EAS Journal of Anaesthesiology and Critical Care
Abbreviated Key Title: EAS J Anesthesiol Crit Care
ISSN: 2663-094X (Print) & ISSN: 2663-676X (Online)
Published By East African Scholars Publisher, Kenya

OPEN ACCESS

Volume-2 | Issue-1 | Jan-Feb-2020 | DOI: 10.36349/easjacc.2020.v02i01.05

Research Article

Comparative Study of Esmolol Hydrochloride and Dexmedetomidine Hydrochloride on Attenuation of Pressure Response to Pneumoperitoneum during Laparoscopic Surgery

Leena P. Patel[*1], Keval P. Patel[2], Anupama Kisku[3] and Jayshree M. Thakkar[4]

[1]Associate professor, Dept. of Anaesthesia, Gujarat Cancer and Research Institute, B.J. Medical College, Ahmedabad, Gujarat, India
[2]MD Anaesthesia (Ex- resident), Dept. of Anaesthesia, Gujarat Cancer and Research Institute, B.J. Medical College, Ahmedabad, Gujarat, India
[3]2nd year resident, Dept. of Anaesthesia, Gujarat Cancer and Research Institute, B.J. Medical College, Ahmedabad, Gujarat, India
[4]Professor and Head of department Anaesthesia, Gujarat Cancer and Research Institute, B.J. Medical College, Ahmedabad, Gujarat, India

Article History
Received: 19.01.2020
Accepted: 05.02.2020
Published: 21.02.2020

Journal homepage:
https://www.easpublisher.com/easjacc

Quick Response Code

Abstract: Anaesthetic manoeuvres like direct laryngoscopy, tracheal intubation, extubation, pneumoperitoneum and CO_2 insufflations necessary in laparoscopic surgeries causes increase in plasma stress hormone which leads to increase in heart rate (HR), mean arterial blood pressure (MAP), systemic and pulmonary vascular resistance and decrease cardiac output. In this randomized open labeled observer blinded study, we compared effect of esmolol and dexmedetomidine to attenuate pressure response to laryngoscopy, intubation and pneumoperitoneum during laparoscopic surgery. Ninety patients belonging to ASA I and II were divided into three groups. Patients of group-D received dexmedetomidine (0.5 mcg/kg) IV as loading dose over 10min, followed by 0.4mcg/kg/hr till the end of pneumoperitoneum and patients of group-E received esmolol (0.5mg/kg) IV as loading dose over 5 min followed by 50mcg/kg/min till the end of pneumoperitoneum. Patients of group-C received same volume of normal saline. During laryngoscopy, intubation, pneumoperitoneum, at reversal and extubation HR, MAP, oxygen saturation and end tidal CO_2 ($EtCO_2$) were observed. Recovery in terms of time to respond to oral-commands, extubation and full orientation was noted along with any adverse effects. In control group, there was significant increase in HR and MAP during intubation, extubation and pneumoperitoneum. In dexmedetomidine group we observed better control of HR and MAP as compare to esmolol and control groups. In esmolol group, only HR was controlled at intubation, while during pneumoperitoneum HR and MAP both were near baseline values. Dexmedetomidine and esmolol both are effective to provide hemodynamic stability in laparoscopic surgery. But dexmedetomidine is more effective than esmolol with minimal incidence of bradycardia.

Keywords: laryngoscopy, laparoscopic surgery, pneumoperitoneum, hemodynamic response, dexmedetomidine, esmolol.

INTRODUCTION:

Laparoscopic procedures include smaller incisions, lower risk of wound complications, reduced postoperative pain and pulmonary complications, shorter hospital stay, more rapid return to normal activity which in turn reduces cost to the patient. (TulunOzturk *et al.*, 2011)

Laparoscopy procedures require pneumoperitoneum for adequate visualisation and operative manipulations which affects many homeostatic systems causing alterations in acid-base status, cardiovascular system, stress response and pulmonary physiology. They cause increase in systemic vascular resistance which increases mean arterial pressure, decreases cardiac output and compromise tissue perfusion. Various pharmacological agents like nitroglycerine (Moon HS *et al.*, 2011), opioids (Damen SL *et al.*, 2004), gabapentin (Pandey CK *et al.*, 2016), pregabalin (Peng PW *et al.*, 2010), magnesium sulfate (Suhrita Pau *et al.*, 2013), clonidine (Singh M *et al.*, 2013), dexmedetomidine (Khanduja S *et al.*, 2014) and beta blocker (Koivusalo AM *et al.*, 1998) has been used to maintain hemodynamic during pneumoperitoneum.

