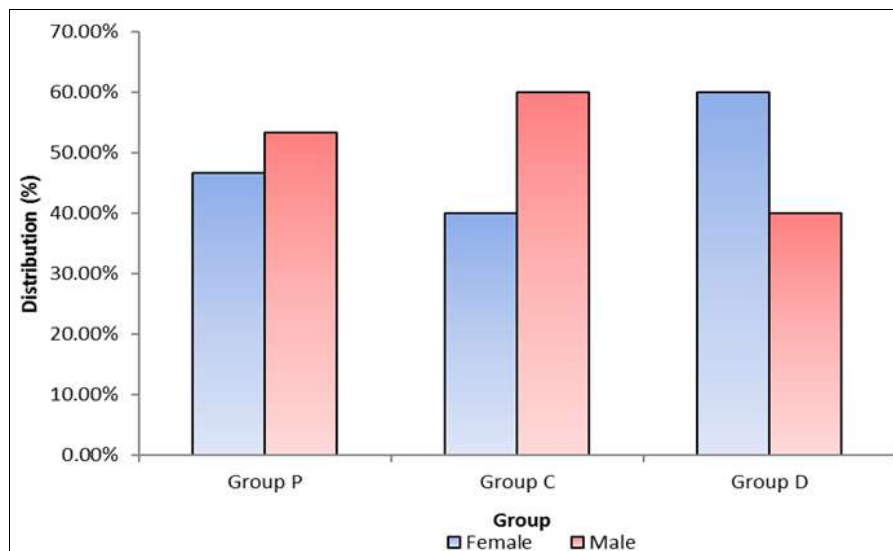
- Preoperative (M1)
- 10 mm after starting Study Drug Infusion(M2)
- At Induction (M3)
- During intubation (M4)
- 1 min after intubation (M5)
- 3 min after intubation (M6)
- 5 min after intubation (M7)
- 10 min after intubation (M8)
- Then every 30 mm till end of surgery
- End of Pneumoperitoneum (N1)
- After Reversal (N2)
- Postoperative in Recovery room (N3)

Data was expressed as mean and standard deviation (SD). The homogeneity in three groups of mean and SD was analyzed using SSPS version 17.0, one-way analysis of variance for each parameter. Scheffe’s test is used to compare pair wise data. Tables of mean and standard deviation were prepared for meaningful comparison of the three groups. A p value of less than or equal to 0.05 was considered as significant.

Observations and Results

Table 1: Tables of mean and standard deviation were prepared for meaningful comparison of the three groups.

Characteristics	Group P	Group C	Group D	‘p’ value
Age (Years)	43.27±13.14	44.93±8.16	45.93±11.20	0.8
Weight (KG)	59.47 ± 8.57	59.27 ± 4.96	53.80 ± 7.31	0.057
Duration of surgery (Mm)	68.13±12.38	83.47±27.67	79.53±19.89	0.127



Graph 1: Sex Distribution

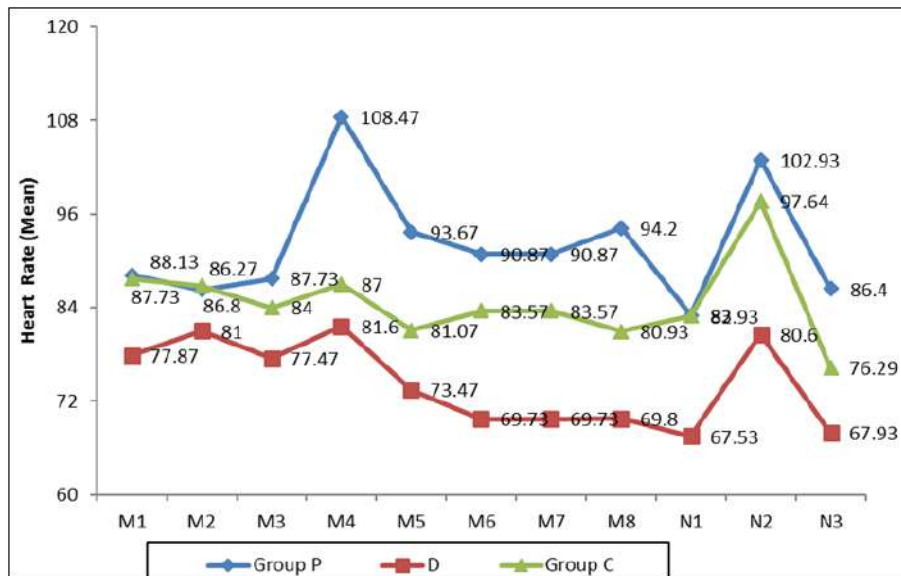
Average age in Group P (Placebo Group) was 43.27 year, in Group C (Clonidine Group) was 44.93 year and in Group D (Dexmedetomidine Group) was 45.93 years. Average weight in Group P (Placebo Group) was 59.47 kg, in Group C (Clonidine Group) was 59.27 yr and in Group D

(Dexmedetomidine Group) was 53.80kg. Average duration of surgery in Group P (Placebo Group) was 68.13 min in Group C (Clonidine Group) was 83.47 min and in Group D (Dexmedetomidine Group) was 79.53 min.

