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Comparison of Oral Pregabalin Versus Bolus Dose of Intravenous Dexmedetomidine in Attenuating the Hemodynamic responses During Laparoscopic Cholecystectomy: A Prospective Randomized double Blind Study

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Abstract

Background and Aims: Laparoscopic cholecystectomy is being preferred surgery for gall bladder diseases under general anesthesia in the present era. This study was designed to compare oral pregabalin versus intravenous dexmedetomidine as premedication in attenuating the hemodynamic responses in laparoscopic cholecystectomy. *Material and Method:* This prospective randomized double blind study was conducted in 90 patients (ASA) grade I or II, divided into two groups of 45 each. Group P- received oral pregabalin 150 mg 1 hr prior to surgery and intravenous normal saline (0.9%). Group D- received oral placebo tab 1 hr prior to surgery and IV dexmedetomidine 1 μg/kg with normal saline. Demographic data and haemodynamic parameter like heart rate, systolic, diastolic and mean blood pressure along with oxygen saturation and end tidal CO_2 were noted. Assessment of pain by visual analogue pain score (VAS) and sedation by Ramsay Sedation Scale (RSS) was done. The time to first rescue analgesic and total dose of analgesics in 24 hrs were noted. Statistical analysis was done using SPSS software (version 17, SPSS, Chicago, IL). *Result:* In group P significant haemodynamic response was observed at laryngoscopy, after intubation and during pneumoperitonium while in group D it was significantly attenuated (p<0.05). In group D VAS score was lower and RSS score was more as compare to group P which was statistically significant (p< 0.05). The time for first resque analgesic was earlier in group P (37.5 ± 9.30) than group D (58.06 ± 11.62) (p<0.001). *Conclusion:* Dexmedetomidine was found to be more effective than pregabalin in maintaining hemodynamic responses along with better postoperative analgesia and more sedation than pregabalin group.

Keywords: Pregabalin; Dexedetomidine; Laproscopic cholicystectomy; Pneumoperitoneum.

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Introduction

Laparoscopic abdominal surgery is being preferred in present era as it has many advantages over open surgery like less postoperative pain, shorter hospitalstay, early mobilization, faster recovery and bettercosmetic results[1]. Laryngoscopy, intubation and pneumoperitoneum during general anesthesia are severe noxious stimuli that can produce an intense sympathetic stimulation leading to increased level of serum catecholamines and vasopressin which further leads to adverse hemodynamic response like tachycardia, hypertension, arrthymias etc[2]. Inaddition toincreased intraabdominal pressure with

raised diaphragmas well as reverse trendelenburg position required for surgery may result in adverse cardiopulmonary changes like diminished venous return, decreased cardiac output, elevated arterial pressure and increased systemic and pulmonary vascular resistance. These adverse hemodynamic changes may predispose to myocardial ischemia which may be life threatening in vulnerable patients[2,3]. Various studies[4,5,6] have been done to attenuate these sympathoadrenal response to pneumoperitoneum and intubation which include deepening the plane of anesthesia with inhalational or intravenous anaesthetic agents. Various drugs like lidocaine, sedatives, sodium nitroprusside, calcium channel blockers, beta blokers, alpha-2agonists (clonidine, dexmedetomidine), magnesium sulphate and GABA analogueslike gabapentin, pregabalin etc. have also been used but the drug of choice is still notproven. This study aims to evaluate and compare the efficacy of oral pregabalin versus intravenous bolus dose of dexmedetomidine as premedication for attenuating the haemodynamic pressor response during intubation, pneumoperitoneum and extubation as well as perioperative stability and requirement of postoperative analgesics.

