

EVALUATION OF DEXMEDETOMIDINE ON HEMODYNAMICS IN PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMYCh. Penchalaiah¹, Sunil Nanjarapalle²**HOW TO CITE THIS ARTICLE:**

Ch. Penchalaiah, Sunil Nanjarapalle. "Evaluation of Dexmedetomidine on Hemodynamics in Patients Undergoing Laparoscopic Cholecystectomy". Journal of Evidence based Medicine and Healthcare; Volume 2, Issue 36, September 07, 2015; Page: 5754-5764, DOI: 10.18410/jebmh/2015/791

ABSTRACT: BACKGROUND: Dexmedetomidine a newer generation highly selective alpha-2 adrenergic agonist are well known to inhibit catecholamine release. The present study compares the effects of intravenously administered dexmedetomidine to attenuate hemodynamic response to pneumoperitoneum to laparoscopic cholecystectomy under general anaesthesia.

METHODOLOGY: 60 patients ASA Physical status I and II, aged between 18 and 50 years of either sex, scheduled for elective laparoscopic cholecystectomy were randomized in to 2 groups (group D and S) in a double blind fashion to receive either Dexmedetomidine (1microgram/kg) in 100ml of 0.9% normal saline or only 0.9% plain normal saline respectively. It is given 30 min prior to induction. Patient vitals like HR, SBP, DBP, MAP were monitored during the study at various time intervals. **RESULTS:** Following intubation and pneumoperitoneum there significant rise in HR, MAP, SBP, DBP in group S but no significant rise in Group D. **CONCLUSION:** Dexmedetomidine given in a dose of 1microgram/kg as a premedication is effective in attenuating the hemodynamic responses in laparoscopic surgery.

KEYWORDS: Dexmedetomidine, Laparoscopiccholecystectomy, Hemodynamic Responses.

INTRODUCTION: The physiological response to surgical stress and anaesthesia is well documented. Kehlet et al provided a clear insight to physiological background of stress response. In earlier review by Kehlet the stress response to surgery is more than anaesthesia drugs and technique. A wide number of anaesthetic drugs have been used in clinical practice to modify the stress response to anaesthesia and surgery.

Laparoscopic surgery which involves insufflation with carbondioxide produces undesirable responses like hypertension, tachycardia and dysrhythmias.

Introduction of Dexmedetomidine which is highly specific and selective alpha 2 agonist has been tried in various studies to modify the stress response to surgery and to have a pleasant anaesthetic outcome with minimal cardiovascular changes.

In our present study we have taken the pharmacological advantage of Dexmedetomidine to study the various cardiovascular parameters at different periods during the laparoscopic procedure.

Very few studies are available till date regarding the usage of Dexmedetomidine in laparoscopic surgeries. The present study will give an insight of the pharmacological effects of Dexmedetomidine to be applied to stress response to laparoscopic surgery which may have implication on patients with serious underlying medical problem.

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AIMS AND OBJECTIVES:

- To study the effectiveness of Dexmedetomidine in attenuating the sympathetic response to laryngoscopy and endotracheal intubation.
- To study the effectiveness of Dexmedetomidine in maintaining hemodynamic stability during laparoscopic cholecystectomy.
- To study the adverse effects of Dexmedetomidine.

PATIENTS AND METHODS: The randomized prospective study "Evaluation of Dexmedetomidine in patients undergoing laparoscopic cholecystectomy" was undertaken at government general hospital, S. V. Medical College, Tirupathi. The institutional ethical committee approved the study and written informed consent was obtained from all the patients before being included in the study.

Selection Criteria:

Inclusion:

1. ASA Grade I and II.
2. Age between 18 to 60 years.

Exclusion:

1. Morbid obesity.
2. Patients with cardiac dysfunction.
3. Hypertensive patients.
4. Patients with Renal dysfunction.
5. Patients with liver dysfunction.
6. Patients with severe endocrine disorders.

The patients were randomly allocated to two groups as below:

- Group D (Dexmedetomidine group; n=30) - Received 1mcg/kg of Dexmedetomidine in 100ml of 0.9% normal saline 30min before induction
- Group S (Saline group; n=30) – Received 100ml of 0.9% normal saline 30min before induction.

