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A Prospective Randomised Study of the Effects of Pregabalin Oral Versus Dexmedetomidine Infusion on Intra Operative Hemodynamic Stability in Patients Undergoing Laparoscopic Cholecystectomy

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Abstract

Context: Many agents are being tried to prevent acute changes in hemodynamics taking place during surgery as a result of intubation and other invasive procedures. Over the period of time dexmedetomidine has evolved as safe and hemodynamically stable anesthetic agent over most of the other agents. *Aims:* To study efficacy of dexmedetomidine over oral pregabalin in patients undergoing laparoscopic cholecystectomy. *Settings and design:* Present study was prospective randomized controlled study carried out at Apollo hospitals, Jubilee Hills, Hyderabad. *Material and methods:* 50 eligible patients undergoing laparoscopic cholecystectomy as per study criteria were divided randomly into two groups. One group with 25 patients received dexmedetomidine (Group D) and other group with 25 patients received oral pregabalin. Both the groups were compared for mean arterial pressure and heart rate from pre-operative period till post-operative period. *Statistical analysis:* Students t test was used to find the association between two mean. p value less than 0.05 was taken as statistically significant. *Results:* Both the groups were comparable to each other in terms of baseline characteristics. Pre-operative mean arterial blood pressure and heart was also comparable between the two groups. But it was significantly lower in group D compared to group P right from induction to extubation. *Conclusion:* We hereby conclude that dexmedetomidine is superior to oral pregabalin and provides better hemodynamic stability to patients undergoing laparoscopic cholecystectomy.

Keywords: Pregabalin; Dexmedetomidine; Hemodynamic Stability; Laparoscopy; Cholecystectomy.

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Introduction

With the advent in the medical sciences, new airway devices have been seen in recent years. But in airway management, even today the gold standards are tracheal intubation and rigid laryngoscopy. Patients undergoing these invasive procedures i.e. tracheal intubation and rigid laryngoscopy are often at risk of hemodynamic instability. During instrumentation, there is stimulation of parapharyngeal and epipharyngeal areas and nerves which leads to discharge of sympathoadrenal products and this in turn leads to changes in the hemodynamic stability of the patients. The heart rate and blood pressure increases. There can also be an increase in the intraocular as well as intracranial pressure. There is increased cardiac output which leads to an increase in the mean arterial blood pressure. Some patients can even experience arrhythmias. If the patient is in

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compromised state like suffering from cardiovascular diseases then this is a challenge for the anesthetists. In such patients hemodynamic changes can lead to serious outcomes like left ventricular failure, and even cerebral hemorrhage or myocardial ischemia. These are more likely to develop in cases of patients having hypertension [1].

To overcome these side effects various agents have been tried so that the patients do not experience these hemodynamic changes. Pregabalin and dexmedetomidine are tried and few studies compared their effects. Dexmedetomidine exerts its effects as it is an α_2-adrenoreceptor agonist. Its effects are exerted by peripheral as well as central mechanisms. At low doses, it causes the reduction in the norepinephrine release and inhibits the neurotransmission in the sympathetic nerves [2]. Thus on an average overall it leads to the decrease in the circulating catecholamines and causes decrease in the blood pressure and also decrease in the heart rate [3].

As mentioned above, during the procedure of intubation, in patients with coronary artery disease, there might be occurrence of myocardial ischemia. Such patients tend to develop myocardial infarction after surgery. Dexmedetomidine is well known to reduce such adverse events. Studies have been carried out to study the effectiveness of dexmedetomidine in patients undergoing cardiac surgery. They found that in patients who were given dexmedetomidine the outcome was better in terms of complications and mortality [4].

Dexmedetomidine when given with other general anesthetic agents improves their action and also reduce the dose required. It provides stable hemodynamics for the patients [5]. Pregabalin is also time tested and has anxiolytic, anticonvulsant and analgesic properties [6]. Pregabalin has been found to be very effective to minimize the requirement of analgesics after surgery for the patients [7]. The pressor response caused by laryngoscopy or caused by endotracheal intubation is attenuated by oral pregabalin [8].

Hence present study was carried out to study of the effects of pregabalin oral versus dexmedetomidine infusion on intra operative hemodynamic stability in patients undergoing laparoscopic cholecystectomy.