Materials and Methods

This prospective randomized doubleblind study was conducted at tertiary care centre from January 2017 to July 2018 after obtaining approval from Institutional Research Ethical Board [IREB] and written informed patient consent A total of 90 patients of American Society of Anaesthesiologists (ASA) grade I or II between the age group of 18-60 years posted for elective laparoscopic Cholecystectomy under general anesthesia were included in this study. Patients with preexisting cardiac disease, uncontrolled hypertension, diabetes and asthma, severe renal & hepatic dysfunction, severe chronic obstructive pulmonary disease, chronic pain syndrome, history of regular use of opiates/ painmedication, antidepressants and anti-epileptic therapy, pregnant or lactating females, patients with anticipated difficult intubation and those with known allergy to study drugs were excluded from the study. Those casesin which procedure was converted to open cholecystectomy were withdrawn from the study. Sample size of 90 patients were included with 45 patients in each group. We took 100 patients considering dropouts from the study. Randomization was performed using computer generated random number table. Patients were randomly assigned to one of the two groups. Group assignments was sealed within opaque envelopes. The envelope was opened by the principle administrator just before the administration of study drug. Anaesthesiologist (who was not one of the observer of the study) prepared the study drug according to randomization group. The anaesthesiologist (who monitored and recorded the hemodynamic parameters), nurses, surgeon, research assistant and the patient were blinded to the randomization. Patients in both the groups received study drug as per the protocol: Group P- received oral pregabalin 150 mg with a sip of water 1 hr prior to surgery and intravenous normal saline (0.9%) 10 ml over 10 mins (10 mins prior toinduction). Groupd- received oral placebo tablet[vitamin c, (celin)] with a sip of water 1 hr prior to surgery and IV dexmedetomidine 1 μg/kg diluted with normal saline to make a volume of 10 ml over 10 mins (10 mins prior to induction). All patients were subjected to thorough preanaesthetic evaluation and educated about visual analogue pain score (VAS) of 0-10 prior to surgery (0-3=no pain, 4-7=discomfort, 8-10=severe pain). Tab alprazolam 0.25 mg at night before surgery and tab ranitidine 150 mg orally at night before and on morning of surgery was given to every patient.

Patients were kept nil orally 8 hrs prior to surgery. An 18 gauge cannula was inserted and intravenous infusion of crystalloid at 6-8 ml/kg was started. Standard monitoring including pulse oximetry, noninvasive blood pressure, end-tidal CO_2 and three-lead electrocardiography was done. Baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure(MAP),oxygen saturation (SpO_2) and $EtCO_2$ were recorded. Oral tab of study drug/placebo was given 1 hr prior to surgery with a sip of water. Anaesthetic and surgical technique was standardized and residual neuromuscular block was reversed with appropriate doses of IV neostigmine 0.05 mg/kg and IV glycopyrrolate 0.01 mg/kg. Patients were extubated when the respiration was spontaneous with adequate efforts and good muscle power and transferred to post anesthesia care unit for further monitoring. Vital parameters like HR, SBP, DBP, MAP, SpO_2 and $EtCO_2$ were noted before premedication and induction (baseline) at the end of induction and at laryngoscopy andat intubation (I_0) and then at 1, 3, 5, 10 mins after intubation as well as at start of pneumoperitoneum (P_0) and then after every 10 mins interval till the deflation of CO_2 and also at the time of extubation and 10 mins thereafter. Assessment of pain by VAS score and Sedation by Ramsay Sedation Scale (RSS) were recorded

at 30 min interval for 2 hrs postoperatively and subsequently at 1 hr intervals for 6 hrs and then at 12 hrs and at 24 hrs postoperatively. If VAS score was more than 3 (at rest), the patient was given inj. Tramadol 100 mg IV as rescue analgesic. The time to first rescue analgesic and total dose of analgesics in 24 hrs were noted. Patients with sedation scale of ≥3 were considered as sedated. Any episodes of nausea and vomiting, headache, dizziness and shoulder pain were recorded. Rescue anti-emetic inj. ondansetron 4 mg IV was given for nausea and vomiting.

Sample size

Sample size was calculated by assuming alpha error 5% and power of study 80%. Assumption of exposed group taken to be 95% with 10% margin of error, so total 90 patients were taken for study.

