Effects of Dexmedetomidine Infusion on Hemodynamic Stress Response, Sedation and Post-operative Analgesic Requirement in Patients Undergoing Laparoscopic Cholecystectomy

Sarada Roja Madhuri[1], Killu Bhagyalakshmi[2], Malapolu Neeraja[3]

[1]Senior Resident, [2,3]Assistant Professor, Siddhartha Medical College, Vijayawada, Andhra Pradesh 520008, India.

Abstract

Dexmedetomidine is a selective α2 agonist with sedative, analgesic and sympatholytic properties and hence, it can be used as an anesthetic adjuvant. *Aims:* We aimed primarily to evaluate the effects of low dose Dexmedetomidine infusion on hemodynamic response to critical incidences such as laryngoscopy, endotracheal intubation, creation of pneumoperitoneum and extubation in patients undergoing laparoscopic cholecystectomy. The secondary aims were to observe the effects on sedation levels, post-operative analgesia requirements and occurrence of adverse effects. *Methods:* Ninety patients of American Society of Anesthesiologists [ASA] physical grades I and II undergoing laparoscopic cholecystectomy were randomly allocated into three groups of 30 patients each as follows:

Group NS: [Saline group; n = 30] – Received 0.9% normal saline infusion;

Group DEX: 0.2-Patients received Dexmedetomidine infusion 0.2 mcg/kg/hr;

Group DEX: 0.4-Patients received Dexmedetomidine infusion 0.4 mcg/kg/hr.

Infusions were started 15 min before induction and continued till end of surgery. Parameters noted were pulse rate, mean arterial pressure, post-operative sedation and analgesia requirements. SPSS 15.0 version software was used for statistical analysis and Continuous data were analyzed by ANOVA test.

Results: In Group NS, significant hemodynamic stress response was seen following laryngoscopy, tracheal intubation, creation of pneumoperitoneum and extubation. In Dexmedetomidine groups, the hemodynamic response was significantly attenuated. The results, however, were statistically better in Dex 0.4 group compared with Dex 0.2 group. Post-operative 24 hour analgesic requirements were much less in Dexmedetomidine groups. No significant side effects were noted. *Conclusion:* Low dose Dexmedetomidine infusion in the dose of 0.4 mcg/kg/h effectively attenuates hemodynamic stress response during laparoscopic surgery with reduction in post-operative analgesic requirements.

Keywords: Dexmedetomidine; Hemodynamic stress response; Laparoscopic cholecystectomy.

Introduction

The development of minimally invasive surgery has revolutionized the field of surgery. Laparoscopic cholecystectomy is one of the most commonly practiced surgeries for gall bladder diseases in the present era.

The physiological response to surgical stress

and anesthesia is well documented. In the earlier review by Kehlet, the stress response to surgery is more than anesthesia drugs and technique. A wide number of anesthetic drugs have been used in clinical practice to modify the stress response to anesthesia and surgery. Laparoscopic surgery which involves insufflation with carbon dioxide produces undesirable responses like hypertension, tachycardia, and dysrhythmias.

Introduction of Dexmedetomidine which is highly specific and selective α2 adrenoceptor agonist has been tried in various studies to modify the stress response to surgery and to have a pleasant anesthetic outcome with minimal cardiovascular changes.

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

Materials and Methods

Type of study: Prospective randomized controlled double blind clinical study.

Duration of study: Jan 2017 to June 2018.

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

90 ASA Grade I and II of *18 to 65 years* of age of either sex posted for laparoscopic cholecystectomy were included in this study.

Exclusion

Elderly, Diabetic patients, Patients with chronic Hypertension, Severe CARDIAC disease, Pregnant or Lactating women, Patients with a history of allergy to egg proteins and α2 agonists were excluded from the study.

The patients were randomly allocated to three groups - 30 Patients each, by envelope method as follows:

Group NS: [Saline group; *n* = 30] – Received 0.9% normal saline infusion;

Group DEX: 0.2-Patients received dexmedetomidine infusion *0.2 mcg/kg/hr*.

Group DEX: 0.4-Patients received dexmedetomidine infusion *0.4 mcg/kg/hr*.

A thorough pre-anesthetic 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.

Infusion was prepared by taking dexmedetomidine *0.5 ml* containing *50 mcg* of the drug withdrawn in a *50 ml* syringe and was diluted up to *50 ml* with normal saline resulting in the final concentration of *1 mcg/ml*. Both normal saline and dexmedetomidine was given through schiller syringe infusion pump. According to the patient weight, the pump was set so as to deliver the targeted infusion rate.