Methods

The present study was undertaken at Apollo Hospitals, Jubilee Hills, Hyderabad during the period of 2012- 2013.

Study Design

A prospective randomized double blind clinical study was carried out on 50 cases that were randomized into two groups; 25 cases for Pregabalin in one group and 25 cases for Dexmedetomidine in another group. Only ASA class I and II between age group of 20 to 55 years were selected for the study.

Study Location

Apollo hospitals, Jubilee Hills, Hyderabad.

Study Period

One year period from 18/08/2012 to 18/08/2013.

Study Inclusion Criteria

1. ASA I and II adult patients.
2. Age between 20 to 55 years.
3. With no systemic disorders.
4. Patients undergoing laparoscopic cholecystectomy.

Study Exclusion Criteria

1. Patients unwilling for the study.
2. Patients with Hypertension
3. Patients with Diabetes mellitus
4. Obese with BMI > 30.
5. Known case of coronary artery disease or cerebro vascular disease.
6. Known case of pre op hypotension.
7. Laparoscopic cholecystectomy converted to open cholecystectomy.

Sample Size

During the study period, 696 patients underwent Laparoscopic cholecystectomy. Out of which, 558 patients belonged to 22-55 yrs of age. Among 558 patients, 462 belonged to ASA- I & ASA –II. 310 patients did not give consent for the study. So finally 152 patients were considered initially but in that 152, 43 members were excluded as they were hypertensive, 26 members were excluded due to diabetes, 21 members due to obesity and 12 cases were converted to open cholecystectomy. So finally the sample size became 50 after meeting the inclusion and exclusion criteria.

Study Procedure

First the fifty patients were screened for Laparoscopic cholecystectomy, and then they were checked to meet the criteria. Informed consent was taken, then assigned them in to study groups Pregabalin (P) and Dexmedetomidine (D) by randomization by taking chits from a box of 25 (P) and 25 (D).

Study proforma used to fill patient demographic details, and enter tabular data of monitoring of hemodynamic parameters.

Equipment Used

Infusion pump

Infusion set.

Monitors used Philips multi Parameter

1. NIBP (non invasive blood pressure).
2. Pulse oximeter (for heart rate and SpO_2 measurement).
3. $EtCO_2$ (side stream).
4. ECG.
5. Urine output.

Anesthetic machine, resuscitation equipment and drugs were checked and kept ready, before undertaking the procedure.

Once the patient arrived in the operation theatre, the patient was kept on routine monitoring like NIBP, Pulse oxymetry and ECG. Recording of baseline parameters like arterial oxygen saturation, mean arterial blood pressure and heart rate was recorded.

Study Drugs

The patients in-group D received Dexmedetomidine 0.4 ug/kg bolus over 20 min followed by 0.2 ug/kg/hr while patients in group P received normal saline in an identical syringe. Patients in group P received Pregabalin 75 mg orally two hour before the surgery while patients in group D received placebo orally two hours before the surgery.

Study Procedure

Fifty (50 ml) identical syringe was used to prepare dexmedetomidine. The dose was 200 μg i.e. 2 ml. It was added in 0.9% normal saline. Normal saline 38 ml plus dexmedetomidine 2 ml total 40 ml volume gave a concentration of 5 μg ml/1. This infusion was given to the patients for 20 min at a rate of 0.4 mcg/kg/hr. they were also given fentanyl in a dose of 2 μg /kg and propofol was given in a dose of 2 mg/kg. Vecuronium was given in a dose of 0.1 mg/kg so that endotracheal intubation can be facilitated.

Carbon dioxide in a dose of 2 lit/min was used to create pneumoperitoneum. Throughout the entire procedure of laparoscopy, the intra abdominal pressure was maintained at less than 14 mmHg. The $EtCO_2$ level was maintained at 35-40 mmHg by mechanical ventilation. Nitroglycerine infusion was given to manage the intra operative hypertension. Dexmedetomidine infusion was stopped immediately after surgery. Neostigmine was given to reverse the neuromuscular block. Finally tracheal extubation was done. Adverse events were noted down during the period after surgery.