Statistical Analysis

Statistical analysis was done using SPSS software (version 17, SPSS, Chicago, IL). Data was presented as mean, standard deviation, median (range) or percentage. Quantitative data was analyzed using paired and unpaired t-test while categorical variables were analyzed by Chi-square test. *p* values less than 0.05 were considered significant.

Results

In our study Group P and group D were comparable regarding mean value of age, sex, weight of patients, duration of surgery and anesthesia (p>0.05) (Table 1). When comparing hemodynamic parameters during laryngoscopy and intubation (I_0), HR remain stable (84.77 ± 15.67) from baseline (84.90 ± 12.38) in group D while there was statistically significant increasein HR (95.5 ± 15.92) in group P (p=0.002) from baseline (86.20 ± 17.49). A significant decrease in the mean heart rate was observed in group D at 3 min after intubation (I_3)(79 ± 14) and at 5 min after intubation(I_5) (80.5 ± 18.1) when compared to baseline (84.90 ± 12.38) (p<0.05)) while in group P, a significant increase in the mean HR at (I_3) (89.59 ± 15.60 and at (I_5) (88.66 ± 16.12) from baseline (86.20 ± 17.49) was observed (Fig 1). No significant change was observed in HR from

Table 1: Comparison of demographic data between two groups

Demographic data	Group D (n=45)	Group P (n=45)	p value
Age (yrs)	42.7 ± 11.47	42.27 ± 11.29	0.846(NS)
Weight (kg)	61.38 ± 7.33	62.87 ± 5.50	0.651(NS)
Sex (M/F)	7/38	10/35	-
Duration of Surgery	59.77 ± 18.92	65.95 ± 13.21	0.06(NS)
Duration of Anesthesia	81.47 ± 20.84	79.13 ± 15.59	0.54(NS)
ASA Grade I/II	27/18	33/12	-

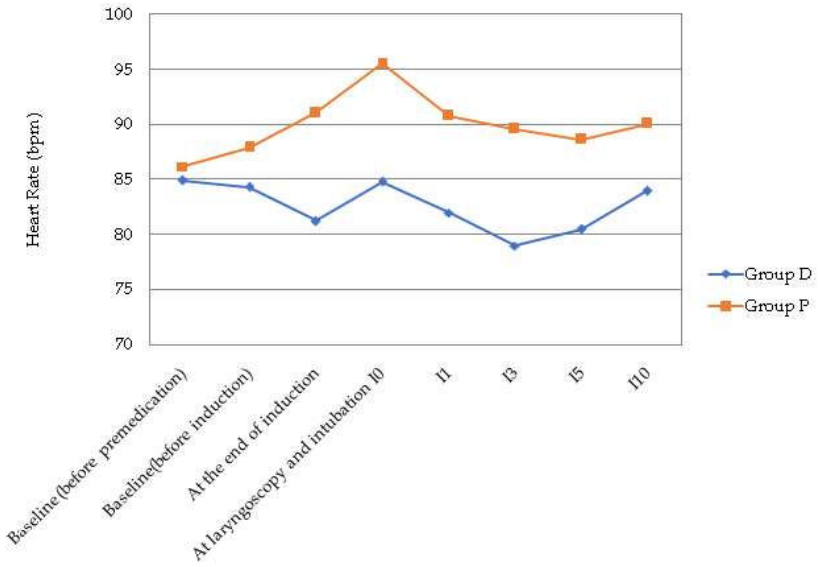

Fig. 1: Comparison of Heart Rate (HR) between two groups duringlaryngoscopy and intubation

