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Title:Comparison ofpremedication with oral pregabalin and i.v. Dexmedetomidine on hemodynamic changes in patients undergoing laproscopic surgery

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Abstract

Background: The major problems during laparoscopic surgery are related to the cardiopulmonary adverse effects of pneumoperitoneum, systemic carbon dioxide absorption, and patient positioning. Due to the requirement of steep head-up position, the chances and severity of unwanted hemodynamic responses such as hypertension and tachycardia are much higher in laparoscopic cholecystectomy when compared with other laparoscopic surgeries.**Objective:** The goal of anesthetic management in laparoscopic surgeries is to minimize these hemodynamic responses along with adequate depth and pain control with the target of minimal stress response and early discharge.

Materials & Methods: The present study was conducted in MLB Medical College and hospital, Jhansi,UP.Participants of eithersex with ASA physical status grade I & II, aged 20 to 50 years and planned for elective laparoscopic cholecystectomy under general anaesthesiawith tracheal intubationwere included in this study.This study was carried out in 100 participants. All selected participants under study were randomely divided into two groups depending on the premedication used.Group A patients were given i.v. dexmedetomidine in a dose of 1ug/kg over a period of 10 minutes, diluted with 100ml normal saline,20minutes prior to induction of anaesthesia.Group B patients were given oral pregabalin 75 milligrams with sips of water 1.5 hour before induction. Data was analysed in SPSS 17.0 using unpaired students t test.

Result: We found that Systolic Blood Pressure and Heart Ratewere decreased after intubation in both the groups but fall was significantly greater in group A when compared to group B .There was also significant fall in Mean Arterial Pressure after intubation in group A as compared to group B.

Conclusion: Therefoe we concluded that Intravenous dexmedetomidine 1 µg/kg is more effective than oral pregabalin 75mg in attenuating hemodynamic response to laryngoscopy and orotracheal intubation in laproscopic surgery.

Keywords-Dexmedetomidine, Pregabalin, Haemodynamics, Premedication

Introduction-Laparoscopic surgery is a modern surgical technique involving insufflation of gas (usually CO2) into the peritoneal cavity under pressure to facilitate visualization,[1] and helps in less postoperative pain and early recovery. Despite multiple benefits, all laparoscopic

surgeries are challenging from an anesthesia point of view, mainly due to significant alteration of hemodynamics, resulting from the combined effects of pneumoperitoneum, patient positioning, and hypercapnia from the absorbed CO2.In addition to this,hemodynamic pressor response to laryngoscopy and tracheal intubation is associated with increased circulating catecholamines, tachycardia, hypertention, increased myocardial oxygen demand and dysrhythmias[2,3]therefore patients with preexisting cardiovascular or cerebral disease may be at increased risk of morbidity and mortality, if subjected to adverse pressor response[4].

There is also an increase in the circulating blood volume, which is due to the shifting of blood from the splanchnic capacitance blood vessels to the systemic circulation.

Dexmedetomidine is an alpha 2 adrenoceptor agonist, is gaining popularity for its sympatholytic, sedative, anesthetic sparing and hemodynamic stabilizing properties without significant respiratory depression.[1,4]

Dexmedetomidine, the pharmacologically active d-isomer of medetomidine [4-[S]-[1-(2,3-dimethyl phenyl)-ethyl]-1h-imidazole is a highly specific and selective alpha-2 adrenoceptor agonist[5,6]. The alpha2: alpha1 binding selectivity ratio of dexmedetomidine is 1620:1 compared to 220:1 for clonidine. Studies have indicated that dexmedetomidine has prominent anesthetic sparing effects .Studies in human volunteers have demonstrated clonidine like analgesic,sedative,sympatholytic and cardiovascular effects[7,8,9].

Gabamimetic drugs like gabapentin and Pregabalin have been successfully used by various authors as oral premedication to attenuate pressor response during airway instrumentation, to decrease the preoperative anxiety and to reduce perioperative opiod consumption[10,11]. Pregabalin has analgesic, anticonvulsant, and anxiolytic effects.[12,13] Several studies have demonstrated the efficacy of oral pregabalin on post-operative pain and reduction of parenteral analgesics. Oral pregabalin attenuates pressor response to laryngoscopy and endotracheal intubation[14,15]. Pregabalin appears to produce an inhibitory modulation of neuronal excitability particularly in areas of CNS (neocortex, amygdala and hippocampus) and results in reduction of various neurotransmitters including glutamate, noradrenalin, serotonin, dopamine and substance P and hence produces analgesic effect[15]. Pregabalin is inactive at GABAA and GABAB receptors. It is not converted metabolically and it does not alter GABA uptake and degradation.

Therefore we hypothesized that these drugs can be used to attenuate the sympathoadrenal responses to laryngoscopy and endotracheal intubation. This study was designed to explore the comparison of effect of premedication with dexmedetomidine versus pregabalin on hemodynamic changes in patients undergoing laparoscopic surgery.