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 guage* 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.

Fifteen minutes after starting the drug infusion, pre-oxygenation was performed for *3 minutes*.

Patients were pre-medicated with Inj. ondansetron *2 mg* I.V.

Inj. Glycopyyrolate *0.2 mg* I.V.

Inj. Ranitidine hydrochloride *50 mg* I.V.

Inj. Fentanyl *1 mcg/kg* I.V.

Patients were induced with Inj. Propofol *2 mg/kg*. Endotracheal intubation was facilitated by succinylcholine *1.5 mg/kg*. Anesthesia was maintained with O_2:N_2O, sevoflurane 0.6 vol% and vecuronium bromide *0.1 mg/kg*. Intermittent positive pressure ventilation was continued by the mechanical ventilator to maintain end-tidal carbon dioxide between *35–40 mm of Hg* Pneumoperitoneum was created by insufflation of carbon dioxide at the rate of *2 liters/min*. Intra abdominal pressure was maintained at 12–14 *mm Hg* 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, Saturation, End-tidal carbon dioxide and electrocardiography were recorded at the following points of time:

Effects of Dexmedetomidine Infusion on Hemodynamic Stress Response, Sedation and
Post-operative Analgesic Requirement in Patients Undergoing Laparoscopic Cholecystectomy

1561

1. Before starting of infusion *15 minutes* after infusion

2. *1 minute* after induction

3. *1 minute* after intubation

4. *1 minute* after Pneumoperitoneum

5. *5 minutes* after Pneumoperitoneum

6. *12 minutes* after Pneumoperitoneum

7. *30 minutes* after Pneumoperitoneum

8. *45 minutes* after Pneumoperitoneum

9. *60 minutes* after pneumoperitoneum

10. *1 min* after the release of Pneumoperitoneum

11. *1 minute* after extubation

After completion of surgery patients were reversed with Glycopyrrolate *0.01 mg/kg* and Neostigmine *0.05 mg/kg*. After thorough suction patients extubated and shifted to the recovery room. Patients were observed for post-operative sedation level, time for first rescue analgesic [inj. Paracetamol *1gr*/I.V.], adverse effects.

Statistical Analysis

The sample size was decided in consultation with the statistician and was based on initial pilot study observations, indicating that approximately 23 patients should be included in each group in order to ensure a power of 0.80 for detecting clinically meaningful difference by 15% in heart rate and mean arterial blood pressure. Assuming a 5% dropout rate, the final sample was set at 30 patients in each group, which would permit a type1 alpha (*a*) error = 0.05, with a type 2 error of beta (*β*) = 0.2 and power of 0.8. the results obtained in the study were presented in a tabulated manner and analysed using Microsoft excel and SPSS 20 Software. The results of the present study between the three groups was compared statistically using Analysis of Variance (ANOVA) and Student "*t*"test. A *p* - value < 0.05 was taken as statistically significant.

Fig. 1: Used materials

Fig. 2: Inducing the drug

Results

All the three groups under study were comparable to each other with respect to age, sex, weight, ASA grading, duration of surgery and anesthesia (shown in **Table 1** and **Graph 1**). There was no significant
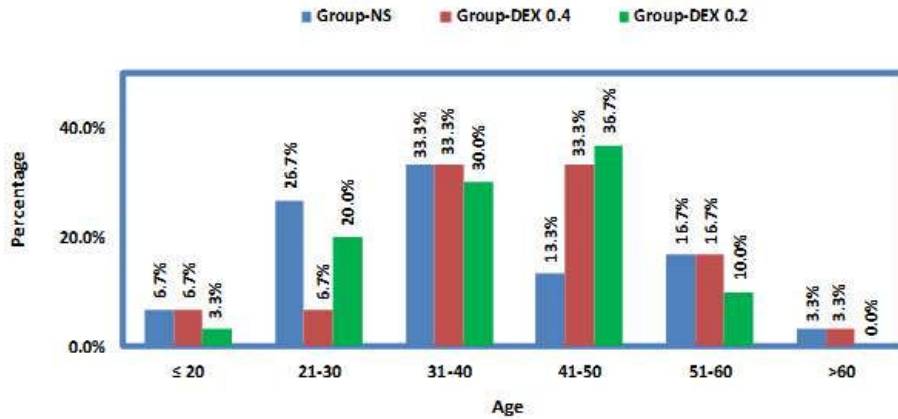
Table 1: Age distribution

Age	Group-NS		Group-DEX 0.4		Group-DEX 0.2	
	Count	%	Count	%	Count	%
≤ 20	2	6.7%	2	6.7%	1	3.3%
21–30	8	26.7%	2	6.7%	6	20.0%
31–40	10	33.3%	10	33.3%	9	30.0%
41–50	4	13.3%	10	33.3%	11	36.7%
51–60	5	16.7%	5	16.7%	3	10.0%
> 60	1	3.3%	1	3.3%	0	0.0%
Total	30	100.0%	30	100.0%	30	100.0%

p = 0.53

difference among the three groups in reference to the baseline PR and the MAP, shown as in **(Tables 2, 3)**.

