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Comparitive Evaluation of Dexmedetomidine and Esmolol on Hemodynamic Responses during Laparoscopic Cholecystectomy

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Abstract **Original Research Article**

Laparoscopic surgical procedure is minimally invasive technique which offers various benefits to the patient compared with the traditional open surgical procedures and is gaining importance in general surgery However creation of pneumoperitoneum has its own disadvantages in terms of adverse hemodynamic cardiovascular, respiratory, stress response.The present study aims to compare the efficacy of dexmedetomidine (α_2 adrenrgic agonist) and esmolol (β_1 receptor antagonist) on hemodynamic responses during laparoscopic cholecystectomy. The study was conducted as an open label single blind prospective randomized controlled study of 100 cases conducted over period of 1 year.100 patients belonging to American Society of Anaesthesiologist physical status I-II were assigned randomly into two groups of 50 patients.Group D was given Dexmedetomidine loading dose 1mcg/kg before induction and maintenance 0.5 mcg/kg/h throughout pneumoperitoneum and Group E was given Esmolol loading dose 1 mg/kg before induction and maintenance 50ug/kg/min throughout pneumoperitoneum. Heart rate,systolic blood pressure, diastolic blood pressure and mean arterial pressure were recorded preoperative, after study drug, after induction, after intubation, after pneumoperitoneum at 5 min intervals, post pneumoperitoneum and postextubation. In group D, there was no statistically significant increase in heart rate and blood pressure after pneumoperitoneum at any time intervals, whereas in Group E, there was a statistical significant increase in heart rate and blood pressure after pneumoperitoneum at various intervals during the whole pneumoperitoneum period. Dexmedetomidine loading dose 1ug/kg before induction and maintenance 0.5 ug/kg/h throughout pneumoperitoneum seems to be an attractive method to maintain hemodynamic stability in laparoscopic cholecystectomy without any side effects.

Keywords: Dexmedetomidine,esmolol,pneumoperitonium,stress response, laparoscopy.

INTRODUCTION

Laparoscopic surgical procedure is minimally invasive technique which potentially offers various benefits to the patient in terms of decreased tissue damage, early ambulation, decreased hospital stay, reduced analgesic needs, earlier returns to normal activities and less postoperative ileus compared with the traditional open surgical procedures and is gaining importance in general surgery. With open surgery most patients experience significant postoperative impairment of pulmonary function, pain, discomfort, ileus, and require prolonged convalescence. Upper abdominal procedures, including open cholecystectomy, produce significant impairment of pulmonary mechanics, ventilation, and defence mechanisms independent of the effects of general anaesthesia.

No other operation has been so profoundly affected by the advent of laparoscopy as cholecystectomy. Laparoscopic cholecystectomy has rapidly become the procedure of choice for routine gallbladder removal and has become the most common major abdominal procedure performed in western countries. The technique was first described in France by Phillipe Mouret in 1988. It was later reported in the literature by Perissat *et al*. and it was refined and popularized in the United States by Reddick and Olsen. However creation of pneumoperitoneum using CO2 has its own disadvantages in terms of adverse hemodynamic cardiovascular, respiratory, stress response and acid base physiology. Several pathophysiological changes occur after CO2 pneumoperitoneum and extremes of patient positioning, it leads to increase in systemic and pulmonary vascular resistance, rise in mean arterial pressure (MAP) and reduced cardiac output. The increase in mean arterial pressure (MAP) and systemic vascular resistance (SVR) occurring immediately at the induction of

pneumoperitoneum is suggestive of involvement of the sympathetic nervous system .The increase in these hemodynamic values significantly increases the incidence of myocardial ischemia, infarction and other complications.

These hemodynamic responses are due to increased release of catecholamine, vasopressin, or both. These complications are not serious enough in ASA I and II patients, but an exaggerated response to pneumoperitoneum has been reported in elderly and ASA III patients particularly with compromised cardiovascular system physiology. The control and modification of these hemodynamic changes have opened a whole new chapter in the field of anesthesiology. Several modifications in technique have been tried to attenuate these responses.