A thorough pre-anaesthetic evaluation was performed by taking history and clinical examination. In all patients age, weight, Systolic blood pressure, Diastolic blood pressure and Heart rate were recorded. All patients were investigated thoroughly to rule out cardiac, renal, hepatic and endocrine problems

On arrival in the operation theatre, monitors were attached and baseline parameters such as heart rate, systemic arterial pressure and oxygen saturation were noted down. Two intravenous lines were secured, one 20 Gauge cannula in the right hand for the infusion and another 18 gauge cannula in left hand for Intravenous fluids and drug administration. 500 ml of crystalloids (Ringer Lactate) was started.

Group -D, received Dexmedetomidine 1mcg/kg as infusion in 100ml of 0.9% normal saline 30min before Induction of anaesthesia whereas Group - S received 100ml of 0.9% normal saline 30min before induction of anaesthesia.

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Patients were premedicated with ondansetron 0.8mg/kg, Glycopyrrolate 0.2 mg, Tramadol 2mg/kg. Patients were induced with Thiopentone 5mg/kg. Endotracheal intubation was facilitated by succinylcholine 2mg/kg. Anaesthesia was maintained with 33% oxygen in nitrous oxide, and vecuronium bromide 0.1mg/kg. Intermittent positive pressure ventilation was continued by mechanical ventilator to maintain end tidal carbon dioxide between 35-40 mm Hg.

Pneumoperitoneum was created by insufflation of carbondioxide at the rate of 2 litres/min. Intra-abdominal pressure was maintained at 14mmHg throughout the surgical procedure. Throughout the procedure, any rise in mean arterial pressure more than 20% from the baseline was treated with nitroglycerine infusion.

Systemic arterial pressure including the systolic, diastolic and mean arterial pressure, heart rate, Oxygen Saturation, Endtidalcarbondioxide and electrocardiography were recorded at the following points of time:

1. Preoperative.
2. After infusion.
3. 1minute after induction
4. 1minute after intubation.
5. After Pneumoperitoneum.
6. 15minutes after Pneumoperitoneum.
7. 30minutes after Pneumoperitoneum.
8. 45minutes after Pneumoperitoneum.
9. 60minutes after Pneumoperitoneum.
10. End of Pneumoperitoneum.
11. Post-operative period.

At the end of surgery patients were reversed with Glycopyrrolate 0.01 mg/kg and Neostigmine 0.05mg/kg. Extubation was performed and patients were transferred to recovery room.

OBSERVATION AND RESULTS: The present study was done in Department Of Anaesthesiology, Government General Hospital, Tirupathi. The patients were divided into two groups.

- Group D - patients received Dexmedetomidine.
- Group S - patients received saline.

The following observations and results were noted.

DEMOGRAPHIC DATA: The mean weight in Group D was 60.56±9.00 and in Group S was 62.03±6.90 respectively.

The mean values are summarized in Table 1

Weight	Mean±SD	t value	P value
GROUP - D	60.56±9.00	0.70811	0.48 NS
GROUP - S	62.03±6.90		

TABLE 1

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The average age in Group D and Group S was 38.56 ± 11.51 and 33.46 ± 10.62 respectively.

The values are summarized in Table 2

Age	Mean \pm SD	t value	P value
GROUP - D	38.56 ± 11.51	1.78264306	0.07.NS
GROUP -S	33.46 ± 10.62		

TABLE 2

The males in Group D and Group S were 14 and 17 respectively.

The females in Group D and Group S were 16 and 13 respectively.

The values are depicted in Table 3.

Sex Distribution	GROUP - D	GROUP - S
MALE	14	17
FEMALE	16	13

TABLE 3

HEMODYNAMICS:

HEART RATE: The Preoperative heart rate in Group D was 93.63 ± 17.73 and in Group S was 87.8 ± 10.17 respectively. The heart rate t value was 1.562 and P value was 0.123 which was statistically not significant.