baseline (P_0) at various time intervals following pneumoperitonium in both the group, however decrease in HR was more in group D as compared to group P at various time intervals. (Fig. 2). Asignificant decrease in MAP from baseline (101.00 ± 14.75) was observed in group D at 1,3,5,10 minute intervals following intubation (p<0.0001)) which was least at 3 min (87.45 +± 17.23) and in group P a significant rise in the mean MAP from baseline (100.93 ± 14.37) was observed at laryngoscopy and intubation(Io) (107.82 ± 18.20) (p<0.05) after that it remained stable at all other time intervals (Fig. 3). During pneumoperitoneum a significant increase in MAP was observed from baseline (start of pneumoperitoneum (P_0) (94.64 ± 16.19) till 30 min in group P which was maximum at 20 min (109.25 ± 15.05) (p<0.001) while in group D no significant rise in MAP was observed from baseline (Po)(89.23 ± 17.88) till deflation of CO_2(89.93 ± 10.91) (Fig 4). Mean values of VAS score postoperatively till 1 hr was less than 3 (2.48) in group D while it was (3.11) in group P, though

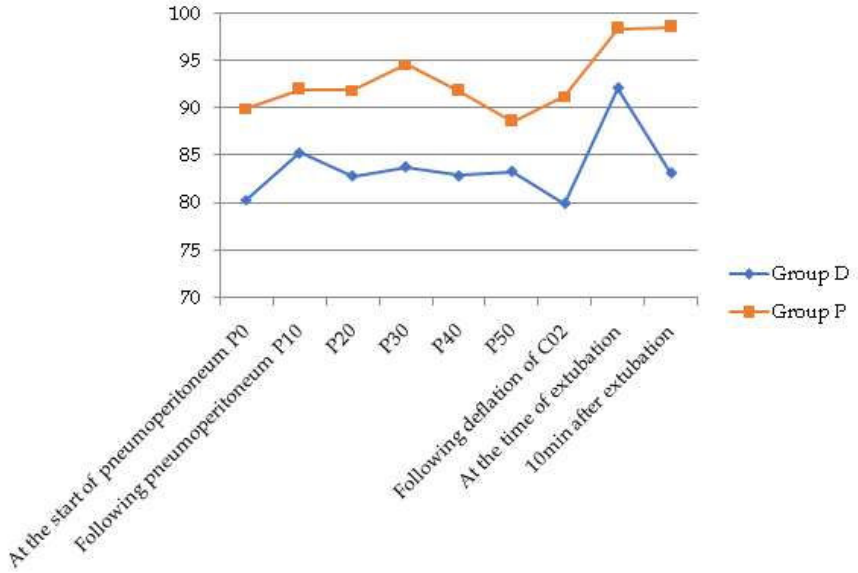

Fig. 2: Comparison of Heart Rate (HR) between two groups during pneumoperitoneum till 10 minutes after extubation in two groups

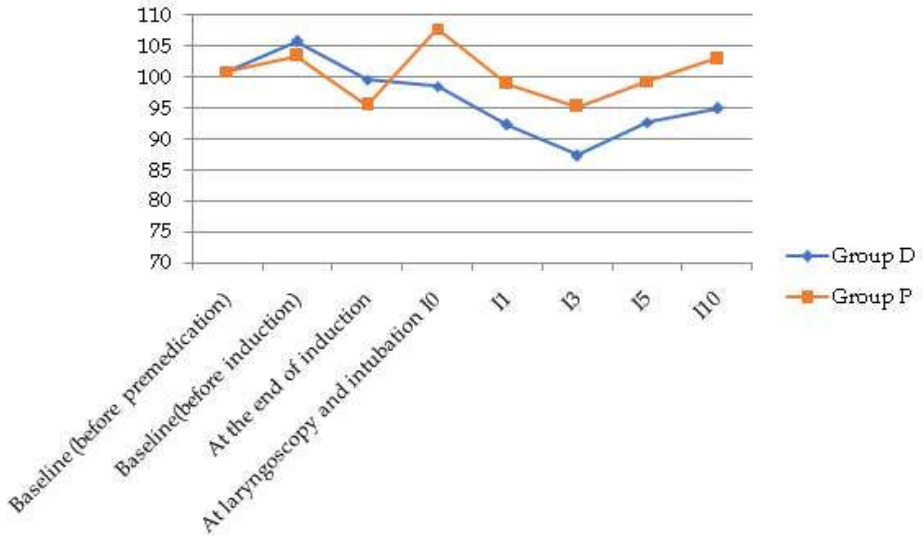

Fig. 3: Comparison of Mean Arterial Pressure (MAP) between two groups during laryngoscopy and intubation