In both the Dexmedetomidine groups, after starting the infusion, the PR decreased highly significantly below the pre-infusion level. The MAP decreased significantly in Dex 0.2 group and highly significantly in Dex 0.4 group. No further significant changes were observed immediately after induction. After intubation and extubation, the PR and MAP increased significantly above the

Graph 1: Age distribution

Table 2: Showing according to weight

Variable	Group-NS		Group-DEX 0.4		Group-DEX 0.2		p-value
	Mean	SD	Mean	SD	Mean	SD	
Weight	58.47	9.07	58.60	8.29	58.00	9.01	0.96
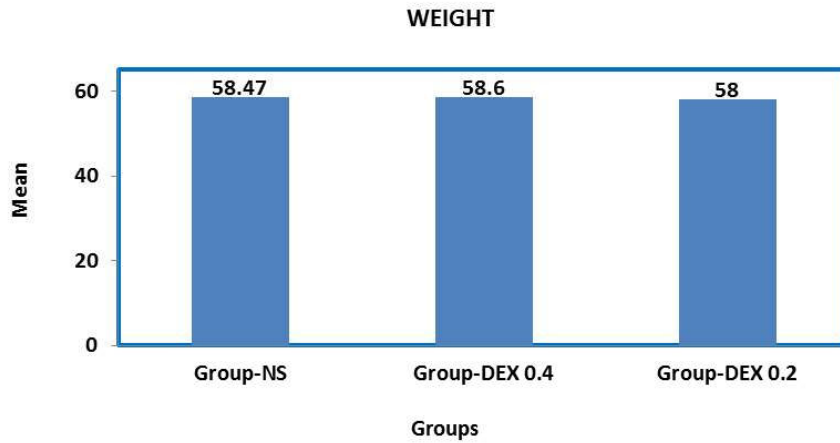
Graph 2: Showing according to weight

Table 3: Showing sex distribution

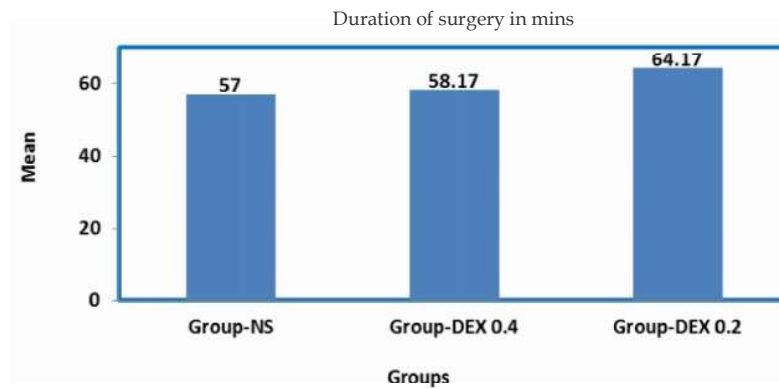| Sex	Group-NS		Group-DEX 0.4		Group-DEX 0.2	
	Count	%	Count	%	Count	%
Female	23	76.7%	20	66.7%	21	70.0%
Male	7	23.3%	10	33.3%	9	30.0%
Total	30	100.0%	30	100.0%	30	100.0%

$p = 0.69$
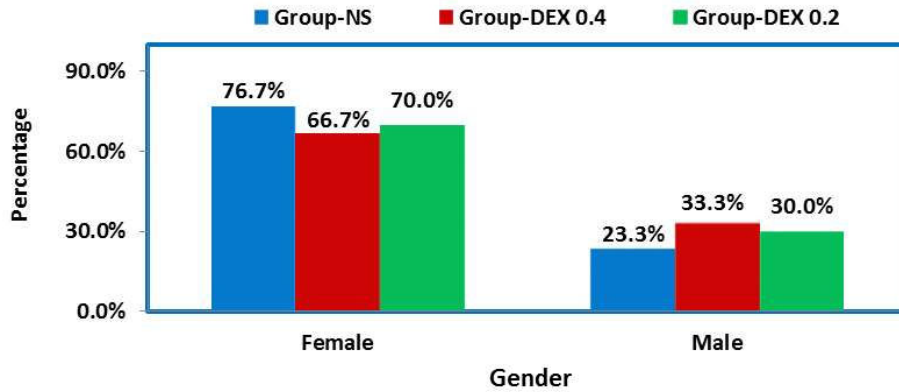
Graph 3: Showing sex distribution