Table 2: Heart Rate

Time interval	Group P	Group D	Group C	'p' value
M1	88.13±13.88	77.87± 8.03	87.73±16.35	0.936
M2	86.27± 12.49	81.00± 12.07	86.80± 14.99	0.423
M3	87.73 ± 16.05	77.47± 13.13	84.00± 15.73	0.179
M4	108.47±17.35#	81.60± 10.40	87.00± 19.65	0.0001
M5	93.67± 15.50*	73.47± 12.56*	81.07+ 19.18	0.005
M6	90.87± 12.55*	69.73 ± 11.55*	83.57±22.38	0.004
M7	90.87± 12.55*	69.73 ± 11.55*	83.57±22.38	0.003
M8	94.20± 14.25	69.80± 11.35*	80.93±20.62	0.001
N1	83.00± 11.10	67.53 ± 12.22	82.93±18.73	0.006
N2	102.93 ± 10.52	80.60 ± 8.83#	97.64±19.02	0.0002
N3	86.40 ± 10.45*	67.93± 9.87*	76.29±16.43	0.001

* - Differ significantly with each other
 #- Differs significantly with other two



Graph 2: Graph heart rate

Group P (Placebo Group) and Group C (Clonidine Group) Heart rate in Group P (placebo group) increased significantly when compared to Group C (Clonidine group) during intubation (M4), after 1 min of intubation (M5), 3 min after intubation (M6), 5 min after intubation (M7), 10 min after intubation (M8), end of pneumoperitoneum (N1), after reversal (N2) and post operatively in recovery (N3) ($p < 0.05$).

Group P (Placebo Group) and Group D (Dexmedetomidine Group)

Similarly, statistically difference in heart rate was found between the two groups during intubation (M4) and after intubation at the time reading of M5, M6, M7 and M8 ($p < 0.05$), when heart rate increased significantly in Group P (Placebo Group) compared to Group D (Dexmedetomidine

Group)

Group C (Clonidine Group) and Group D (Dexmedetomidine Group)

The decrease in heart rate appeared more in Group D (Dexmedetomidine Group) at all intervals when compared to Group C (Clonidine Group) but the decrease was found to be statistically significant at end of pneumoperitoneum (N1) and after reversal (N2) ($p < 0.05$) when heart rate was found to be more in Group C (Clonidine group).

The difference in HR between the Dexmedetomidine group (D) and the clonidine group (C) remained statically significant during intubation, at 1 and 3 min of the assessment ($p < .05$). The difference in HR between Dexmedetomidine group (d) and clonidine group (C) was not significant at 5 and 10 mm (M5 and M6) ($p > .05$).

Table 3: Systolic Blood Pressure (mean)

Time interval	Group P	Group D	Group C	'p' value
M1	121.17±13.88	120.97	121.47	.859
M2	122.97	123.11	122.19	.785
M3	122.15	113.15	115.43	.9494
M4	163.97	130.17	144.23	.001
M5	164.89	122.115	127.27	.001
M6	160.73	120.17	125.27	.003
M7	155.93	119.97	123.43	.015
M8	153.73	120.15	122.45	.025

The changes in the SBP and their statically comparisons indicates that though there was an increase in SBP in all three group, measured just after drug administration, the difference was not significant. However, during induction (about 2 min after drug administration) both Dexmedetomidine group (D) and clonidine group (C) started to decrease SBP, whereas in the placebo group (P) SBP remained elevated with a difference that has statically significant compared to Dexmedetomidine group (D) ($p < .01$), but not compared to clonidine group (C) ($p > .05$). Statically significant difference was observed with the Dexmedetomidine and clonidine group and compared to the control group during intubation and subsequent assessment at 1,3,5 and 10 min ($p < .001$). The attenuation of the SBP as highly significant in the

Dexmedetomidine (D) group as compared to that in the clonidine group ($p < .05$) at intubation, 1 and 3 min and $p < .005$ at 5 and 10 min. During the laryngoscopy and intubation, a maximum rise of only 7.19% (135.3 ± 15.21) was observed from its baseline (124.44 ± 14.19) as compared to the 14.76% (148.09 ± 10.1) increase in the clonidine group from its baseline (129.54 ± 11.5) ($p < .05$) and 25.657% (167.9 ± 15.79) increase in the control group from baseline (133.5 ± 17.83). At 10 min the SBP, which was recorded was 4.67% (120.52 ± 7.88) lower than the basal value in Dexmedetomidine group, which was nearly equal to baseline in clonidine group (129.54 ± 11.5) and 16.45% (155.4 ± 5.58) more than the baseline value (133.5 ± 17.83) in control group ($p < .001$).