after 1 hr VAS score was <3 in both group till 24 hrs. When comparing two group it was lower in group D at all time intervals (p<0.05). Mean values of RSS was lower in group P (1.00 ± 0.00) as compared to group D (1.14 ± 0.35) till 4 hours postoperatively after that it remained stable in both groups upto 24 hrs (Table 2). The time to request for first rescue analgesic was earlier in group P (37.5 ± 9.30) when compared to group D (58.06 ± 11.62), which was highly significant (p<0.001). Total requirement of rescue analgesic in 24 hrs period postoperatively was comparable in both the groups (Table 3) The incidence of intraoperative adverse effects and postoperative complications like hypotension, hypertension, tachycardia, bradycardia intraoperative and postoperative complication nausea, vomiting, dizziness, headache and shoulder pain were comparable between two groups (Table 4).

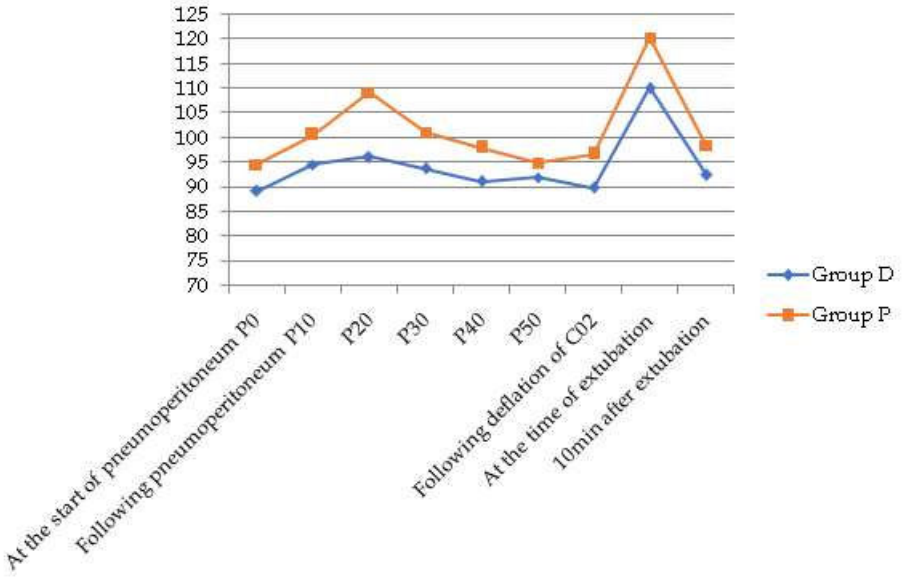

Fig. 4: Comparison of Mean Arterial Pressure (MAP) between two groups during pneumoperitoneum till 10 minutes after extubation in two groups

Table 2: Comparison of Visual Analogue Scale (VAS) Score and Ramsay Sedation Score (RSS) in between two groups