During Study Procedure and Monitoring

1. Patients under study should not receive benzodiazepines on the day of procedure.
2. Intra abdominal pressure was restricted to 14 mmHg.
3. $EtCO_2$ was maintained below 35 mmHg at any course of the procedure.
4. Isofluorane, and nitroglycerin and metoprolol were kept as rescue drugs.
5. Atropine was kept ready to counter the bradycardia, and inotropes was kept ready to counter any untoward hypotension.

Two groups (Group D and Group P) are compared in terms of relative efficacy and analgesia with regards to Age, Sex (male/female), Weight, Heart rate, Mean arterial pressure,

Statistical Analysis

All the study data entered in to an electronic data spread sheet and quantitative data is presented as mean±standard deviation. Comparison among the study groups was done by using unpaired t-test. The statistical analysis was done using unpaired t-test, Welch's corrected Graph pad instat version 3.00 for windows 7 Graph pad software, San Diego, California, USA. P value < 0.05 is considered as statistically significant. Data entry and analysis was done using Excel program.

Results

Fifty patients were divided into two groups randomly.

a. Group D (Dexmedetomidine) – 25 patients.

b. Group P (Pregabalin) – 25 patients.

The patients in-group D received Dexmedetomidine 0.4 ug/kg bolus over 20 min followed by 0.2 ug/kg/hr while patients in group P received normal saline in an identical syringe. Patients in group P received Pregabalin 75 mg orally two hour before the surgery while patients in group D received placebo orally two hours before the surgery.

Table 1 shows comparison of baseline characteristics among the two groups. Both the groups of the patients were comparable in age and weight. The parameters were normally distributed. There was no significant difference in age and weight between the both groups as the p value is 0.4 for Age and 0.6 for weight of the patients respectively.

Table 2 shows comparison of mean arterial pressure (MAP) among the two groups. The parameters were normally distributed. The MAP was not significantly different pre operatively. But was significantly lower in dexmedetomidine group from induction of anesthesia till extubation compared to pregabalin group ($p<0.05$).

Table 3 shows comparison of heart rate among the two groups. The heart rate was not significantly different pre operatively. But was significantly lower in dexmedetomidine group from induction of anesthesia till extubation compared to pregabalin group ($p < 0.05$).

Table 1: Comparison of baseline characteristics among the two groups

Baseline characteristics	Group D		Group P		P value	Interpretation
	Mean	SD	Mean	SD		
Age (years)	40.5	11.35	42.56	9.3	0.4	Not significant
Sex (M/F)	13/12		13/12			
Weight (kg)	55.24	10.16	56.34	9.5	0.6	Not significant

Table 2: Comparison of mean arterial pressure (MAP) among the two groups

MAP (mmHg)	Group D		Group P		P value	Interpretation
	Mean	SD	Mean	SD		
Pre operative	99.42	7.01	102.48	8.16	0.16	Not significant
Induction	65.17	7.48	92.68	6.56	0.0001	Significant
Intubation	89.76	5.39	99.56	5.08	0.0001	Significant
15 min	92.13	5.57	101.32	4.02	0.0001	Significant
30 min	92.17	6.84	99.6	4.19	0.0001	Significant
45 min	86.5	7.64	99.36	4.5	0.0001	Significant
60 min	87.3	7.94	95.56	4.87	0.0001	Significant
75 min	90.79	6.47	98.2	4.61	0.0001	Significant
Extubation	87.42	5.84	107.4	4.61	0.0001	Significant
1 hour post op	91.44	5.56	90.79	6.74	0.6	Not significant

Table 3: Comparison of heart rate among the two groups

MAP (mmHg)	Group D		Group P		P value	Interpretation
	Mean	SD	Mean	SD		
Pre operative	81.17	10.80	83.68	8.37	0.30	Not significant
Induction	76.54	7.96	78.24	11.51	0.0001	Significant
Intubation	76.54	7.80	96.76	8.84	0.0001	Significant
15 min	75.17	8.98	94.73	11.43	0.0001	Significant
30 min	76.54	8.70	91.72	6.41	0.0001	Significant
45 min	76.33	8.35	94.60	7.47	0.0001	Significant
60 min	76.63	6.61	92.84	8.06	0.0001	Significant
75 min	75.04	6.61	92.84	8.06	0.0001	Significant
Extubation	84.76	8.66	91.04	11.43	0.0001	Significant
1 hour post op	90.44	6.65	88.17	8.55	0.40	Not significant

Discussion

In this study, the mean age of the patients in group D was 40.5 years and in Group P it was 42.56 years. There was no significant difference in age between the two groups ($p > 0.05$). The mean weight in Group D patients was 55.24 kg and group P patients were 56.34 kg and had no significant difference ($p > 0.05$). In Group D out of 25 patients, there were 13 male and 12 female. In Group P also same number of male and females were there.