The heart rate half an hour after infusion of Dexmedetomidine was 77.23 ± 11.34 . In Group S where normal saline was given the mean heart rate was 83.23 ± 7.45 . When two groups were compared after infusion, the t value was 2.419 and P value was 0.018 which was statistically Significant.

The heart rate one minute after intubation in Group D was 93.16 ± 11.40 and in Group S was 107.26 ± 12.74 . When compared between both groups, the t value was 4.515 and P value was 0.000001 which was statistically Significant.

After pneumoperitoneum with time lapse of 15 min, the mean heart rate in Group D was 89.76 ± 13.50 and 98.36 ± 13.00 in Group S. When compared between both groups it was statistically significant (P value 0.0147). After 60 minutes of insufflation, the mean heart rate in Group D was 88.70 ± 13.61 and 101.37 ± 13.27 in Group S respectively. When compared between two groups, the test value (t) was 2.977 and P value was 0.0048 which was statistically Significant.

In the postoperative period, the mean heart rate was 92.73 ± 12.07 in Group D and 106.13 ± 9.91 in Group S respectively. When both the groups were compared, the P value was 0.00001 which was statistically Significant

The data is shown in the following table 4.

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HEARTRATE	GROUP - D	GROUP - S	t value	P value
	Mean±SD	Mean±SD		
PREOPERATIVE	93.63±17.73	87.8±10.17	1.56250644	0.123 NS
AFTER INFUSION	77.23±11.34	83.23±7.45	2.41983305	0.018 Sig
1MIN AFTER INDUCTION	81.1±7.74	85.63±6.04	2.52710983	0.014 Sig
1MIN AFTER INTUBATION	93.16±11.40	107.26±12.74	4.51520586	0.000001 Sig
AFTER PNEUMOPERITONEUM	90.56±11.57	97.1±13.37	2.02321169	0.0476 Sig
15 MIN	89.76±13.50	98.36±13.00	2.51258793	0.0147 Sig
30 MIN	88.26±13.18	98.06±10.93	3.13311761	0.0027Sig
45MIN	87.55±13.89	94.40±11.48	2.00362274	0.0138 Sig
60 MIN	88.70±13.61	101.37±13.27	2.97722085	0.0048 Sig
END OF PNEUMOPERITONEUM	85.96±6.76	91.36±8.43	2.73563283	0.0082 Sig
POSTOPERATIVE PERIOD	92.73±12.07	106.13±9.91	4.69685233	0.00001 Sig

TABLE 4

SYSTOLIC BLOOD PRESSURE: Mean preoperative systolic blood pressure in Group D was 125.26±8.01 and 122.63±8.19 in Group S respectively. When comparison was made between the two groups, it was not statistically significant.

After infusion with Dexmedetomidine the mean systolic blood pressure in Group D was 113.73±8.55 and 123.33±7.35 in Group S respectively. When comparison was made between Group D and Group S, the mean systolic blood pressure was found to be statistically significant (P value 0.000001).

The mean systolic blood pressure one minute after intubation in Group D was 128.93±9.15 and 144.46±7.63 in Group S respectively. When compared between the two groups, the values were statistically significant.

The mean systolic blood pressure 15 min after pneumoperitoneum in Group D was 126.03±11.11 and 144±15.27 in Group S respectively. When compared between both the groups, the values were statistically significant.

Mean systolic blood pressure when compared between Group D and Group S at 30 minutes, 45 minutes and 60 minutes was statistically significant.

The mean systolic blood pressure in the postoperative period in Group D was 127.93±9.99 and 142.8±10.02 in Group S, when compared was found to be statistically significant (P value 0.00001)

The mean systolic blood pressure values were given in following table 5.