Dexmedetomidine by its agonist effect on α2-adrenergic receptor thereby inhibiting the release of catecholamine and vasopressin released during laparoscopic surgery (Ghodki PS *et al.*, 2012) controls hemodynamic response of pneumoperitoneum. Esmolol, an ultra-short acting cardio-selective β1-receptor antagonist, blunts hemodynamic responses to perioperative noxious stimuli during laryngoscopy, intubation and pneumoperitoneum (Koivusalo AM *et al.*, 1998). Our aim of study was to compare the effect

***Corresponding Author:** Leena P. Patel **Email**: leenagcridr[at]gmail.com

of esmolol and dexmedetomidine on pressure response during laryngoscopy, intubation and pneumoperitoneum in laparoscopic surgery under general anaesthesia because their mechanism of action is different. Our secondary aim was to compare the time and quality of recovery after both the drugs and to study incidence of complications.

MATERIALS AND METHODS:

This was a randomized open labelled observer blind, prospective control type of study. Ninety patients aged between 25-60 years, belonging to ASA I or II of either sex posted for elective laparoscopic surgery under general anaesthesia were selected for the study.

Patients who refuses or with history of hypertension, diabetes mellitus, morbid obesity, allergy to study drugs, renal and hepatic insufficiency, cardiopulmonary or respiratory disease, patients on beta blocker drugs, anticipated difficult intubation, pregnant or breast feeding female were excluded from the study. Patients were allocated randomly in to three groups (30 patients in each group).

Group D - Inj. Dexmedetomidine hydrochloride.
Group E - Inj. Esmolol hydrochloride.
Group C - Inj. 0.9% normal saline was administered to the control group.

The study was approved by institutional ethical committee. Informed written consent was taken from each patient enrolled in the study.

Pre-anaesthesia check-up was conducted and a detailed history and complete physical examination was done. Routine investigations like complete blood count, random blood sugar, renal function test, liver function test, chest x-ray and electrocardiogram were done. Monitors for pulse oximetry, electrocardiography, NIBP and $EtCO_2$ were applied with Drager fabius plus multipara monitor. Baseline values of heart rate (HR), non-invasive blood pressure (NIBP) were recorded. Intravenous access was secured.

All the patients were premedicated with intravenous Inj. glycopyrrolate 0.004 mg/kg, Inj. ondansetron 0.01 mg/kg, Inj. ranitidine 1 mg/kg and antibiotic.

Preparation of Study Medication and Administration:

Group D:

Inj. Dexmedetomidine hydrochloride intravenously (IV) bolus of 0.5 μg/kg was given over 10 minutes by infusion pump starting 5 minutes before induction following which infusion rate was set at 0.4 mcg/kg/hr till the end of pneumoperitoneum.

Group E:

Inj. Esmolol hydrochloride IV bolus of 0.5 mg/kg was given over 5 minutes by infusion pump starting 2 minutes before induction, followed by infusion was set at 50 mcg/kg/min till the end of pneumoperitoneum.

Group C:

0.9% normal saline was given as bolus 3 ml/min starting 5 min before induction by infusion pump following which infusion was continued till the end of pneumoperitoneum.

The patients were pre oxygenated with 100% oxygen by face mask for 3 min. Anaesthesia was induced with intravenous Inj. fentanyl 2 mcg/kg, Inj. thiopentone 6mg/kg and Inj. Vecuronium 0.1mg/kg to facilitate intubation. Oro-tracheal intubation with Macintosh laryngoscope was done with an appropriate sized portex cuffed endotracheal tube. Intubation was done by experienced anaesthesiologist. Patients were maintained with oxygen, nitrous oxide (O_2:N_2O, 50:50), Isoflurane 1 MAC and intermittent boluses of Inj. vecuronium (0.01 mg/kg). Patients were ventilated with Drager Fabius plus ventilator with tidal volume 8–10 ml/kg and respiratory rate 12–14 breaths/min. Ventilation was adjusted to maintain an $EtCO_2$ 35-40 mm of Hg. Intraabdominal pressure was maintained to 12-14 mm of Hg. CO_2 insufflation flow was maintained at the rate of 6 L/min. Electrocardiography, HR, oxygen saturation (SpO_2), $EtCO_2$, urine output and blood loss was monitored. As soon as the pneumoperitoneum was released, study drug infusion was stopped. At the end of procedure, residual neuromuscular blockade was reversed with IV glycopyrrolate (0.4mg) and neostigmine (0.05 mg/kg).