Hence objectives of the current study are to compare the changes in Heart Rate between the two groups, To compare the changes in Systolic Blood Pressure, Diastolic Blood Pressure and Mean Arterial Pressure and to study the side effects of the two drugs.

Material and Methods: Present study was conducted in the Department of Anesthesiology and Critical Care Medicine, MLB medical college, Jhansi. The study was conducted as continuous prospective double blind randomized control trial. After getting the ethical approval from college ethics committee, subjectswere included in the study . A total of 100 participants were admitted for this study.An informed consent was taken either from patients or their first degree relatives. Theinclusion criteria adopted in this study are:

1-Prebooked patients who had given consent for the procedure

2-Age: 20 to 50 years

3- Patients of either sex with ASA classification status I & II .

Exclusion criteria:

1-Patients with difficult airway

2-Patients with medical disorders like cardiovascular, renal and liver diseases, COPD, Epilepsy

3- Patients taking drugs like Beta blockers, Calcium channel blockers, Tricyclic antidepressants, serotonin reuptake inhibitors

Sample size: Sample size for the current study was calculated using power analysis. The power for the current study was set to 0.9 and the two-sided type I error is set at 0.05. The exact sample size was coming out to be 88 which was arbitrarily increase to 100.

ANAESTHETIC TECHNIQUE

All the participants who met the inclusion criteria were randomized in to two groups (Group A and Group B) using computer generated randomization.AllPatients were premedicated on the night before surgery with Tablet Ranitidine 150mg and Tablet Alprazolam 0.5mg. Intravenous line was secured with l8 Gauze cannula. Baseline heart rate, Systolic blood pressure, Diastolic blood pressure and Mean arterial pressure was recorded before giving study drug.

Group A patients were given iv dexmedetomidine in a dose of 1ug/kg over a period of 10 min diluted with 100ml normal saline,20min prior to induction of anesthesia through an infusion pump.Group B patients were given pregabalin 75 milligram orally with sips of water 1.5 hour before induction.On arrival in the operating room, monitors were attached and the patient's heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and oxygen saturation (SPO_2) were recorded.All the patients of both groups were given inj. Glycopyrrolate0.2mg I.V.,InjOndansetron 4mg IV, inj.Fentanyl2ug/kg I.V. and Inj. midazolam 1mg I.V. All the patients were preoxygenated with 100% oxygen for 5 minutes and Induction was done with Inj. propofol in a dose sufficient for loss of verbal command, followed by Inj. Vecuronium bromide(0.1mg/kg) to provide neuromuscular blockade and ventilated by mask for at least 3 minutes using 100% oxygen and 1 MAC of isoflurane. Laryngoscopy was performed with a macintosh laryngoscope and trachea was intubated with appropriate size cuffed Endotracheal tube and connected to anesthesia machine through closed breathing circuit and air entry over the both sides of chest was checked and confirmed by End tidal CO2 graph. Anesthesia was maintained with 66% N2O, 33% O2, Isoflurane 1 MAC and I.V. Vecuronium boluses (1/4 of loading dose)as per requirement.

At the end of surgical procedure, residual neuromuscular blockade was antagonized with Inj. neostigmine 0.05mg/kg and Inj. glycopyrrolate 0.01mg/kg I.V. Extubation was carried out as

a routine procedure and stress response to extubation was recorded. Patients were shifted to recovery room and were monitored for postoperative complications.

Statistical analysis: Data have been collected and entered in Microsoft excel sheet and imported to SPSS17.0 for the statistical analysis. Unpaired student's t test was applied to find out the significance of the difference of mean. The results were expressed as mean±SD.

Results: There was no significant difference in the baseliine values of heart rate in two groups but after intubation fall in heart rate was significantly more in group- A as compared to group- B (p values<0.0005). Table-1

Table-1: Changes in Mean Heart Rate.

Heart Rate (bpm)	GROUP- A	GROUP- B	P-VALUE
Baseline (before premedication)	88.45±8.72	86.5±9.88	0.3029
After premedication	86.45±8.37	85.5± 7.84	0.5589
After induction	80.4±10.23	84.0± 9.72	0.8416
Afterintubation(minutes)			
Immediately	78.12±10.02	89.76± 10.45	<0.0001
5	75.45±11.8	86.33± 11.59	<0.0001
10	78.0±12.45	84.46 ±10.37	<0.0001
15	77.4±11.68	83.85± 9.76	<0.0001
30	74.50±8.67	77.4± 9.24	0.1064

Table-2: Changes in Systolic Blood Pressure.