Dexmedetomidine modulates the hemodynamic changes induced by pneumoperitoneum by inhibiting the release of catecholamine and vasopressin.Dexmedetomidine is highly selective alpha 2 adrenergic agonist with sedative, anxiolytic, and analgesic, sympatholytic and antihypertensive effects. It stimulates alpha 2 adrenergic inhibitory neurons thus decrease the sympathetic activity manifested as peripheral vasodilatation and decrease in blood pressure. Thus it modulates the hemodynamic changes induced by pneumoperitoneum by inhibiting the release of catecholamine, thus causing decrease in blood pressure and heart rate.

Esmolol, an ultra-short acting cardio selective ß1- receptor antagonist, the arterial blood pressure is specifically decreased. Reduced cardiac output and renin release have been the suggested mechanisms for decrease in blood pressure. Because of its hydrolysis by esterase it has short half-life. Esmolol has been shown to blunt hemodynamic responses to perioperative noxious stimuli.

Both esmolol and dexmedetomidine are short acting and reduce catecholamine release and thus the pharmacological profiles suggest that the drugs could be suitable anaesthetic adjuvants for attenuating acute intraoperative hemodynamic stress response in laparoscopic cholecystectomy without interfering with recovery process. Hence, the present prospective, randomized study is designed to evaluate and compare the efficacy of esmolol and dexmedetomidine on hemodynamic response during laparoscopic cholecystectomy.

MATERIALS AND METHODS

This study was carried out after obtaining permission from institutional ethical committee(IEC/Certi/78/16) and obtaining written informed consent of the patient's relative. We recruited total 100 patients for our prospective randomized controlled study.

Inclusion Criteria

Patient undergoing laparoscopic cholecystectomy, ASA grade I and II patients, Age between 18 to 70 years**,** both genders.

Exclusion Criteria

Patient's refusal,ASA grade III patients and above, Patients on beta-blockers**,** Patients with uncontrolled asthma and COPD despite treatment, Pregnant women and lactating mothers, Morbid obesity, Patients with acute cholecystitis, Patients having severe hepatic and renal disease and those taking medications for same, Cardiopulmonary or respiratory problems, Previous allergic reaction to dexmedetomidine and esmolol.

Study Design

The study was an open label single blind prospective randomized controlled study of 100 cases conducted over period of 1 year.The patients were assigned randomly into either of following two groups with each group including 50 patients.Group D: Dexmedetomidine loading dose 1mcg/kg before induction and maintenance 0.5 mcg/kg/h throughout pneumoperitoneum.Group E: Esmolol loading dose 1 mg/kg before induction and maintenance 50ug/kg/min throughout pneumoperitoneum

Study Procedure

Following approval by the institutional ethics committee and written informed consent, 100 patients of ASA (American Society of Anaesthesiologists) I or II aged 18-70 years scheduled for elective laparoscopic surgery under general anaesthesia were recruited for the comparative study.All the patients were examined on previous day of surgery and were assessed for fitness of anaesthesia. The detailed history was taken regarding any major illness, drug allergy, drug therapy, emotional status, drug addiction, previous surgery and anaesthesia exposure and any complications if occurred. Physical examinations of all the systems were carried out. Routine investigations were carried out in all cases and specific investigations were done if indicated and required. Baseline vitals were recorded. In the operative room, monitoring was done with Electrocardiography (ECG), Non-invasive blood pressure (NIBP), SpO2, Et Co2. Intravenous line was secured and i.v. fluids were started. Premedication given Inj. Glycopyrrolate 0.004mg/kg, Inj. Ondansetron 0.15mg/kg, Inj. Fentanyl 2mcg/kg

Preparation of study medication and administration

Group 'D': Study medication was prepared in a 20 ml syringe. Inj. Dexmedetomidine 100µg (1ml) was added to 19 ml normal saline making a total volume of 20 ml resulting in a concentration of 5 µg/ml. A bolus of 1µg/kg was given over 10mins, 5 minutes before induction and the drug was infused at a rate of 0.5µg/kg/hr throughout pneumoperitoneum. Group 'E': Study medication was prepared in a 20 ml syringe. Inj.

Esmolol 100mg (10ml) was added to 10 ml normal saline making a total volume of 20 ml resulting in a concentration of 5mg/ml. A bolus of 1mg/kg was given over 1 minute 5 minutes before intubation and the drug will be infused at a rate of 50 ug/kg/ min throughout pneumoperitoneum.