Time (min)	Visual Analogue Scale (VAS)			Ramsay Sedation Score(RSS)		
	Group D (Mean±SD)	Group P (Mean±SD)	P value	Group D (Mean±SD)	Group P (Mean±SD)	*p* value
30 min	3.05 ± 0.53	3.68 ± 0.56	0.000	3.57 ± 0.73	2.45 ± 0.50**	0.000
60 min	2.48 ± 0.59**	3.11 ± 0.49**	0.000	3.02 ± 0.66**	2.09 ± 0.29**	0.000
90 min	1.86 ± 0.55**	2.61 ± 0.49**	0.000	2.39 ± 0.72**	1.75 ± 0.44**	0.000
2 hr	1.50 ± 0.55**	2.16 ± 0.37**	0.000	1.95 ± 0.61**	1.23 ± 0.42**	0.000
3 hr	1.02 ± 0.66**	1.91 ± 0.29**	0.000	1.50 ± 0.51**	1.02 ± 0.15**	0.000
4 hr	0.66 ± 0.53**	1.57 ± 0.50**	0.000	1.14 ± 0.35**	1.00 ± 0.00**	0.011
6 hr	0.52 ± 0.51**	1.11 ± 0.32**	0.000	1.00 ± 0.00**	1.00 ± 00**	0.00
12 hr	0.09 ± 0.29**	0.98 ± 0.26**	0.000	1.00 ± 0.00**	1.00 ± 0.00**	0.00
24 hr	0.00 ± 0.00**	0.77 ± 0.42**	0.000	1.00 ± 0.00**	1.00 ± 0.00**	0.00

Data are mean ± SD, NS= Nonsignificant

D-Dexmedetomidine P- Pregabalin

**- Statistically significant (p<0.001).

Table 3: Data of patients requiring rescue analgesics in both groups

	Group D (n=45) (mean ± SD)			Group P (n=45) (mean ± SD)			*p* value
Time of 1st rescue Analgesic	58.06 ± 11.62			37.5 ± 9.30			0.0001
Total no of patients requiring rescue analgesics	1st dose	2nd Dose	3rd dose	1st dose	2nd Dose	3rd dose	–
	28	13	1	23	15	3	
Total dose of analgesic in 24 hrs	134.09 ± 52.57			147.72 ± 62.83			0.26

Data are mean±SD, NS= Nonsignificant
D-Dexmedetomidine P- Pregabalin
**- Statistically significant (p<0.001)

Table 4: Comparison of intraoperative adverse effect and postoperative complications between two groups

Variable	Group D (n=45)		Group P (n=45)		*p* value
Hypotension	3	6.66%	8	17.77%	0.10
Hypertension	2	4.44%	5	11.11%	0.23
Tachycardia	3	6.66%	9	20%	0.06
Bradycardia	5	11.11%	1	2.22%	0.09
Nausea	1	2.22%	3	6.66%	0.29
Vomiting	1	2.22%	2	4.44%	0.55
Dizziness	2	4.44%	6	13.33%	0.13
Headache	1	2.22%	4	8.88%	0.16
Shoulder pain	1	2.22%	2	4.44%	0.55

Data are mean±SD, NS= Nonsignificant
D-Dexmedetomidine P- Pregabalin
**- Statistically significant (p<0.001).

Discussion

Laparoscopic cholecystectomy is considered gold standard and one of the preferred surgery for gall bladder diseases under general anesthesia in the present era due to its well known advantages. However, like any other surgery it is also associated with sympathoadrenal response occurring due to direct laryngoscopy, tracheal intubation, extubation and pneumoperitoneum which evokes hemodynamic instabilities. Various methods have been used to attenuate stress response. This study was designed to compare oral pregabalin versus bolus dose of intravenous dexmedetomidine as premedication in attenuating the hemodynamic responses to laryngoscopy, intubation and also during pneumoperitoneum in laparoscopic cholecystectomy. The incidence of bradycardia was 11.11% in group D while 2.22% in group P, this difference may be due to highly selective α2 agonist action of dexmedetomidine resulting in sympatholysis. The incidence of tachycardia was 6.66% in group D while it was 20% in group P which reflects better hemodynamic stability of dexmedetomidine than pregabalin. A significant reduction in HR following loading dose of Dexmedetomidine (6 mcg/kg) after intubation and after 20 min of pneumoperitoneum as compared to saline group was observed in a study done by Vora K.S *et al.*[13]. Rastogi B *et al.*[10] studied the effect of two different doses of oral pregabalin (75 mg and 150 mg) as premedication and observed an increase in HR in group P_{150} from baseline (80.65 ± 3.84) after 1min of laryngoscopy (107 ± 2.41) which was similar to our study. Gupta K *et al.*[9] reported that after premedication with oral pregabalin (150 mg) and placebo, there was a significant increase in HR in both groups but the increase was less in pregabalin group. We recorded a decrease in MAP (98.61 ± 19.21) from baseline (101 ± 14.75) in group D at the time of laryngoscopy and intubation, while in group P there was a significant increase in MAP (107.82 ± 18.20) from baseline (100.93 ± 14.37). Maximum decrease in MAP was found in group D, at 3 min after intubation (87.45 ± 17.23) although there was no significant change in MAP from baseline was found in group P following intubation. When comparing both the groups, fall in MAP was significantly more in group D than in group P (p<0.05). This may be attributed to sympatholytic action of dexmedetomidine on α2A receptors located in brainstem vasomotor centre and difference in the route of administration of study drugs. Similar to our study Rastogi B *et al.*[10]