Table 4: Showing duration of surgery in minutes

Variable	Group-NS		Group-DEX 0.4		Group-DEX 0.2		p - value
	Mean	SD	Mean	SD	Mean	SD	
Duration of surgery in mins.	57.00	13.56	58.17	11.48	64.17	13.90	.079

Duration of surgery in mins

Graph 4: Showing duration of surgery in minutes

Table 5: Showing duration of anesthesia in minutes

Variable	Group-NS		Group-DEX 0.4		Group-DEX 0.2		p - value
	Mean	SD	Mean	SD	Mean	SD	
Duration of anesthesia in mins.	78.00	16.06	80.33	9.55	82.37	12.97	.439

Duration of Anesthesia in Min
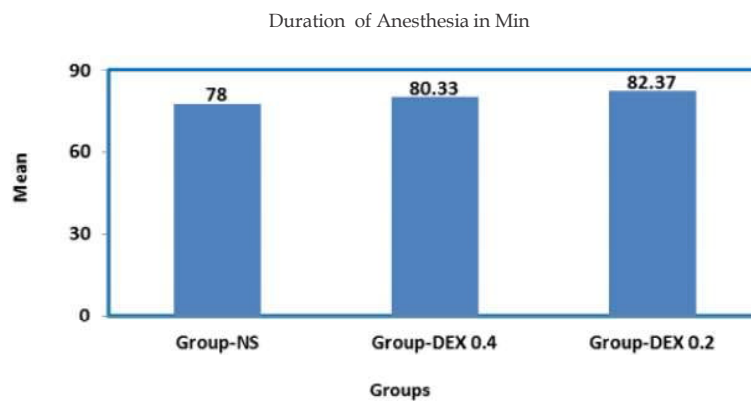
Graph 5: Showing duration of anesthesia in minutes

Table 6: Heart rate

HR	Group-NS		Group-DEX 0.4		Group-DEX 0.2		p - value
	Mean	SD	Mean	SD	Mean	SD	
Before infusion	89.70	12.54	94.00	18.50	84.27	11.37	.038
Infusion at 15 *min*	87.63	11.96	85.60	25.52	83.60	12.49	.681
Induction at 1 *min*	90.10	10.72	90.63	15.68	80.67	10.73	.004
Intubation at 1 *min*	95.73	10.95	90.13	20.68	97.37	11.42	.154
Pneumoperitoneum at 1 *min*	97.07	11.68	84.90	11.35	85.70	16.80	.001
Pneumoperitoneum at 5 *min*	96.97	12.70	85.33	11.66	84.50	18.70	.002
Pneumoperitoneum at 12 *min*	95.93	11.66	83.50	18.35	85.43	12.86	.003
Pneumoperitoneum at 30 *min*	93.63	13.22	78.11	11.72	81.96	14.25	< 0.001
Pneumoperitoneum at 45 *min*	89.38	11.75	80.21	12.55	77.80	17.54	.011
Pneumoperitoneum at 60 *min*	91.65	12.99	78.64	15.07	66.92	13.69	< 0.001
Pneumoperitoneum release at 1 *min*	84.47	8.62	74.73	11.24	76.28	13.68	.003
Extubation at 1 *min*	92.03	13.00	76.77	17.26	90.10	16.18	< 0.001
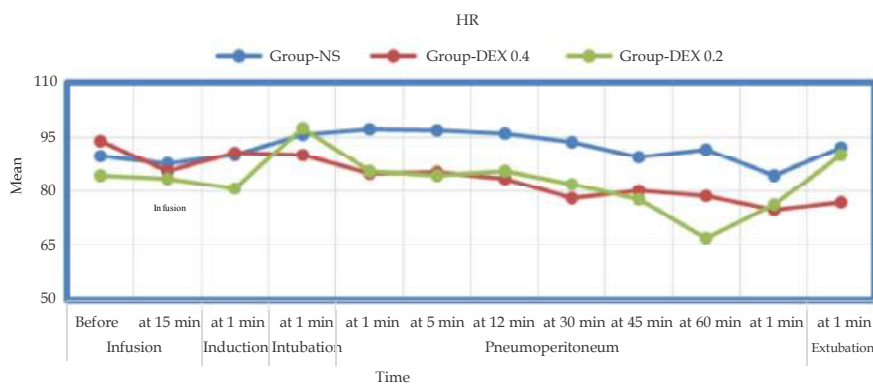
Graph 6: Heart rate