Preoxygenation was done with 100% oxygen. Induction agent used was Inj. Propofol 2mg/kg iv and Inj. Suxamethonium 2mg/kg the muscle relaxant was given. Patients were intubated with appropriate sized cuffed endotracheal tubes. Anaesthesia was maintained by nitrous oxide in oxygen 50:50 and 1% sevoflurane and loading dose of vecuronium bromide 0.01mg/kg followed by maintence 0.0025mg/kg. Intra-abdominal pressure was maintained at 10-15 mm Hg and CO2 insufflation rate at 6L/min. Patient's hemodynamic parameters i.e. Heart Rate,Systolic Blood Pressure ,Diastolic Blood Pressure ,Mean Blood Pressure, spo2 was recorded pre-operatively, preinduction after the loading dose of study drugs, induction, intubation, then every five minutes and then every 10 minutes after establishment of pneumoperitoneum and then postpneumoperitoneum and then post operatively. At the end of surgery, neuromuscular blockade was reversed with Inj. Neostigmine 0.05mg/kg and Inj. Glycopyrrolate 0.008mg/kg**.** Extubation was done after thorough orophayngeal suction, when the patient had established protective reflexes with adequate tidal volume and hemodynamic stability.

Complications were recorded and treated

a) Hypotension–Mean Arterial Pressure <20% preoperative value was managed with a fluid bolus of normal saline 250-300 ml. If hypotension did not respond to fluid administration, then inj. Mephentermine 5 mg i.v. was administered. If hypotension not responded to 2 repeat doses of mephentermine then dopamine infusion was started to maintain the blood pressure.

b)Hypertension – Mean Arterial Pressure >20% preoperative was managed with nitroglycerine infusion.

c)Bradycardia – Pulse Rate<60/min was treated with inj. atropine 0.6 mg i.v.

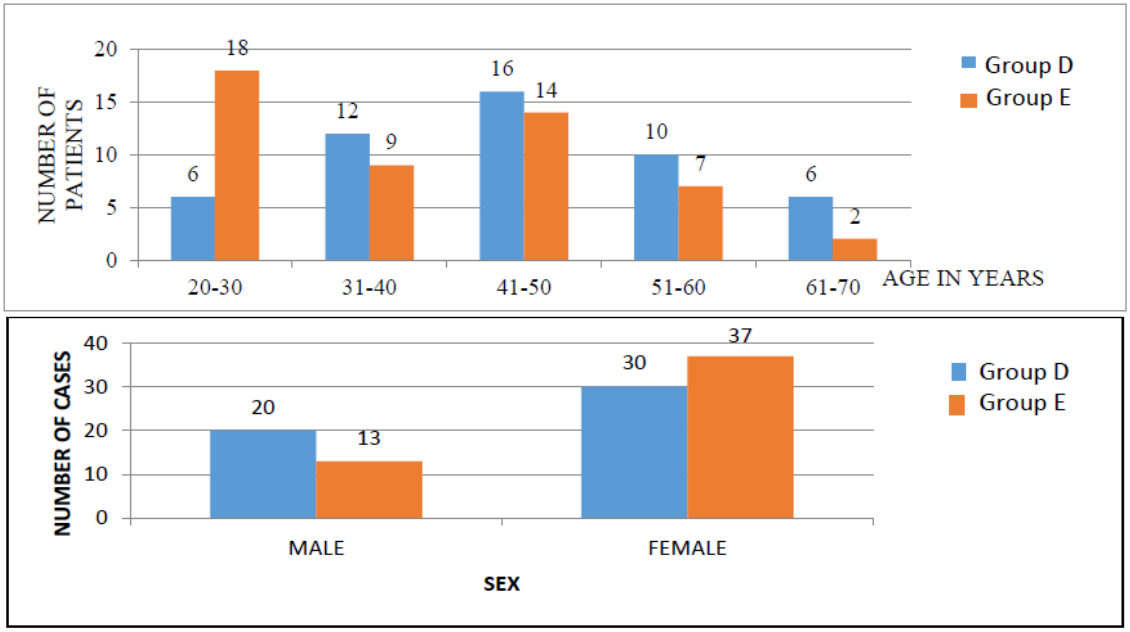
d)Tachycardia – Pulse Rate>160/min corrected with inj. Metoprolol 1mg boluses.