HR, MAP, $EtCO_2$ and SpO_2 were recorded at baseline, after study drug administration, after induction, immediately after intubation, at the time of gas insufflation, at every 5 minute interval after pneumoperitoneum, at the end of pneumoperitoneum, at the time of reversal and at the time of extubation. Patient's recovery profile was observed in form of time to respond to verbal commands, time to extubation and time to full orientation. Hypotension (MAP <20% preoperative) was managed with bolus of normal saline 250-300 ml. If hypotension did not respond to fluid administration, Inj. mephentermine 6 mg IV was given. Hypertension (MAP >110 mmHg) was treated with intermittent bolus of Inj. Propofol. Bradycardia (HR<50/min) was treated with inj. atropine 0.6mg IV. Any case of failure to intubate within 15 second, massive blood loss, laparoscopic surgery converted to open laparotomy and surgical time extended more than 3 hr was excluded from the study.

Statistical Analysis:

Statistical analysis was carried out using the Graph pad prism 6.0 statistical software. Results of continuous measurements were presented as Mean ± SD and results of categorical measurements are presented in number and percentage (%). Patient characteristic data were analysed with one-way analysis of variance (ANOVA) for continuous variables and Chi-square test for categorical variables. Inter group comparison of HR, MAP was done with ANOVA, followed by an unpaired t-test.

Repeated measure analysis of variance (ANOVA) with the post-hoc Tukey test was used to compare means for hemodynamic variables in intragroup statistically significant comparison to baseline parameters. A P-value of <0.05 was considered statistically significant.

Sample Size:

The sample size is calculated by power analysis, using a two sample t- test, with 95% confidence interval (CI), a two-sided type I error of 5% (α=0.05) and power at 80.37 (α= 0.19), therefore 25 patients in each group were needed. We enrolled 30 patients in each group.

OBSERVATION AND RESULTS

Our study included ninety adult patients of ASA grade I and II posted for laparoscopic surgery. They were randomly assigned into three groups of 30 patients in each. None of the patient was excluded from the study.

Table 1. Demographic Data

Variables	Group C Mean+ SD	Group D Mean+ SD	Group E Mean+ SD	P-value
Age (year)	52.2+9.06	49.26±10.34	48.8+10.43	0.30
Sex (Male/Female)	14/16	15/15	14/16	
Weight (kg)	54.66±7.89	52.86±9.58	53.71±8.83	0.67
Duration of surgery(min)	147.33±36.69	144±41.11	150.4+31.73	0.79

(Values are expressed as Mean±SD. P value <0.05 was considered as significant)

Table 2: Types of laparoscopic surgical procedure

Types of laparoscopic surgery	GROUP C	GROUP D	GROUP E
Laparoscopic APR	12	13	14
Laparoscopic hemicolectomy	6	5	6
Laparoscopic cholecystectomy	4	5	4
Others	8	7	6

As shown in Table 1 and Table 2, there was no significant difference in age, sex, weight, duration and type of surgery (P value >0.05) in all groups.