in compared the effect of two different doses of oral pregabalin (75 mg and 150 mg) and observed a decrease in MAP (87.06 ± 3.90) from baseline (93.15 ± 2.59) after induction in patients receiving pregabalin (150 mg). Meena R *et al.*[14] in 2016 studied the effect of oral diazepam [10 mg (HS) + 5 mg (1 hr before surgery)] with two different doses of oral pregabalin [75 mg (HS) + 150 mg, 300 mg (1 hr before surgery)] and reported significant increase in MAP (106.44 ± 6.24) from baseline (91.14 ± 4.16) with diazepam while increase in MAP was less in pregabalin group P_{150} (98.43 ± 7.78) from baseline (91.22 ± 6.90) which was similar to our study.

CO_2 insufflation along with trendelenburg position required in laparoscopic surgeries causes significant release of catecholamines, cortisol, renin and vasopressin leading to increase in systemic vascular resistance and pulmonary vascular resistance and tachycardia[7]. In our study an increase in MAP from baseline during pneumoperitoneum in bothgroups were observed, however this increase was more in pregabalin group when compared to dexmedetomidine groupthat shows dexmedetomidine is better than pregabalinin attenuating the stress response during pneumoperitionium, Vora KS *et al.*[13] also reported that dexmedetomidine is better than pregabalin in attenuating the stress response during pneumoperitonium. Manne GR *et al.*[15] reported significantdecreaseinMAPafterstartingtheinfusion (dexmedetomidine 1 µg/kg) and there was no significant rise in MAP during pneumoperitonium till release of CO_2 (p<0.001). Gupta K *et al.*[9] studied the effect of clonidine (200 µg) and pregabalin (150 mg) as oral premedication during laparoscopic cholecystectomy and observed that haemodynamic responses were attenuated by both drugs and were maintained throughout intraoperative period, however clonidine was superior to pregabalin for attenuation of haemodynamic responses to laryngoscopy and laparoscopy. Analgesic efficacy of dexmedetomidine and pregabalin in different doses has been studied in various studies with different results. Dexmedetomidine had a moderate analgesic effect with sedation due to its action on postsynaptic alpha-2 adrenergic receptor, located in locus coeruleus and receptors in the dorsal horn of spinal cord[20,21] The analgesic effect of pregabalin is due to binding of pregabalin at α-2-delta site with consequent reduction in release of excitatory neurotransmitter like norepinephrine, glutamate, substance P.[8,22-24] In our study, group P patients experienced more postoperative pain as compared to group D (p<0.05). The time to first request for rescue analgesic was earlier (37.5 ± 9.30) in group P than group D (58.06 ± 11.62)(p<0.001). The total dose of analgesic in 24 hrs was higher in group P (147.72 ± 52.57) as compared to group D (134.09 ± 62.83). Though this difference was statistically insignificant (p=0.26) but we observed that patients in group D were pain free in immediate postoperative period and more comfortable in 24 hrs. Pathak AS *et al.*[7] compared the two different doses of dexmedetomidine (1 mcg/kg and 0.7mcg/kg) given preoperatively as bolus in patients undergoing laparoscopic surgery and found better postoperative analgesia with lower VAS scores and delayed time for first rescue analgesia in patients receiving dexmedetomidine 1 µg/kg. Esmat IM *et al.*[12] observed a significant reduction in VAS Score in patients receiving two different doses of pregabalin (150 mg, 300 mg) 1 hr prior to surgery. Pain scores were lower in pregabalin 300 mg. Sundar AS *et al.