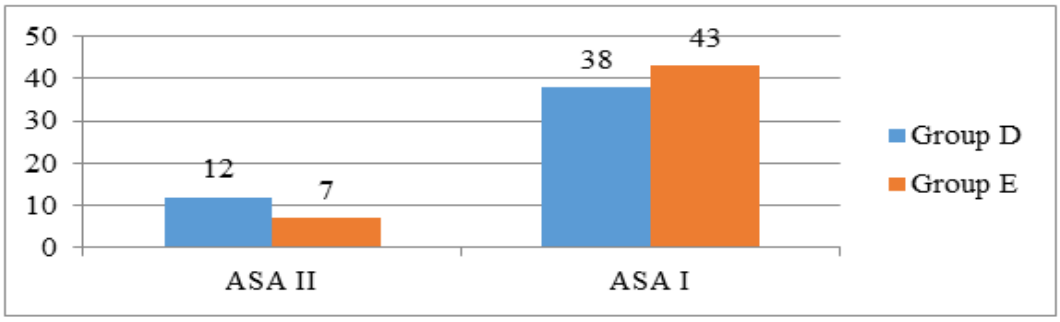
Parameters observed included Pulse, Systolic Blood Pressure, Diastolic Blood Pressure, Mean Arterial Blood Pressure, SPO2, End tidal CO2, Electrocardiography

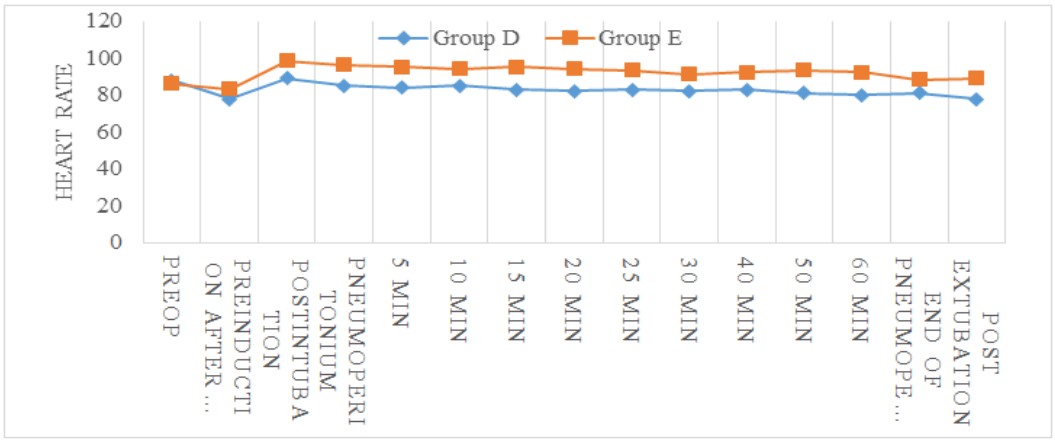
Statistical analysis

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean +/- SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 1 % level of significance. Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups, inter group analysis and on metric parameters. Chi-square test has been used to find the significance of study parameters on categorical scale between two or more groups. Significant P value <0.01 Statistical software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