Table 4: Diastolic Blood Pressure

Time interval	Group P	Group D	Group C	'p' value
M1	79.18± 8.65	80.07±9.47	80.91 ± 8.67	0.936
M2	80.53± 8.36	81.67 ± 7.52	82.58 ± 8.86	0.779
M3	82.09 ± 11.64	75.20 ± 9.44	82.20 ± 8.39	0.860
M4	100.98±14.03#	82.69± 10.97	95.22±8.94	0.0001
M5	100.27± 18.52	80.51 ± 12.70	94.06± 12.86	0.209
M6	100.64±12.03*	79.62±11:08*	85.50±17.05	0.014
M7	101.67 ±6.82*	78.33 ± 9.32*	82.64±16.34	0.034
M8	99.71±8.93*	78.60±10.25	80.52± 11.87	0.007
N1	101.87±6.15*	91.60±10.15*	95.55± 13.01	0.025
N2	111.62±8.70*	97.69±7.23*	105.66±14.22	0.003
N3	101.64±8.26#	90.00±6.19	91.95±11.08	0.001

Group P (Placebo Group) and Group C (Clonidine Group) Diastolic BP in Group P (Placebo Group) were significantly higher during intubation (M4), 1 min after intubation (M5), 3 min after intubation (M6), 5 min after intubation (M7) 10 min after intubation (M8) end of pneumoperitoneum (N1), after reversal (N2) and post operatively in recovery (N3) ($p < .05$) compared to Group C (Clonidine group). Group P (Placebo Group) and, Group D (Dexmedetomidine Group)

Diastolic BP in Group P (Placebo Group) were significantly higher during intubation (M4) and the subsequent assessment at 1, 3, 5 and 10 min and post operatively in recovery (N3) ($p < .5$) compared to Group III (Dexmedetomidine group).

Group C (Clonidine Group) and Group D (Dexmedetomidine Group)

There was no statistically significant difference in DBP between two groups MAP between the two groups were found to be comparable.

There was no significant difference in DBP among all the groups just after drug administration. However, during

induction (about 2 min after drug administration) dexmed. Group (D) had a significant decrease in DBP compared to placebo group (P) ($p < .001$) and clonidine group (C) ($p < .05$), though no significant difference in between placebo and clonidine group was observed.

A significant difference was observed from placebo group in both dexmed. and clonidine group ($p < .001$) during intubation and at all the subsequent levels. The maximum rise was only 3.57% (83.05 ± 9.7) in Dexmedetomidine group, statically significant than 19.32% (93.54 ± 7.9) in clonidine group ($p < .001$) and 30.75% (100.08 ± 7.78) in the control group ($p < .001$) during intubation.

Dexmedetomidine was efficient in the attenuation of the DBP compared to clonidine at all the time internal after intubation that is, at 1, 3, 5 and 10 min ($p < .05$) it achieved 5% (76 ± 8.81) lower values than the basal DBP value (79.59 ± 10.12) at 10 min compared to 3.84% (81.7 ± 6.50) higher than basal DBP value of clonidine (78.5 ± 9.23) and 27.72% (98.5 ± 3.80) higher than basal value of control (77.2 ± 9.48), which was statically significant ($p < .05$ & $p < .001$, respectively for clonidine and placebo group).

Table 5: Recovery time following extubation

Time (Min)	Group P	Group D	Group C	'p' value
Ability to vocalize following extubation	6.8 ± 2.40#	2:67 ± 0.98	3.46 ± 2.03	<0.0001

Ability to vocalize following extubation was significantly prolonged in Group P (Placebo Group) when compared to Group C (Clonidine Group) and Group D (Dexmedetomidine group).

There was no significant difference in recovery profile between Group C (Clonidine Group) and Group D (Dexmedetomidine group).

Table 6: Isoflurane requirement (Number of patients requiring 1 to 1.5% Isoflurane)

Drug	Group P	Group D	Group C
Isoflurane	15 (100%)	4 (26.67%)	5 (33.33%)

All the patients in group P required 1 to 1.5% isoflurane during the intraoperative period whereas 26.67% patients in

group D and 33.33% patient in group C required isoflurane 1 to 1.5% isoflurane during the intraoperative period.