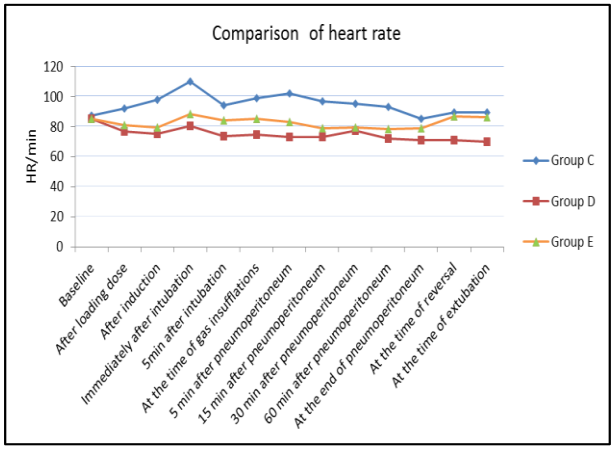

Figure 1-: Comparison of heart rate at various time intervals

As shown in figure 1, there was no significant difference in baseline HR between the groups. After administration of the study drugs and induction agent, there was a significant decrease in HR in group-D and group-E as compared to group-C (p<0.05). Immediately after induction there is rise in HR during intubation was 25 % in group-C and 4% in group-E, while in Group-D there was no rise. Gas insufflation caused an increase in HR from baseline values in group-C, however this increase was not seen in group-D and group-E (P<0.001). In group-E, HR was maintained near baseline values and below baseline value in group-D. There was no significant difference in HR between

group-C and group-E at the time of reversal and at the time of extubation (p>0.05) however HR was statistically lower in group-D (P<0.05).

As shown in figure 1, in group-C there was significant rise from baseline value in the HR immediately after intubation and remained higher till the end of pneumoperitoneum. In group-E, there was minimal increase in HR from baseline value immediately after intubation which came to baseline values within 3 min after intubation and remained near baseline values till the end of pneumoperitoneum. In group-D, after loading dose HR was decrease from baseline value and remained decreased at all time intervals till the end of surgery.

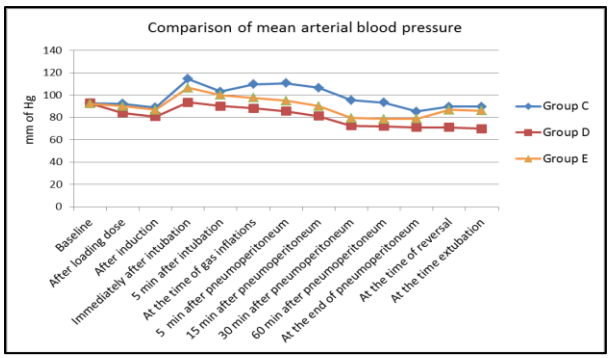

Figure 2 -: Comparison of mean arterial blood pressure at various time intervals

As shown in figure- 2, there was no statistically significant difference in baseline MAP between the groups but after administration of the study drugs and induction agent, significant decrease was seen in MAP in group-D, while no significant difference between group-C and group-E (P>0.05) was found. The rise in MAP immediately after intubation was 24% in group-C and 15% in group-E . Gas insufflation caused an increase in MAP from baseline values in group-C, it was not seen in group-D and group-E (P<0.001). There was significant difference in MAP values between all the groups during pneumoperitoneum (p<0.001). During pneumoperitoneum MAP was higher in group-C at all time intervals as compared to baseline values. Whereas in group-E, MAP was maintained near baseline values, while it was below baseline value in group-D. There was no significant difference in MAP values between group-C and group-E at the end of gas insufflation, at the time of reversal and at the time of extubation (P>0.05), however MAP was statistically lower in group-D (P<0.05). While comparing group-D and group-E, there was significant difference between the groups in MAP at all time interval during pneumoperitoneum (P<0.001). In group-C and group-E, statistically significant increase in MAP after intubation and during pneumoperitoneum was observed. Decrease in MAP was found in group-D after administration of dexmedetomidine, which was persisted till the end of surgery and extubation.

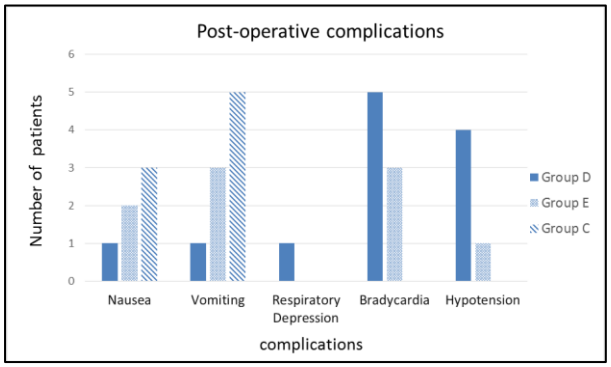

Figure 3: Post-operative complications

As shown in figure-3, incidence of nausea and vomiting was lower in group-E and group-D. Bradycardia was found in 5 patients of group-D and 3 patients in group-E which responded to inj. atropine (0.6mg) IV stat. Hypotension was found in 4 patients of group-D and 1 patient of group-E. Respiratory depression was found in 1 patient of group-D.