RESULTS AND DISCUSSION




50
40
30
20
10
0
12
7
38
43
ASA II
ASA I
Group D
Group E


HEART RATE
120
100
80
60
40
20
0
Group D
Group E
PREOP
PREINDUCTION AFTER ...
POSTINTUBATION
PNEUMOPERITONIUM
5 MIN
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25 MIN
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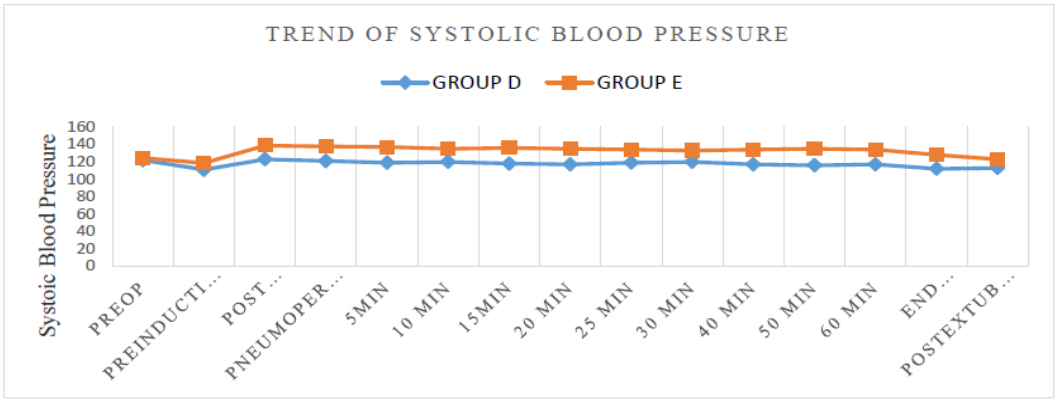
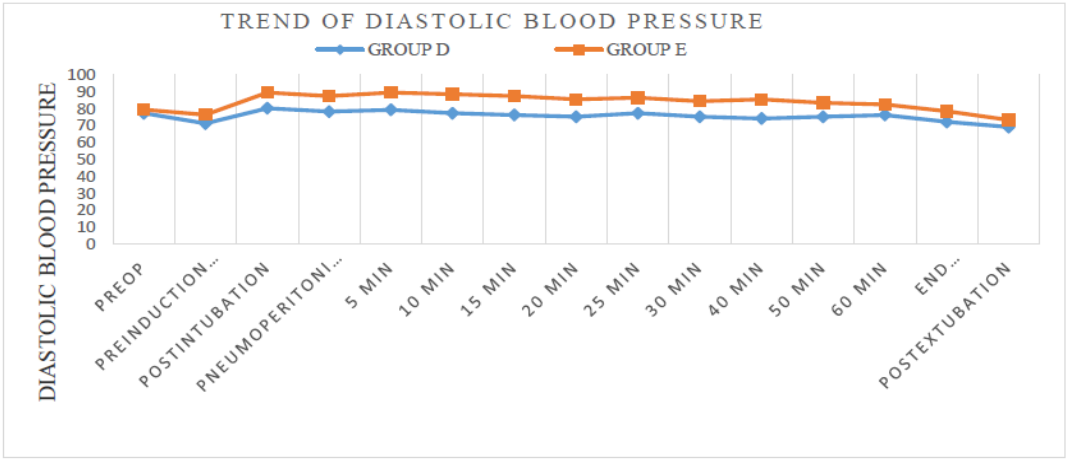
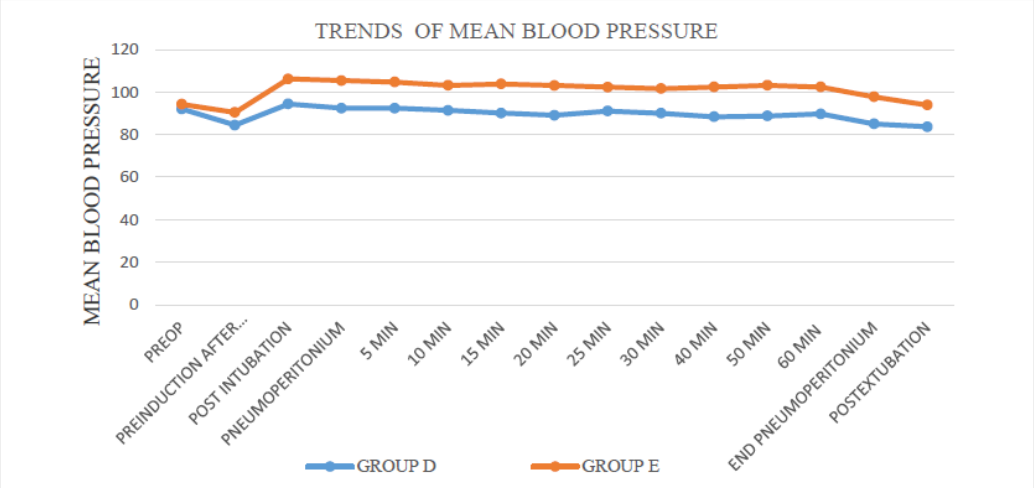
PNEUMOPE... END OF
POST EXTUBATION


TREND OF SYSTOLIC BLOOD PRESSURE
GROUP D
GROUP E
Systoic Blood Pressure
160
140
120
100
80
60
40
20
0
PREOP
PREINDUCTI...
POST ...
PNEUMOPER...
5MIN
10 MIN
15MIN
20 MIN
25 MIN
30 MIN
40 MIN
50 MIN
60 MIN
END...
POSTEXTUB...