Table 7: Use of Atropine (0.6 mg IV)

Drug	Group P	Group D	Group C
Atropine	0 (0%)	3 (20%)	1 (6.67%)

In this study atropine requirement was found in 20% of the patients (3/15) in group D whereas, 6.67% patients (1/15) required atropine in group C.

Discussion

Hypertension, tachycardia and dysrhythmia are common hemodynamic disturbance in patient undergoing laryngoscopy and intubation. In addition, there is increased in systemic vascular resistance, and is associated with a decrease in cardiac index and metabolic changes. Above mentioned effect may have serious repercussion on the high-risk patient like those with cardiovascular disease, increased intracranial pressure, or anomalies of the cerebral vessels. Attenuation of such response is of great importance in the prevention of the perioperative morbidity and mortality. Previously it was thought that the stimulation of the upper respiratory tract provoked an increased in the vagal acting. Now it is found that the pressure response is provoked by the stimulation of the epipharynx and the laryngopharynx^[10-12]. A diversity of result exists about the protective measure against the hemodynamic and the catecholamine responses to laryngoscopy and intubation, but no single anesthetic technique has become generally accepted as being effective in preventing or attenuating these responses. Many techniques have been recommended. The drugs which were used were either partially effective or they produced other undesirable effect on patients^[13, 14]. In any study which is conducted, the criteria for the selection of the appropriate drug to prevent a sympathetic response must include the following.

The drug must be applicable, regardless of the patient collaboration, and it must prevent impairment of the cerebral blood flow and avoid the arousal of the patient. The administration of the drug should neither be time consuming nor should it affect the duration or the modality of the ensuing anesthesia. Intravenous Dexmedetomidine and clonidine appear to best fulfill the above criteria.

In our study we compare the efficacy of Dexmedetomidine and clonidine infusion on hemodynamic stability during laryngoscopy and intubation in patient undergoing laparoscopic cholecystectomy.

The alpha 2-adenoreceptor agonist have been used as premedicants because of their beneficial properties in anesthesia. Clonidine, which is mainly used as an anti-hypertensive agent, has many properties of an ideal premedicant, and it also has beneficial effect on the hemodynamics during stressful conditions like laryngoscopy and endotracheal intubation^[15]. The effect of clonidine on the hemodynamic variable are dose related, but increase in dose to more than 4 micrograms/kg do not further enhance the efficacy. Hence in this study, we used 2 micrograms/kg.

Dexmedetomidine is highly selective alpha 2-receptor agonist having eight times high affinity and alpha 2 selectivity compared to clonidine and has a shorter duration of action than clonidine. With Dexmedetomidine use, there is significant reduction in circulating catecholamine with a decrease in blood pressure and a modest reduction in HR

^[16]. Sagrigolu *et al.*^[17] conducted a study with different doses of Dexmedetomidine and found that to control hemodynamic response to tracheal intubation, Dexmedetomidine 1 micrograms/kg is more effective than Dexmedetomidine 0.5 micrograms /kg without any side-effect. Hence, we conducted the study with a dose of 1 microgram/kg of Dexmedetomidine. In this study, pretreatment with alpha 2 adrenergic agonist Dexmedetomidine 1 micrograms /kg attenuated, but did not totally abolish the cardiovascular and catecholamine surge response to laryngoscopy and tracheal intubation after induction of anesthesia.

After administration of Dexmedetomidine and clonidine before intubation there was a fall in mean HR compared to control group, which was statically significant in case of Dexmedetomidine at 1 and 2 min ($p < 0.01$ and 0.001 respectively) and clonidine at 2 min. ($p < 0.001$), but not statically significant in clonidine at 1 min ($p > 0.05$). Kaniya *et al.*^[18], also observed bradycardia in their study with Dexmedetomidine both SBP and DBP increased after 1 min of drug administration, but the difference was not significant. Similar increase in blood pressure was observed by Bloor *et al.*^[19]. At 2 minute Dexmedetomidine started to decrease in blood pressure and the difference was now significant compared to clonidine and control group ($p < 0.05$).

During laryngoscopy and intubation and immediately after it, the rise in HR and the blood pressure was maximum in all the groups. This finding was in agreement with those of the studies by Smith *et al.*^[20] they also concluded that the plasma catecholamine concentration increased to the maximum within 1 minute after the laryngoscopy. The rise was statically highly significant within each group.

We found, the Dexmedetomidine group showed better attenuation of the HR as compared to the other two groups, which was statically highly significant ($p < 0.001$) up to 3 minutes of observation. Thereafter, the HR attenuation effect become comparable between Dexmedetomidine and clonidine, but both remained significantly better than the control group.