Table 7: Showing systolic blood pressure

SBP	Group-NS		Group-DEX 0.4		Group-DEX 0.2		p - value
	Mean	SD	Mean	SD	Mean	SD	
Before infusion	138.40	16.73	133.93	15.85	137.50	8.90	.443
Infusion at *15 min*	134.93	15.23	128.40	11.36	131.03	7.68	.105
Induction at *1 min*	129.87	17.83	119.60	25.32	129.27	10.71	.067
Intubation at *1 min*	148.57	14.42	138.60	12.68	156.03	18.72	< 0.001
Pneumoperitoneum at *1 min*	150.97	16.12	127.63	10.22	135.90	12.74	< 0.001
Pneumoperitoneum at *5 min*	155.93	13.68	135.27	14.42	140.40	11.28	< 0.001
Pneumoperitoneum at *12 min*	154.57	10.85	137.00	14.40	133.23	10.86	< 0.001
Pneumoperitoneum at *30 min*	142.47	14.70	131.00	14.04	131.43	13.92	.003
Pneumoperitoneum at *45 min*	143.46	7.41	129.42	7.68	130.56	9.53	< 0.001
Pneumoperitoneum at *60 min*	142.24	8.09	127.86	10.72	131.08	13.41	.001
Pneumoperitoneum release at *1 min*	138.77	8.24	122.30	10.65	124.90	9.31	< 0.001
Extubation at *1 min*	152.47	9.04	138.87	13.57	141.80	13.93	< 0.001

Graph 7: Showing systolic blood pressure

Effects of Dexmedetomidine Infusion on Hemodynamic Stress Response, Sedation and
Post-operative Analgesic Requirement in Patients Undergoing Laparoscopic Cholecystectomy

1565
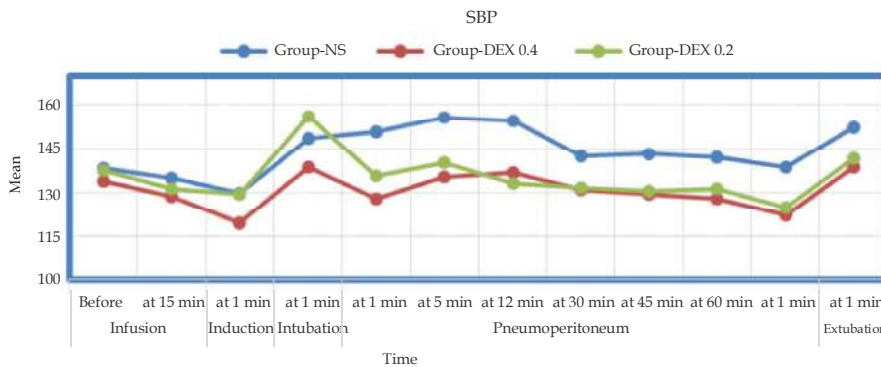
Table 8: Showing diastolic blood pressure