TREND OF DIASTOLIC BLOOD PRESSURE
GROUP D
GROUP E
DIASTOLIC BLOOD PRESSURE
100
90
80
70
60
50
40
30
20
10
0
PREOP
PREINDUCTION...
POSTINTUBATION
PNEUMOPERITONI...
5 MIN
10 MIN
15 MIN
20 MIN
25 MIN
30 MIN
40 MIN
50 MIN
60 MIN
END...
POSTEXTUBATION



Our study compared dexmedetomidine and esmolol because both of these drugs are short acting, reduce catecholamines. The pharmacologic profiles and anaesthetic sparing effects of dexmedetomidine and esmolol suggested that these drugs could be a suitable anaesthetic adjuvant for attenuating acute intraoperative hemodynamic stress responses in laparoscopic cholecystectomy without interfering with the postoperative recovery process.

Various studies report using dexmedetomidine infusion rates ranging from 0.1 to 10 micrograms/kg/hr. Higher infusion rates had higher incidence of adverse events like hypotension and bradycardia. In our study we used dexmedetomidine at rate of 1 mcg/kg bolus dose followed by infusion at rate of 0.5mcg/kg/hr without any incidence of adverse effects.Esmolol is an ultra-short-acting selective β-2 blocker. In our study we used esmolol at rate of 1mg/kg bolus dose followed by infusion at rate of 50ug/kg/min without any incidence of adverse effects.

Our study shows demographic profile (age, weight). It shows that both the groups were comparable in their demographic profiles. Age distribution range in group D was 20-65 years with a mean 46 ages of years. Range in group E was 18-65 years with mean 39 age of years (p Value=0.94). Thus we see that both the groups were comparable in terms of age profile and no statistically significant difference was observed in both groups. Weight distribution range in group D was 50-80 kg with a mean 63kg. Range in group E was 45-70 kg with a mean 60 kg. Both the groups were comparable in terms of weight profile and no statistically significant difference (p Value=0.52) was observed in both groups.

Hemodynamic Parameters

We observed that the control of heart rate was significantly better in the dexmedetomidine group than the esmolol group. In the present study, in Group D baseline heart rate was 88±6.23 v/s86±4.97 Group E, showing no statistical significance. The HR after intubation in Group D was 89±6.85 v/s 98±5.68 in the Group E. There is a statistically significant increase heart rate in the esmolol group compared to dexmedetomidine after intubation. From insufflation to the end of pneumoperitoneum, heart rate was lower in the dexmedetomidine group than in the esmolol group, which was statistically significant. During reversal and extubation heart rates were higher in the esmolol group than in the dexmedetomidine group, which was statistically significant.

Our study was comparable with study done by Hazra R *et al*.[1] who compared the effects of intravenously administered clonidine versus dexmedetomidine to attenuate hemodynamic responses to pneumoperitoneum during laparoscopic cholecystectomy under general anaesthesia observed that administration of clonidine or dexmedetomidine attenuates hemodynamic response to pneumoperitoneum, dexmedetomidine being more effective in this regard.Srivastava VK *et al.* [2] Nirav Kotak *et al*. [3]Bhattacharjee DP *et al*.[4] also had similar conclusions that dexmedetomidine and esmolol attenuated response to laryngoscopy and to pneumoperitonium. Dexmedetomididne maintained a better control of heart rate as compared to esmolol with was statistically significant.

The control of the systolic blood pressure was significantly better in dexmedetomidine group compared to esmolol group. In the present study baseline in Group D was 122±6.78 mmHg v/s 124±6.54 mmHg in Group E, which is statistically not significant (P>0.05). There was statistically significant increase in systolic blood pressure in group E 138±7.27 at the time of intubation in comparison to Group D 123±7.24 (P<0.001) and remained elevated till extubation. The statistical difference in systolic blood pressure between two groups was significant after CO2 insufflation at various time intervals.

Our study was comparable with study done Nirav Kotak *et al*. [3] compared the efficacy of dexmedetomidine and esmolol to attenuate

hemodynamic in case of laparoscopic cholecystectomies. They compared the use of dexmedetomidine and esmolol in attenuation of pressure response during pneumoperitoneum during laparoscopic cholecystectomy. 100 patients belonging to ASA physical status I and II were randomly divided into two groups. Group received dexmedetomidine 0.5mcg/kg IV bolus over 10min and followed by 0.4mcg/kg/hr infusion till the end of surgery. Group E received esmolol 500mcg/kg bolus followed by 50mcg/kg/min infusion till the end of surgery. Variation in systolic blood pressure in the esmolol group compared to the dexmedetomidine group. They concluded that both esmolol and dexmedetomididne attenuated the pressure response to pneumoperitonium,but dexmedetomidine attenuation of the response was more than esmolol and was statistically significant. Hazra R *et al*. [1] Srivastava VK [2] *et al*. Bhattacharjee DP *et al*. [4] also conducted similar studies and there results with coraborative with results of our study showing the control of the systolic blood pressure was significantly better in dexmedetomidine group compared to esmolol group.