The SBP and DBP increased after intubation compared to baseline, but an increase is significantly less with Dexmedetomidine compared to clonidine and control group ($p < 0.05$) at all level of assessments. During laryngoscopy and intubation, the maximum rise of only 7.14% was observed in Dexmedetomidine from its baseline as compared to 14.76% increase in the clonidine group from its baseline ($p < 0.05$) and 25.65% increase in control group from baseline ($p < 0.001$).

In the Dexmedetomidine group pressure came to baseline or below baseline at 3 minutes of intubation. In the clonidine group, this return of blood pressure towards baseline occurred generally over 10 minutes, whereas the increased blood pressure was maintained even at 10 minutes in the control group.

Scheinin *et al.*^[21], also observed that Dexmedetomidine attenuated the cardiovascular response to laryngoscopy and tracheal intubation. In their study, they measured catecholamine concentration of noradrenaline in mixed venous plasma was smaller in the Dexmedetomidine group during all phase of induction.

In a study clonidine 4 microgram/kg and Dexmedetomidine and 2.5 microgram/kg were given 40-50 min before the anticipated induction of anesthesia and it was found that

heart rate and MAP were found to be lower in clonidine and Dexmedetomidine group when compared to placebo group [22]. In our study we found that heart rate and MAP were significantly lower in the Dexmedetomidine group when compared to saline group than the clonidine group.

A study [23] found the intraoperative fluctuation in both heart rate and blood pressure to less than 20% of the pre induction value, and also blunted the cardiovascular response to intubation effectively, in patient receiving clonidine 5 microgram/kg orally 90 minutes before induction. They found the heart rate mean systolic and diastolic blood pressure consistently lower in clonidine group when compared to control group during the intraoperative period. In our study too we found the similar result.

Prevention of tachycardia, slowing of the heart rate and preventing hypertension following laryngoscopy and intubation is probably due to a complex mechanism. Centrally the activation of alpha 2 adenoreceptors cause a reduction in peripheral sympathetic tone and an increase of vagal induced reflex bradycardia and peripherally it causes stimulation of pre synaptic alpha 2 adenoreceptor and which lead to diminished release of NE from the nerve ending towards the vasculature and reducing the peripheral sympathetic towards the heart. Clonidine and Dexmedetomidine therefore serves as a effective and specific regimen to blunt the cardiovascular response. In our study, we observed that requirement of propofol was significantly ($p < 0.001$) less in Dexmedetomidine group than in the clonidine group as was found by Scheinin *et al.* [21] regarding the requirement of thiopentone.

Sedation was significantly more in Dexmedetomidine group at 1 minute and 2 minute after infusion of the drug, but SPO₂ was not affected. Segirolu *et al.* also found no respiratory depression or decrease in SPO₂ with similar dose of Dexmedetomidine. In another study, in which the infusion of opioid and alpha 2-adrenergic agonist were compared, it was concluded that Dexmedetomidine does not cause significant respiratory depression and it decrease the risk of apnea.

Many other have used single dose Dexmedetomidine prior to induction and have achieved suppression of hemodynamic response during laryngoscopy and intubation and also have noticed the reduction of anesthetic requirement. Stress response to extubation is equally suppressed by Dexmedetomidine given prior to reversal.

Conclusions

Based on the present clinical comparative study, the following conclusion can be made.

1. Both the drugs, Clonidine and Dexmedetomidine, maintained cardiovascular stability during laparoscopic cholecystectomy. But Dexmedetomidine appears more effective in maintaining perioperative cardiovascular system stability during laparoscopic cholecystectomy.
2. Dexmedetomidine was superior to clonidine in the attenuation of pressor response and Dexmedetomidine is also helpful in providing sedation and decreasing requirement in anesthetic agent for intubation.
3. Clonidine also reduced the pressor response, but its effect was far lower than that of Dexmedetomidine in attenuating the response.
4. Dexmedetomidine significantly attenuated the sympathetic response to laryngoscopy and intubation.
5. Side effect like hypotension and specially bradycardia

was more pronounced in Dexmedetomidine group probably due to more selectivity on α -2 of Dexmedetomidine than clonidine. Also clonidine being more cost effective than Dexmedetomidine.

6. There was some limitation in study. Propofol (inducing agent) requirement was much less in the Dexmedetomidine group, but depth of anesthesia was not monitored by BIS.
7. Measuring plasma catecholamine level would have established hemodynamic stability offered by Dexmedetomidine more firmly.
8. Further study with larger sample would solidify the evidences.

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