SYSTOLIC BLOOD PRESSURE	GROUP - D	GROUP - S	t value	P value
	Mean±SD	Mean±SD		
PREOPERATIVE	125.26±8.01	122.63±8.19	1.25821682	0.2133 NS
AFTERINFUSION	113.73±8.55	123.33±7.35	4.65855326	0.000001 Sig

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1MIN AFTER INDUCTION	105.76±10.57	118.13±8.13	5.07654486	0.000001 Sig
1MIN AFTER INTUBATION	128.93±9.15	144.46±7.63	7.13856339	0.000001 Sig
AFTER PNEUMOPERITONEUM	126.5±10.88	133.9±9.98	2.74465997	0.0080 Sig
15 MIN	126.03±11.11	144±15.27	5.20979473	0.000001 Sig
30 MIN	123.83±13.02	138.63±10.72	4.80345917	0.000001 Sig
45 MIN	128.10±10.34	138.29±14.27	3.07531015	0.0032 Sig
60 MIN	127.70±11.99	141.81±14.57	3.4406951	0.0013 Sig
END OF PNEUMOPERITONEUM	124.43±9.78	129.33±6.41	2.29266158	0.0255 Sig
POSTOPERATIVE PERIOD	127.93±9.99	142.8±10.02	5.750569	0.00001 Sig

TABLE 5

DIASTOLIC BLOOD PRESSURE: The mean diastolic blood pressure preoperatively was 78.1±5.57 in Group D and 76.36±4.21 in Group S respectively. When compared the P value was not statistically significant. (P value 0.17).

After infusion, the mean diastolic blood pressure was 72.76±8.63 in Group D and 78.36±4.07 in Group S respectively, which when compared was statistically significant. (P value 0.002)

The mean diastolic blood pressure one minute after intubation was 82.06±5.99 in Group D and 91.96±8.43 in Group S. When compared it was found to be statistically significant. (P value 0.000001)

The mean diastolic blood pressure 15 minutes after pneumoperitoneum was 80.8±7.84 in Group D and 89.56±11.51 in Group S, which was statistically significant. (P value 0.001)

The mean diastolic blood pressure 30 minutes, 45 minutes and 60 minutes after pneumoperitoneum in Group D and Group S was found to be statistically significant. (P values 0.0005, 0.0002, 0.0001 respectively)

In the postoperative period, the mean diastolic blood pressure in Group D was 79.96±6.75 and 88.76±5.90 in Group S, when compared was statistically significant.

The data are shown in the table 6 below;

DIASTOLIC BLOOD PRESSURE	GROUP - D	GROUP - S	t value	P value
	Mean±SD	Mean±SD		
PREOPERATIVE	78.1±5.57	76.36±4.21	1.35881775	0.17 NS
AFTER INFUSION	72.76±8.63	78.36±4.07	3.21210367	0.002 Sig
1 MIN AFTER INDUCTION	70.46±6.42	74.8±5.34	2.83944476	0.006Sig
1MIN AFTER INTUBATION	82.06±5.99	91.96±8.43	5.23716312	0.000001 Sig
AFTER PNEUMOPERITONEUM	81.46±7.02	86.96±8.75	2.68283205	0.0094 Sig
15 MIN	80.8±7.84	89.56±11.51	3.44614458	0.001 Sig
30 MIN	78.93±7.87	86.5±8.24	3.63521445	0.0005 Sig
45 MIN	79.82±7.42	87.48±7.22	3.90347876	0.0002 Sig
60 MIN	79.37±7.29	88.62±6.13	4.25776839	0.0001 Sig

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END OF PNEUMOPERITONEUM	76.66±7.18	80.96±8.17	2.16383768	0.034 Sig
POSTOPERATIVE PERIOD	79.96±6.75	88.76±5.90	5.37000754	0.00001 Sig

TABLE 6

MEAN ARTERIAL BLOOD PRESSURE: The mean arterial blood pressure in the preoperative period in Group D was 93.26±5.75 and 91.7±4.38 in Group S which when compared was not statistically significant.

The mean arterial blood pressure after infusion was 86.36±7.47 in Group D and 93.33±3.77 in Group S respectively. When compared between two groups, the values were statistically significant. (P value 0.000001)

The mean arterial blood pressure one minute after intubation was 97.2±5.70 in Group D and 109.03±7.79 in Group S respectively. When compared between groups, P value was statistically significant.

The mean arterial blood pressure 15 minutes after pneumoperitoneum was 95.56±7.71 in Group D and 107.43±11.69 in Group S respectively. When compared between groups P value was statistically significant. (0.000001)

The mean arterial blood pressure 30 minutes, 45 minutes and 60 minutes after pneumoperitoneum was found to be statistically significant.