From induction to extubation, mean arterial pressures were at significantly lower side in Group D compared to Group P. Intubation response was also less in group D. At 15 minutes and 30 minutes of intra operative period, the mean arterial pressures were raised: 92.13 mmHg at 15 minutes and 92.17 mmHg at 30 minutes in Group D and 101.32 mmHg at 15 minutes and 99.6 mmHg at 30 minutes in Group P. This might be because of skin incision, laparoscopic ports insertion, carbon-dioxide pneumoperitoneum. From induction to extubation, comparison of mean arterial pressure in Group D and Group P was highly statistically significant (p value < 0.01). Pre operative changes in mean heart rate 81.17 beats/min in Group D and 83.68 beats/min in Group P showed no significant difference in these findings (p value 0.30), so these values were taken as base line values. From induction to extubation, there was significant change in mean heart rate compared between Group D and Group P (p value < 0.01), which was highly statistically significant. There was increase in 20-25 beats/min in group P compared to group D during intra operative period. One hour after post operative period, there was no significant change in mean heart rate compared between these two groups (p value 0.40), which was not statistically significant.

Peng PWH et al. [9] found in their study that perioperative administration of pregabalin 75 mg provided limited analgesic benefit in the postoperative period. The fall in blood pressure and heart rate with induction was more in Group D than Group P, might be due to the synergistic with propofol, and dexmedetomidine as both causes hypotension. Extubation was smooth and uneventful in Group D with good control of haemodynamics. But in Group P, there was increase in mean arterial pressures and heart rate during the extubation.

Guler G et al. [10] observed and compared the effects of pregabalin and dexmedetomidine among patients who underwent laparoscopic cholecystectomy on hemodynamics. They noted that the dexmedetomidine group was hemodynamically more stable than pregabalin group. These findings are similar to the findings of the present study.

Hall JE et al. [11] and Guo TZ et al. [12] underlined the mechanism of action of dexmedetomidine. They narrated that dexmedetomidine acts by activating the receptors in brain and spinal cord and this leads to the inhibition of firing by neurons. This inhibition is the reason for low blood pressure, low heart rate and analgesia exerted by dexmedetomidine.

Our study confirms that hemodynamic changes (rise in mean arterial pressure and heart rate) were attenuated by dexmedetomidine infusion during laparoscopic cholecystectomy more than in comparison to the pregabalin.

In several study reports, dexmedetomidine infusion rates ranging from 0.1 to 10-μg kg-1 hr-1 have been used. The studies with higher infusion rates had more incidences of adverse effects like hypotension and bradycardia. In this study, we used dexmedetomidine in an infusion rate of 0.2 μg kg-1hr-1 during laparoscopic cholecystectomy and did not observe significant incidence of hypotension or bradycardia. Dexmedetomidine causes sedation but it does not cause delay in the recovery time as shown in the study.

Conclusions

1. Stress response or pressor response was better attenuated with Dexmedetomidine than Pregabalin.
2. Good attenuation of heart rate response was achieved with Dexmedetomidine compared to Pregabalin.
3. Dexmedetomidine provides good intraoperative protection against hemodynamic response to surgical stimuli, laparoscopic port insertion, and carbon dioxide pneumoperitoneum.
4. Good attenuation of extubation response was more with Dexmedetomidine.
5. Dexmedetomidine provides good sedative effect in comparison with Pregabalin.

Key messages

Dexmedetomidine should be used instead of any other anesthetic drugs in patients undergoing laparoscopic cholecystectomy.

Prior publication: Nil

Support: Nil

Conflicts of interest: Nil

Permissions: All necessary permissions have been taken

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