DBP	Group-NS		Group-DEX 0.4		Group-DEX 0.2		p - value
	Mean	SD	Mean	SD	Mean	SD	
Before Infusion	86.37	9.18	84.00	10.42	88.73	6.09	.118
Infusion at *15 min*	83.50	7.84	81.47	8.25	84.27	8.82	.407
Induction at *1 min*	83.60	7.93	79.03	8.10	81.63	10.18	.137
Intubation at *1 min*	92.70	6.50	85.90	11.62	100.67	20.22	< 0.001
Pneumoperitoneum at *1 min*	99.03	12.31	81.40	8.21	93.53	11.90	< 0.001
Pneumoperitoneum at *5 min*	102.23	9.83	89.67	12.64	95.60	8.29	< 0.001
Pneumoperitoneum at *12 min*	97.67	7.04	86.43	13.21	90.23	8.47	< 0.001
Pneumoperitoneum at *30 min*	90.30	8.23	83.89	9.26	84.86	11.02	.026
Pneumoperitoneum at *45 min*	90.23	6.69	84.17	6.03	85.56	7.73	.006
Pneumoperitoneum at *60 min*	90.47	5.30	84.21	7.15	89.00	5.95	.022
Pneumoperitoneum release at *1 min*	89.20	6.70	77.93	6.32	82.07	7.65	< 0.001
Extubation at *1 min*	97.67	8.16	90.07	12.50	98.30	13.52	.012
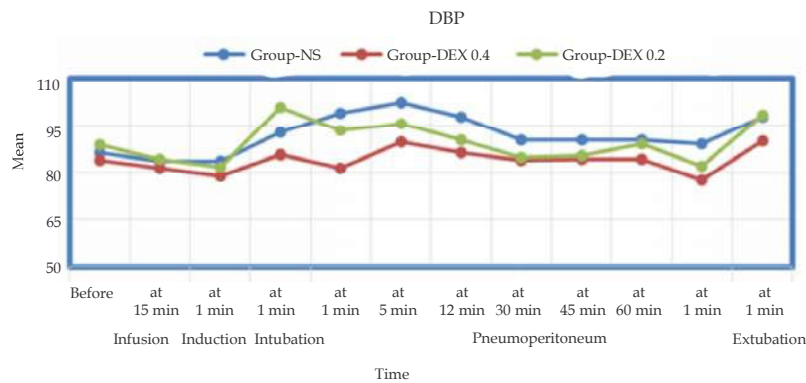
Graph 8: Showing diastolic blood pressure

Table 9: Map

Map	Group-NS		Group-DEX 0.4		Group-DEX 0.2		p- value
	Mean	SD	Mean	SD	Mean	SD	
Before infusion	101.00	12.51	102.57	14.08	104.17	9.49	.604
Infusion at *15 min*	98.37	10.08	98.47	9.98	100.03	7.85	.742
Induction at *1 min*	98.20	8.79	95.60	8.94	97.97	11.10	.517
Intubation at *1 min*	109.90	7.34	103.43	12.46	120.03	20.38	< 0.001
Pneumoperitoneum at *1 min*	117.33	10.93	98.30	10.23	106.37	11.50	< 0.001
Pneumoperitoneum at *5 min*	118.43	12.90	103.57	17.00	108.80	10.10	< 0.001
Pneumoperitoneum at *12 min*	115.90	8.96	99.13	15.99	104.00	10.61	< 0.001
Pneumoperitoneum at *30 min*	104.37	10.93	97.07	13.18	100.07	11.88	.072
Pneumoperitoneum at *45 min*	105.96	7.70	87.38	19.50	99.44	7.15	< 0.001
Pneumoperitoneum at *60 min*	108.18	7.12	97.71	9.10	102.08	9.44	.005
Pneumoperitoneum release at *1 min*	104.03	7.68	88.47	9.90	95.80	8.63	< 0.001
Extubation at *1 min*	114.67	9.48	106.00	13.22	112.40	13.49	.020
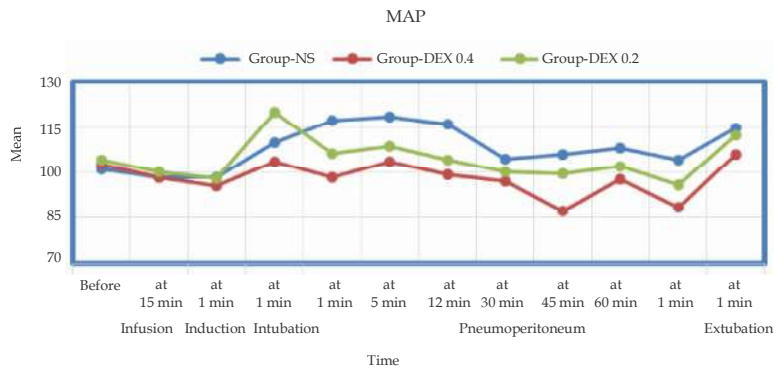
Graph 9: Map