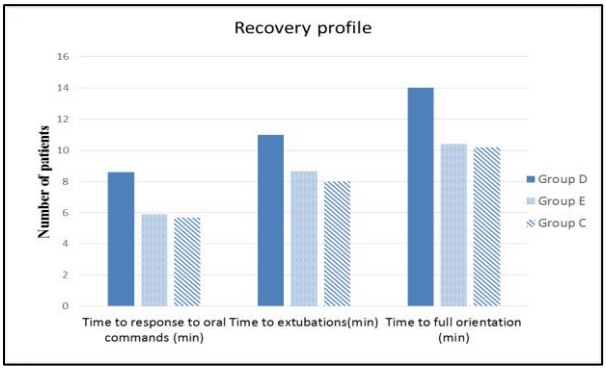

Figure 4-: Recovery profile

As shown in figure-4, time to respond to oral commands was longer in dexmedetomidine (8.5±1.3 min) as compared to esmolol group (5.8±0.99 min) and control group (5.7±0.97 min) which is statistically significant(P<0.001). There was no significant difference in time to respond to oral commands between esmolol group and control group (P>0.05). The time to extubation was longer in dexmedetomidine group (11±1.86 min) as compared to esmolol group (8.7±1.4 min.) and control group (8±1.03 min) which is statistically significant (P<0.01). There was no significant difference in time to extubation between esmolol group and control group in our study. Time to full orientation was longer in dexmedetomidine (14.03±2.78min) as compared to esmolol group (10.43±1.45min) and control group (10.2±1.32min) which is statistically significant (P<0.001). There was no significant difference in time to full orientation between esmolol group and control group (P>0.05). In group-D decrease in respiratory rate (RR) 10/min and tidal volume (300 ml) was found in one patient. Patient was observed in operation theatre, RR was improved to 14/min and tidal volume to 500 ml within 30 min.

DISCUSSION:

Administration of general anaesthesia, laryngoscopy, tracheal intubation and extubation are one of the critical events which lead to transient yet marked sympathoadrenal response leading to hypertension and tachycardia (Kayhan Z *et al.*, 2005). For laparoscopic procedures, CO_2 is used to create pneumoperitoneum because of which intra-abdominal pressure increases, which causes stretching and stimulation of peritoneum by CO_2 which leads to activation of sympathetic nervous system which in turn increases plasma catecholamine and vasopressin level, which further activates renin angiotensin aldosterone system leading to abrupt increase in HR, MAP, cardiac output and systemic vascular resistance (Claude Mann

et al., 1999). This can leads to complications like myocardial ischemia, infarction, etc.

Bon Sebastian *et al.,* (2017) conducted study for an optimal bolus dose of dexmedetomidine by comparing two doses 0.5 mcg/kg and 0.75 mcg/kg with placebo to attenuate stress response during laryngoscopy and endotracheal intubation and found that both the doses were effective in attenuating the pressure response. If dexmedetomidine given as rapid infusion, it leads to a biphasic response on blood pressure which is initial hypertension followed by fall in blood pressure due to stimulation of α2 receptors in vascular smooth muscles (Gurudatt C.L, 2013). In our study, we choose lower dose 0.5 μg/kg and administered slowly as an infusion over 10 min as bolus and found it effective to control pressure response during laryngoscopy and intubation as compared to control group.

Siddareddigari Reddy *et al.,* (2014) compared dexmedetomidine (1mcg/kg) and esmolol (2mg/kg) for attenuating hemodynamic response and found esmolol effectively control HR after intubation but no effect on systolic blood pressure whereas, dexmedetomidine suppressed both HR as well as MAP to laryngoscopy and tracheal intubation. In our study, we found that both the drugs blunted HR response to laryngoscopy and intubation significantly ($P<0.05$). However, MAP was effectively controlled in dexmedetomidine group ($P <0.001$).

Ebert TJ (2000) studied dexmedetomidine has been used in infusion in dose ranging from 0.2-10mcg/kg/hr and documented that incidence of hypotension and bradycardia was more with higher dose. While low dose infusion of dexmedetomidine 0.25–0.5mcg/kg/h resulted in a monophasic response of 10–15% fall in MAP and HR (Bloor BC *et al.,* 1992). We used low dose dexmedetomidine infusion (0.4mcg/kg/hr) and found it effective to control the hemodynamic changes due to pneumoperitoneum during laparoscopic surgeries.