In the postoperative period the mean arterial blood pressure in Group D was 95.53±5.78 and 106.53±6.36 in Group S and was found to be statistically significant. (P value 0.00001).

The data are shown in the table 7 below;

MEAN ARTERIAL BLOOD PRESSURE	GROUP - D	GROUP - S	t value	P value
	Mean±SD	Mean±SD		
PREOPERATIVE	93.26±5.75	91.7±4.38	1.18597765	0.2404 NS
AFTERINFUSION	86.36±7.47	93.33±3.77	4.55667791	0.000001 Sig
1MIN AFTER INDUCTION	81.73±6.78	88.2±4.88	4.23690708	0.000001 Sig
1MIN AFTER INTUBATION	97.2±5.70	109.03±7.79	6.70998507	0.000001 Sig
AFTER PNEUMOPERITONEUM	95.96±7.35	102.66±8.24	3.32166087	0.0015 Sig
15 MIN	95.56±7.71	107.43±11.69	4.63740925	0.000001 Sig
30 MIN	93.26±8.13	102.83±8.22	4.53121323	0.000001 Sig
45MIN	95.51±6.94	103.96±8.94	3.96242004	0.0002 Sig
60 MIN	95.03±7.91	106.43±8.56	4.43085379	0.00001 Sig
END OF PNEUMOPERITONEUM	92.93±6.84	96.73±5.93	2.29762462	0.0252 Sig
POSTOPERATIVE PERIOD	95.53±5.78	106.53±6.36	7.00560122	0.00001 Sig

TABLE 7

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DISCUSSION: The present study was prospective randomized trial done to evaluate the effects of single premedication dose of Dexmedetomidine on Hemodynamic Response due to Anaesthesia and laparoscopic surgical procedures.

Laparoscopic procedures involve peritoneal insufflations with Carbondioxide and create pneumoperitoneum. This induces intraoperative ventilatory and hemodynamic changes that complicates anaesthetic management for laparoscopy.⁽¹⁾

Several studies have demonstrated that the cardiac index was markedly decreased after CO₂ peritoneal insufflations because of alterations in the ventricular loading conditions resulting from the increased intra-abdominal pressure.^(2,3,4,5)

The hemodynamic variability due to laparoscopy is due to release of humoral factors and potential mediators are catecholamines, prostaglandins and vasopressin.⁽⁶⁾

Surgical stimulation and postoperative stress evoke a general sympathetic stimulation by increasing blood pressure and heart rate, a state of hypercoagulopathy, and thermal instability. All these are associated with an increased myocardial oxygen demand and an increased incidence of postoperative complications. Perioperative ischemia is associated with a 9-fold increase in the risk of having postoperative cardiac death, nonfatal myocardial infarction (MI), or unstable angina while in the hospital⁽⁷⁾ The long-term risk for adverse cardiac events increases 2-fold in patients who have perioperative ischemia alone and 14-fold to 20-fold in patients who have perioperative MI or unstable angina⁽⁸⁾ α 2-Adrenoceptor agonists blunt hemodynamic variability during surgery and recovery, may exert anti-ischemic effects in the perioperative setting, and may also be effective in reducing these high rates of early postoperative ischemic events.

Dexmedetomidine offers a unique pharmacological profile with sedation, sympatholysis, analgesia, cardiovascular stability associated with the great advantage to avoid respiratory depression. In particular Dexmedetomidine can provide dose dependent "cooperative sedation" that allows ready interaction with the patient.

α 2 - Adrenoceptor agonists do not affect the synthesis, storage, or metabolism of neurotransmitters and do not block the receptors, thus providing the possibility of reversing the hemodynamic effects with vasoactive drugs or the α 2-agonist effects with a specific α 2-adrenoceptor antagonist. Alpha2-receptors are located on blood vessels, where they mediate vasoconstriction, and on sympathetic terminals, where they inhibit norepinephrine release.^(9,10)

Alpha 2-receptors also are located within the central nervous system, and their activation leads to sedation. In addition, alpha2-receptors within the spinal cord modulate pain pathways, thereby providing some degree of analgesia.^(11,12)

Dexmedetomidine has been demonstrated to have significant analgesic effects and consistently reduce opioid requirements⁽¹³⁾ It is believed that the spinal cord is probably the major site of analgesic action, where the activation of α 2c-adrenoreceptor agonist subtype seems to increase the analgesic action of opioids in lowering the transmission of nociceptive signals to braincenters⁽¹⁴⁾ Dexmedetomidine also inhibits the release of substance P from the dorsal horn of the spinal cord, leading to primary analgesic effects.