Systolic Blood Pressure (mmhg)	GROUP- A	GROUP- B	P-VALUE
Baseline (before premedication)	131.98±8.76	130.89±9.62	.5550
After premedication	127.08±6.16	130.92±7.46	.0060
After induction	107.56±5.39	109.44±6.79	.1284
After			

intubation(minutes)			
Immediately	118.04±6.00	126.68±7.33	<0.0001
5	117.96±3.65	124.68±4.74	<0.0001
10	109.12±3.50	118.52±4.53	<0.0001
15	109.32±4.37	117.08±4.33	<0.0001
30	112.72±4.38	114.24±4.07	<0.0753

Table-2shows there was no significant difference in baseline values of the Systolic Blood Pressure in both groups but after intubation fall in Systolic Blood Pressure was significantly more in group A- when compared to group- B(p value <0.0005).

Table-3: Changes in Diastolic Blood Pressure.

Diastolic Blood Pressure (mmhg)	GROUP- A	GROUP- B	P-VALUE
Baseline (before premedication)	66.46±6.78	65.8±7.43	.6844
After premedication	63.48±4.73	65.4±4.83	.0452
After induction	53.4±5.51	54.08±3.55	.4782
After intubation(minutes)			
immediately	59.04±5.51	63.28±4.88	.0001
5	58.52±2.88	62.96±4.75	<0.0001
10	54.66±2.58	59.24±4.34	<0.0001
15	54.04±2.36	58.04±4.28	<0.0001
30	56.52±2.49	57.16±4.89	.4115

Table-3 shows there was no significant difference in baseline values of the Diastolic Blood Pressure in both groups but there was significant fall in Diastolic Blood Pressure only after intubation in group- A as compared to group- B (p<0.0005).

Table-3: Changes in Mean Arterial Pressure

Mean Arterial Pressure (mmhg)	GROUP- A	GROUP- B	P-VALUE
Baseline (before premedication)	97.73±8.78	98.68±9.82	0.6112
After premedication	95.63±7.92	97.66±8.56	0.2213
After induction	80.54±9.79	84.45±8.74	0.0377
After intubation(minutes)			
Immediately	86.57±10.95	96.82±10.98	<0.0001
5	84.79±11.47	93.53±10.53	<0.0001
10	81.04±12.29	88.67±10.98	<0.0001
15	82.17±11.06	88.35±11.20	0.0066
30	84.11±9.34	86.0±10.65	0.3317

Table-4shows there was no significant difference in the baseline values of mean arterial pressure in two groups but there was significant fall in MAP only after intubation in group A as compared to group B

Discussion-Present study evaluates the comparison of efficacy of dexmedetomidine and pregabalin as premedication drugs to attenuate hemodynamic pressure response during laryngoscopy and intubation. Hemodynamic responses to laryngoscopy and tracheal intubation should be attenuated due to associated risk of myocardial ischemia or cerebral hemorrhage. If no specific measures are taken to prevent hemodynamic response, the heart rate can increase from 26 to 66%, depending on the method of intubation, and systemic blood pressure can increasefrom 36 to 45% due to exaggerated sympathetic outflow or receptor hypersensitivity. These hemodynamic changes can be detrimental in elderly and hemodynamically compromised patients. More recently, Aronson and Fontes[16] found that among the various component of blood pressure, preoperative pulse pressure was independently and significantly associated with postoperative stroke, renal failure, and mortality in patients undergoing coronary artery bypass surgery. Rise in pulse pressure as few as 10 mm Hg in both normotensive and hypertensive individual is associated with 20% or more increase risk of renal, coronary, and cerebral events. Numerous techniques have been used to reduce the incidence and severity of these hemodynamic responses.

In order to reduce the incidence and severity of the hemodynamic responses of laryngoscopy and intubation, many pharmacological methods were evaluated either in the premedication or during induction,with controversial results. Tachycardia and rhythm disturbances can be attenuated by omitting atropine as premedicant. Many studies have reviewed the impact of different drugs on blood pressure following laryngoscopy. The most important were lidocaine, esmolol, sodium nitroprusside, and fentanyl. Among opioids, remifentanil (1.0 μg kg^{-1}), alfentanil (10-20 μg kg^{-1}), or fentanyl (0.5-1.0 μg kg^{-1}) were reported to have the most stable effect on hemodynamic responses to laryngoscopy and tracheal intubation, but they prolonged the recovery time[17,18,19] Intranasal nitroglycerine attenuated the hypertensive response to laryngoscopy and intubation, but tachycardia was observed.Singh H, Vichitvejpaisal P *et al.*,[16]. Reported that 150 mg esmolol bolus was superior to intravenous high-dose lidocaine or low-dose fentanyl in preventing the tachycardia associated with intubation.

Conclusion: The primary outcome of our study showed that intravenous dexmedetomidine is more effective than oral pregabalin in attenuating hemodynamic responses to laryngoscopy and endotracheal intubation in laproscopic surgery.Dexmedetomidine produces hyper-polarization of noradrenergic neurons and suppression of neuronal firing in the locus cerelous that leads to decrease in systemic noradrenalin release and attenuation of sympathoadrenal responses during laryngoscopy and intubation

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