Similar to our study, Gourishankar Reddy *et al.,* (2014) studied dexmedetomidine (0.4mcg/kg/hr) infusion for hemodynamic stability and found it effective in attenuating hemodynamic stability.

Arti *et al.,* (2002) conducted a study to determine an effective bolus dose of esmolol among three doses 50mg, 100mg and 150mg to attenuate the pressure response of laryngoscopy and endotracheal intubation. They concluded that esmolol demonstrated prevention of rise in HR in dose dependant manner i.e more blunting in rise of HR with higher dose. Decrease in MAP was significant only at higher dose. In our study, bolus dose of 0.5mg/kg esmolol significantly blunted rise in HR but did not blunted blood pressure response. The rise in HR during intubation was 4 % in esmolol group whereas; the rise in blood pressure during intubation was 14 % in esmolol group.

Similar to this, A. M. Koivusalo *et al.,* (1998) studied effects of esmolol (1 mg/kg bolus followed by 200 mcg/kg/min infusion) on hemodynamic response to CO_2 pneumoperitoneum for laparoscopic surgery. They concluded that esmolol effectively prevent the pressure response to induction and maintenance of CO_2 pneumoperitoneum. In our study, we found effective control of HR and MAP throughout the pneumoperitoneum with esmolol 0.5mg/kg bolus followed by 50mcg/kg/min infusion as compared to control group without intra-operative complication. Effect on HR was faster while control of MAP was delayed, which may be related to the gradual decline in the plasma renin activity occurring with a half- life of 11.9 minutes**.** Ahmed nabil ibrahim *et al.,* (2016) compared the efficacy of clonidine (2 mcg/kg bolus) versus esmolol (1.5 mg/kg bolus followed by 10 mcg/kg/min infusion) on the hemodynamic response during laparoscopic cholecystectomy and concluded that esmolol and clonidine both provided hemodynamic stability in laparoscopic cholecystectomy but clonidine was associated with postoperative sedation. We compared esmolol with dexmedetomidine and found more sedation in dexmedetomidine group with better control of hemodynamic response to laryngoscopy, intubation and pneumoperitoneum.

In accordance to our study, Nirav kotak *et al.,* (2016) also compared dexmedetomidine and esmolol in similar dose for attenuation of pressure response during pneumoperitoneum in patients undergoing laparoscopic cholecystectomy. They concluded dexmedetomidine was better to control both HR and blood pressure while esmolol controls HR only. In esmolol group HR was significantly controlled during intubation and pneumoperitoneum. However, MAP was not significantly controlled during intubation but values were lower compared to control group. Study done by Vinit K. Srivastava *et al.,* (2015) with dexmedetomidine (bolus dose of 1mcg/kg followed by 0.5mcg/kg/h infusion) and esmolol (bolus dose of 1mg/kg followed by 0.5mg/kg/h infusion) during laparoscopic cholecystectomy also showed dexmedetomidine is better than esmolol for attenuation of hemodynamic response to pneumoperitoneum. During pneumoperitoneum, esmolol significantly blunted stress response compare to control group but did not blunt the extubation response may be because of short elimination half-life.

Recovery Profile

Kol *et al.,* (2009) studied desflurane with esmolol or dexmedetomidine for controlled hypotension during tympanoplasty. They found significantly shorter extubation and recovery times and significantly less postoperative sedation in esmolol group as compare to dexmedetomidine.

In accordance to our study Ibraheim *et al.*, (2013) compared esmolol and dexmedetomidine in similar dose and found dexmedetomidine was associated with prolonged recovery as compared to control group. In consistent to above studies we also found prolong recovery time with dexmedetomidine as compared to control and esmolol group. The study by Islam M. Massad *et al.*, (2009) and NeclaDereli *et al.*, (2015) demonstrated less postoperative nausea and vomiting with dexmedetomidine and esmolol infusion during laparoscopic surgery respectively. Similarly we also found less incidence of nausea and vomiting with both dexmedetomidine and esmolol group as compared to control group.