*[25] found no difference in VAS Score and total fentanyl requirement postoperatively among group P (PG_{150mg}) and group C (NS) at 6, 12 or 24 hrs after coronary artery bypass grafting (CABG) surgery. Dexmedetomidine and pregabalin also have anxiolytic and sedative properties. Dexmedetomidine provides sedation by stimulation of α2A and α2C receptors which are located in locus ceruleus in the spinal cord.Theanxiolytic property of pregabalin is by decreasing the synthesis of neurotransmitter glutamate to act on central nervous system. In our study the sedation score was higher in group D than group P at all time intervals (p < 0.05) but none of the patients in bothgroups had sedation score more than ≥4. Dexmedetomidine in a dose of 1 mcg/kg has been shown to cause increased sedation levels and need for oxygen supplementation by few authors[26,27]. Sebastian B *et al.*[17] found higher sedation scores in Dexmedetomidine groups (dex 0.5, 0.75 µg/kg) than normal saline (p < 0.05), Similarly Manne. GR *et al.*[15] also observed increased sedation levels in patients receiving low dose dexmedetomidine infusion (0.2 µg/kg/h, 0.4 µg/kg/h). In contrast to our study Parveen S *et al.*[19] found higher sedation score in pregabalin group (2.73 ± 0.55) as compared to oral clonidine (2.20 ± 0.41), this can be attributed to difference in the route of administration as we administered alpha-2 agonist dexmedetomidine IV. Anand LK *et al.*[18] showed that sedation score measured by somnolence sedation scale wascomparable between the control and pregabalin group (150 mg) (p > 0.05). No patient had sedation score of 3 and all patients were free of sedation at 6 hrs which is similar to our study. The adverse effects were found to be statistically insignificant in our study (p > 0.05).

In our study, the incidence of postoperative nausea and vomiting (PONV) was found higher in Pregabalin group (6.66%) than the dexmedetomidine group (2.22%), 2 patients from group D (4.44%) while 6 patients from group P (13.33%) experienced postoperative dizziness, 1 patient from group D while 4 patients in group P experienced headache and shoulder pain. All these complications were statistically insignificant in our study ($p > 0.05$). Esmat IM *et al.*[12] observed that postoperative vomiting was statistically significant in patients receiving pregabalin 300 mg ($p < 0.01$). Gupta P *et al.*[16] in 2017 and Meena R *et al.*[14] observed that only one patient in group P (150 mg) and 2 patients in group P (300 mg) suffered dizziness but it was statistically insignificant ($p > 0.05$).

Limitation of our study was that we could not measure stress mediators such as endogenous catecholamines or cortisol and dial concentration of sevoflurane. We did not use BIS monitoring and invasive blood pressure monitoring. A control group was not included in the study for comparison.

Conclusion

This studyconcluded that both dexmedetomidine (1 µg/kg IV bolus) and pregabalin (150 mg orally) is effective in attenuating haemodynamic stress response during laryngoscopy, intubation and pneumoperitoneum when given as premedication for laparoscopic cholecystectomy. Dexmedetomidine was found to be superior in ameliorating the haemodynamic responses to laryngoscopy and laparoscopy along with better postoperative analgesia without any significant adverse effects.

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