Table 10: Post-operative sedation score

Post-operative sedatio score	Group-NS		Group-DEX 0.4		Group-DEX 0.2		p - value
	Mean	SD	Mean	SD	Mean	SD	
At 1 min	1.00	0.00	2.63	0.49	2.00	0.00	< 0.001
At 30 min	1.67	0.48	2.23	0.43	1.50	0.51	< 0.001
At 60 min	1.73	0.45	2.17	0.38	2.07	0.25	< 0.001
At 120 min	1.13	0.35	2.00	0.00	2.07	0.25	< 0.001
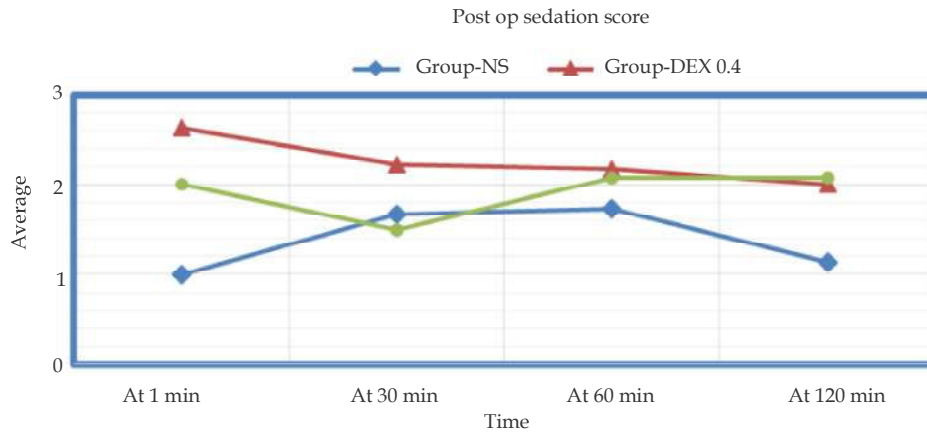
Graph 10: Post-operative sedation score

pre-infusion level in Dex 0.2 group, though, this increase was less compared to increase in group NS [$p < 0.05$]. Unlike these changes in Dex 0.2 group, PR and MAP in Dex 0.4 group remained below pre-infusion level after intubation and extubation [$p < 0.05$ when compared with Dex 0.02]. Pneumoperitoneum did not produce a significant effect in both the Dex groups.

The post-operative means sedation scores were observed using Ramsay Sedation score (RSS) at 1 min, 30 min, 60 min, 120 minutes. When compared to Group NS patients sedation scores are more in dexmedetomidine groups. Group DEX 0.4 patients had better sedation than Group DEX 0.2. The patients were co-operative, oriented and tranquil all the time. In Group NS, less sedation score was observed initially; the later score was improved due to the early requirement of analgesia in this group (**Table 4**).

The mean Rescue analgesia time in Group NS patients was 21.50 ± 10.76 minutes, in Group DEX 0.4 - 299.27 ± 86.64 minutes and in Group DEX 0.2 - 172.00 ± 75.13 minutes. When compared between three groups p - value was < 0.001 which was statistically significant (**Tables 5–10**).

Discussion

Laparoscopic procedures involve peritoneal insufflations with Carbon dioxide and create pneumoperitoneum. This induces intra-operative ventilatory and hemodynamic changes that complicate anesthetic management for laparoscopy.[1]

The hemodynamic variability due to laparoscopy is due to release of humoral factors, and potential mediators are catecholamines, prostaglandins, and vasopressin.[2] The reverse trendelenburg position required for surgery leads to diminished venous return and thereby further reduction in cardiac output.[3]

Dexmedetomidin offers a unique pharmacological profile with sedation, sympatholysis, analgesia, cardiovascular stability associated with the great advantage to avoid respiratory depression.[4,5] In particular, Dexmedetomidine can provide dose-dependent "co-operative sedation" that allows ready interaction with the patient.[6] Hence, we have decided to use Dexmedetomidine infusion for laparoscopic cholecystectomy 2 important issues that are noted in this study are Pharmacological actions of Dexmedetomidine and physiological

responses to surgery, anesthesia, and Laparoscopy. a2-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 a2-agonist effects with a specific a2-adrenoceptor antagonist. Therefore, they may have a role in anesthesia for patients who are at high risk of myocardial ischemia while undergoing major surgery.

The α2-receptors regulate the autonomic and cardiovascular systems. a2-receptors are located on blood vessels mediate vasoconstriction, and on sympathetic terminals, where they inhibit norepinephrine release.[7,8]

Manne *et al.* in a pilot study, they used low dose infusionsof dexmedetomidine without any bolus. Initially, they used dexmedetomidine *0.2 mcg/kg/h* infusion, it controlled the rise in PR and MAP after the creation of pneumoperitoneum, the control was not very effective at the time of endo tracheal intubation and extubation.