Nirav *et al.*, (2016) used dose as our and found hypotension in 11 patients out of 50 patients in dexmedetomidine group and 1 patients out of 50 patients in esmolol group. In our study, 4 patients out of 30 developed hypotension in dexmedetomidine group and 1 patient out of 30 in esmolol group.

Limitations of Our Study:

This study was done on patients belonging to ASA I and II so effects in high risk patients have not been seen. We did not use invasive blood pressure monitoring. Plasma catecholamine and anti-diuretic hormone levels were not assessed. We did not assess requirement of anaesthetic agents.

CONCLUSION:

Both dexmedetomidine hydrochloride and esmolol hydrochloride were effective in attenuating pressure response to laryngoscopy, intubation and pneumoperitoneum in patients undergoing laparoscopic surgeries. Dexmedetomidine was more effective to control HR and MAP as compared to esmolol. With dexmedetomidine, the recovery from anaesthesia was prolonged than esmolol.

REFERENCES

1. Bloor, B. C., Ward, D. S., Belleville, J. P., & Maze, M. (1992). Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. *Anesthesiology*, *77*(6), 1134-1142.
2. Damen, S. L., Nieuwenhuijs, V. B., Joosten, W., Houweling, P. L., & Clevers, G. J. (2004). The effects of remifentanil and sufentanil on the quality of recovery after day case laparoscopic cholecystectomy: a randomized blinded trial. *Journal of Laparoendoscopic & Advanced Surgical Techniques*, *14*(2), 87-92.
3. Dereli, N., Tutal, Z. B., Babayigit, M., Kurtay, A., Sahap, M., & Horasanli, E. (2015). Effect of intraoperative esmolol infusion on anesthetic, analgesic requirements and postoperative nausea-vomitting in a group of laparoscopic cholecystectomy patients. *Revista brasileira de anestesiologia*, *65*(2), 141-146.
4. Ebert, T. J., Hall, J. E., Barney, J. A., Uhrich, T. D., & Colinco, M. D. (2000). The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology-Philadelphia Then Hagerstown-*, *93*(2), 382-394.
5. Ghodki, P. S., Thombre, S. K., Sardesai, S. P., & Harnagle, K. D. (2012). Dexmedetomidine as an anesthetic adjuvant in laparoscopic surgery: An observational study using entropy monitoring. *Journal of anaesthesiology, clinical pharmacology*, *28*(3), 334.
6. Gurudatt, C. L. (2013). Dexmedetomidine-The Wonder Drug, for the Present and the Future. *RGUHS Journal of Medical Sciences*, *3*(3), 170-176.
7. Ibraheim, O. A., Abdulmonem, A., Baaj, J., Zahrani, T. A., & Arlet, V. (2013). Esmolol versus dexmedetomidine in scoliosis surgery: study on intraoperative blood loss and hemodynamic changes. *Middle East J Anaesthesiol*, *22*(1), 27-33.
8. Ibrahim, A. N., Kamal, M. M., & Lotfy, A. (2016). Comparative study of clonidine versus esmolol on hemodynamic responses during laparoscopic cholecystectomy. *Egyptian Journal of Anaesthesia*, *32*(1), 37-44.
9. Kayhan, Z., Aldemir, D., Mutlu, H., & Öğüş, E. (2005). Which is responsible for the haemodynamic response due to laryngoscopy and endotracheal intubation? Catecholamines, vasopressin or angiotensin?. *European journal of anaesthesiology*, *22*(10), 780-785.
10. Khanduja, S., Ohri, A., & Panwar, M. (2014). Dexmedetomidine decreases requirement of thiopentone sodium and pentazocine followed with improved recovery in patients undergoing laparoscopic cholecystectomy. *Journal of anaesthesiology, clinical pharmacology*, *30*(2), 208.
11. Koivusalo, A. M., Scheinin, M., Tikkanen, I., Yli-Suomu, T., Ristkari, S., Laakso, J., & Lindgren, L. (1998). Effects of esmolol on haemodynamic response to CO2 pneumoperitoneum for laparoscopic surgery. *Acta anaesthesiologica scandinavica*, *42*(5), 510-517.
12. Kol, I. O., Kaygusuz, K., Yildirim, A., Dogan, M., Gursoy, S., Yucel, E., & Mimaroglu, C. (2009). Controlled hypotension with desflurane combined with esmolol or dexmedetomidine during tympanoplasty in adults: A double-blind, randomized, controlled trial. *Current therapeutic research*, *70*(3), 197-208.
13. Kotak, N., Patil, N., & Rathod, Y. (2016). Attenuation of Intra-Operative Pressure Response to Pneumoperitoneum in Patients Undergoing Laparoscopic Cholecystectomy–A Comparative Study between Dexmedetomidine and Esmolol. *J Dent Med Sci*, *15*(2), 85-95.