The concern with the use of high concentrations of Dexmedetomidine is the potential for both systemic and pulmonary hypertension and direct or reflex bradycardia.

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At higher plasma levels, peripheral alpha 2-receptor mediated vasoconstriction over-ride the sympatholytic effects, resulting in increased pulmonary artery and systemic blood pressure. Dexmedetomidine infusion in healthy volunteers in lower doses resulted in monophasic reduction in mean blood pressure whereas larger doses resulted in biphasic response.

In our present study Dexmedetomidine was infused at 1 microgram/kg over 20 to 30 min the biphasic blood pressure response was not seen. This effect was probably due to slow infusion rate which was given over 30minutes period which may be important in patient with Compromised cardiac function. In all patients the heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure were lower in patients who received Dexmedetomidine.

Tracheal Intubation is associated with increases in arterial pressures, heart rate and catecholamines concentrations.

In the present study pre-treatment with Dexmedetomidine 1 mcg/kg attenuated but not totally obtunded cardiovascular response due to laryngoscopy and intubation.

Aho et al⁽¹⁵⁾ has reported that intraoperative infusion of Dexmedetomidine reduced the anaesthetic requirement by over 90%. In our study only tramadol used as part of medication were set by protocol. We did not alter the dose of anaesthetic agents because we were to study the hemodynamic using premedication with 1 microgram/kg of Dexmedetomidine.

Even in spite of limitations from our study, use of Dexmedetomidine as a single premedication dose effectively control haemodynamic responses to laryngoscopy, intubation and stress response to laparoscopic surgery. No serious adverse events were noted in our study. The bradycardia was seen in small group of patients (10%) after administration of Dexmedetomidine. This may be due to the central sympatholytic action and partly by baroreceptor reflex and enhanced vagal activity. This effect is frequently observed in younger patients with high levels of vagal tone. All patients in our study were ASA grade I and II. Bradycardia seen in small group of patients was treated with atropine.

The data from our study is convincing that Dexmedetomidine used as premedicant prevents undesirable hemodynamic changes due to anaesthesia, surgical stress and laparoscopic procedures. This may be extrapolated to patients with hypertension and ischemic heart disease who may be at risk from undesirable hemodynamic responses.

LIMITATIONS OF THE STUDY: Dexmedetomidine attenuates hemodynamic response and it was very difficult to assess depth of anaesthesia. No volatile anaesthetic was used in our study. BIS monitoring and catecholamines estimation was not practical in cases we have studied. Postoperative analgesic requirement was not considered as this was not part of our study.

CONCLUSIONS:

1. Dexmedetomidine may provide an attractive alternative to anesthetic adjunctive agents now in use because of their anesthetic-sparing and hemodynamic-stabilizing effects.
2. Dexmedetomidine given at dose of 1microgram/kg as premedication is quite effective for laparoscopic sugery.

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3. It provides better perioperative hemodynamic stability than many agents now in use and may offer protection from ischemia due to the attenuated neuroendocrine response.
4. Drug is to be given in infusion rather bolus to avoid complications like bradycardia and hypotension.
5. Dexmedetomidine may have a role in anesthesia for patients who are at high risk of myocardial ischemia while undergoing laparoscopic surgery.
6. Dexmedetomidine a new, more selective α_2 -adrenoceptor agonists with improved side effect profiles may provide a new concept for the administration of perioperative anesthesia and analgesia.

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Date of Submission: 29/08/2015.
Date of Peer Review: 31/08/2015.
Date of Acceptance: 04/09/2015.
Date of Publishing: 07/09/2015.