The control of diastolic blood pressure was better in the dexmedetomidine group than the esmolol group during intubation and throughout the period of pneumoperitoneum. Baseline diastolic pressure was comparable between both the groups Group D 77±4.75 mmHg v/s Group E 79±4.58 mmHg (p value 0.024). From the period following intubation the diastolic pressure was higher in group E compared to group D till extubation and the difference between two groups remained statistically significant.Srivastava VK *et al*. [2] compared the efficacy of dexmedetomidine and esmolol on hemodynamic responses during laparoscopic cholecystectomy on 90 patients aged 20-60 years. The patients were randomly divided into three. Group D received dexmedetomidine loading dose 1 mcg/kg over a period of 15 min and maintenance 0.5 mcg/kg/h throughout the pneumoperitoneum. Group E received esmolol loading dose 1 mg/kg over a period of 5 min and maintenance 0.5 mg/kg/h throughout the pneumoperitoneum. Group C received same volume of normal saline.In group D; there was no statistically significant increase in diastolic blood pressure after pneumoperitoneum at any time intervals, whereas in Group E, there was a statistical significant increase in diastolic blood pressue after pneumoperitoneum at 15, 45, and 60 min and during the whole pneumoperitoneum period. Thus it was concluded that Dexmedetomidine is more effective than esmolol for attenuating the hemodynamic response to pneumoperitoneum in elective laparoscopic cholecystectomy. Hazra *et al*. [1] Bhattacharjee DP *et al*. [4]Nirav Kotak *et al.* [3] also did similar studies and there results were coraborative with our results that dexmedetomidine more effectively reduced diastolic blood pressure both during intubation and during pneumoperitonium as compared to esmolol in laparoscopic cholecystectomy.

The control of mean blood pressure was better in the dexmedetomidine group than the esmolol group during intubation and throughout the period of pneumoperitoneum. The Baseline mean pressure was comparable between both the groups Group D 92±3.68 mmHg v/s Group E 94±3.87 mmHg (p value 0.054). From the period following intubation the mean pressure was higher in group E compared to group D till the end of pneumoperitoneum and the difference between two groups remained statistically significant. Our study was comparable with study done Nirav Kotak *et al*.[3] compared the efficacy of dexmedetomidine and esmolol to attenuate hemodynamic in case of laparoscopic cholecystectomies. They compared the use of dexmedetomidine and esmolol in attenuation of pressure response during pneumoperitoneum during laparoscopic cholecystectomy. 100 patients belonging to ASA physical status I and II were randomly divided into two groups. Group received dexmedetomidine 0.5mcg/kg IV bolus over 10min and followed by 0.4mcg/kg/hr infusion till the end of surgery. Group E received esmolol 500mcg/kg bolus followed by 50mcg/kg/min infusion till the end of surgery. Variation in systolic blood pressure in the esmolol group compared to the dexmedetomidine group. They concluded that both esmolol and dexmedetomididne attenuated the pressure response to pneumoperitonium, but dexmedetomidine attenuation of the response was more than esmolol and was statistically significant. Hazra R[1] *et al.* Srivastava VK *et al.* [2] Bhattacharjee DP *et al.* [4] also conducted similar studies and there results with corroborative with results of our study showing the control of the mean blood pressure was significantly better in dexmedetomidine group compared to esmolol group.

CONCLUSION

From our study, we conclude that Dexmedetomidine loading dose 1ug/kg before induction and maintenance 0.5 ug/kg/h throughout pneumoperitoneum is more effective than Esmolol loading dose 1 mg/kg before induction and maintenance 50 ug/kg/min throughout pneumoperitoneum for attenuating the hemodynamic response to pneumoperitoneum in elective laparoscopic cholecystectomy. Dexmedetomidine seems to be an attractive method to maintain hemodynamic stability in laparoscopic cholecystectomy.

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