14. Mann, C., Boccara, G., Pouzeratte, Y., Eliet, J., Serradeil-Le Gal, C., Vergnes, C., ... & Colson, P. (1999). The relationship among carbon dioxide pneumoperitoneum, vasopressin release, and hemodynamic changes. *Anesthesia & Analgesia*, *89*(2), 278-283.
15. Manne, G. R., Upadhyay, M. R., & Swadia, V. N. (2014). Effects of low dose dexmedetomidine infusion on haemodynamic stress response, sedation and post-operative analgesia requirement in patients undergoing laparoscopic cholecystectomy. *Indian journal of anaesthesia*, *58*(6), 726.
16. Massad, I. M., Mohsen, W. A., Basha, A. S., Al-Zaben, K. R., Al-Mustafa, M. M., & Alghanem, S. M. (2009). A balanced anesthesia with dexmedetomidine decreases postoperative nausea and vomiting after laparoscopic surgery. *Saudi Med J*, *30*(12), 1537-1541.
17. Moon, H. S., Lee, S. K., Choi, Y. S., In, C. B., & Choi, E. J. (2011). The effect of nitroglycerin on hemodynamic changes during laparoscopic low anterior resection. *Korean journal of anesthesiology*, *61*(5), 388.
18. Pandey, C. K., Priye, S., Ambesh, S. P., Singh, S., Singh, U., & Singh, P. K. (2006). Prophylactic gabapentin for prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: a randomized, double-blind, placebo-controlled study. *Journal of postgraduate medicine*, *52*(2), 97.
19. Paul, S., Biswas, P., Bhattacharjee, D. P., & Sengupta, J. (2013). Effects of magnesium sulfate on hemodynamic response to carbon dioxide pneumoperitoneum in patients undergoing laparoscopic cholecystectomy. *Anesthesia, essays and researches*, *7*(2), 228.
20. Peng, P. W. H., Li, C., Farcas, E., Haley, A., Wong, W., Bender, J., & Chung, F. (2010). Use of low-dose pregabalin in patients undergoing laparoscopic cholecystectomy. *British journal of anaesthesia*, *105*(2), 155-161.
21. Rathore, A., Gupta, H. K., Tanwar, G. L., & Rehman, H. (2002). Attenuation of the pressure response to laryngoscopy and endotracheal intubation with different doses of esmolol. *Indian J Anaesth*, *46*(6), 449-452.
22. Reddy, S. V., Balaji, D., & Ahmed, S. N. (2014). Dexmedetomidine versus esmolol to attenuate the hemodynamic response to laryngoscopy and tracheal intubation: A randomized double-blind clinical study. *International Journal of Applied and Basic Medical Research*, *4*(2), 95.
23. Sebastian, B., Talikoti, A. T., & Krishnamurthy, D. (2017). Attenuation of haemodynamic responses to laryngoscopy and endotracheal intubation with intravenous dexmedetomidine: A comparison between two doses. *Indian journal of anaesthesia*, *61*(1), 48.
24. Singh, M., Choudhury, A., Kaur, M., Liddle, D., Verghese, M., & Balakrishnan, I. (2013). The comparative evaluation of intravenous with intramuscular clonidine for suppression of hemodynamic changes in laparoscopic cholecystectomy. *Saudi journal of anaesthesia*, *7*(2), 181.
25. Srivastava, V. K., Nagle, V., Agrawal, S., Kumar, D., Verma, A., & Kedia, S. (2015) Comparative evaluation of dexmedetomidine and esmolol on hemodynamic responses during laparoscopic cholecystectomy. *Journal of Clinical and Diagnostic Research* *9*(3), 1-5.
26. TulunOzturk *et al.*, (2011) Risks associated with laparoscopic surgery, advanced laparoscopy. Intech; 953-978.