The Pulse Rate and Mean Arterial Pressure both increased above pre-infusion levels. Hence, they increased the dose to *0.4 mcg/kg/hr* infusion in our next two patients. The results were quite satisfactory with this dosing regime. PR and MAP were always below pre-infusion levels in Dex 0.4 group. We also studied few cases with Dex *0.6 mcg/kg/hr* dose but the hypotension was seen in a greater number of patients, and the sedation was more (RSS 4–5). Hence, they have taken three groups in their study, which were Group NS, Group Dex 0.2 and Group Dex 0.4. Their study confirmed the fact that critical incidences like laryngoscopy and intubation, pneumoperitoneum and extubation do significantly increase the Mean Arterial Pressure and Pulse Rate in patients undergoing laparoscopic cholecystectomyas seen in group NS. Dexmedetomidine attenuatesthis sympathoadrenal response and provides hemodynamic stability. The effective attenuation dose with minimum side effects noted in our study was *0.4 mcg/kg/hr* infusion.[9]

In present study, *0.2 & 0.4 mcg/kg/hr* were used as study dose and found to be effective which correlates with the above study.

The Pulse Rate and Mean Arterial Pressure both increased above pre-infusion levels *15 minutes* after infusion and after intubation in group DEX 0.2 group. But it controlled the rise in PR Bhattacharjee *et al.*[10] also observed no significant effect of Dexmedetomidine on response to verbal command and extubation time. Dexmedetomidine has been found to reduce the intra and post-operative requirement of opioids.[11–14] This effect is called as an Opioid-sparing effect. The time for first rescue analgesic is increased in dexmedetomidine groups. In our study, we observed two patients of DEX 0.2 group did not require any analgesia on the day of surgery.

Providing post-operative analgesia and comfort to the patient was also anesthetist concern only. With this consideration the drug which was used in present study helped with its analgesic property.

Group NS patients in present study, had pain post-operatively around 20–30 minutes after the surgery. In 2 patients of group NS were given injection Paracetamol *1 gr* intravenously immediately after surgery also.

Group DEX 0.2 patients have post-operatively analgesia siginifically when compared to group DEX 0.4. Surprisingly two patients who received DEX *0.2 mcg/kg/hr* had no pain for *24 hours* and did not require any rescue analgesic. Three pateints of DEX 0.2 had pain immediately after extubation, so we have given injection Paracetamol I.V. for them in the recovery room.

Group DEX 0.4 patients were pain-free and very comfortable in the post-operative period. They have received rescue analgesia around *300 minutes* [*5 hours*] after surgery.

Adverse effects

No serious adverse effects were observed in this study.

In one patient endobronchial intubation occurred. Saturations were reduced, immediately endotracheal tube position adjusted and saturations became normal.

Limitations of the study

The limitations of the present study are inability to assess the depth of Anesthesia. Dexmedetomidine attenuates hemodynamic response, and it was very difficult to assess the depth of anesthesia. BIS monitoring and catecholamines estimation were not practical in cases studied.

Conclusion

Dexmedetomidine may provide an attractive alternative to anesthetic adjunctive agents now in use because of their anesthetic-sparing and

hemodynamic-stabilizing effects. Low dose Dexmedetomidine infusion given at the rate of *0.4 µgram/kg/hr* is quite effective for laparoscopic surgery. It provides better peri-operative hemodynamic stability than many agents now in use and may offer protection from ischemia due to the attenuated neuroendocrine response. The drug is to be given in infusion rather bolus to avoid complications like bradycardia and hypotension. Dexmedetomidine may have a role in anesthesia for patients who are at high risk of myocardial ischemia while undergoing laparoscopic surgery. Dexmedetomidine a new, more selective *a*2-adrenoceptor agonist may provide a new concept for the administration of peri-operative anesthesia and analgesia.

Abbreviations

ASA - American Society of Anesthesiologists

BP - Blood Pressure

BPM - Beats per minute

DBP - Diastolic Blood Pressure

$EtCO_2$ - End-tidal carbon dioxide concentration

G - Gauge

MAP - Mean Arterial Pressure

HR - Heart Rate

SBP - Systolic Blood Pressure

References

1. Cunningham AJ. Anesthetic Implications of Laparoscopic Surgery. Yale J Biol Med. 1998 Nov-Dec;71(6):551-78.

2. Mc I_z.iughlin JG, Bonnell BW, Seheeres DE, *et al.* The adverse hemodynamic effects related to laparoscopic cholecystectomy. Anesthesiology. 1992;77:A70.

3. Wilcox S, Vandam LD. Alas, poor Trendelenburg and his position! A critique of its uses and effectiveness. Anesth Analg. 1988;67:574–78.

4. Khan ZP, Munday IT, Jones RM, *et al.* Effects of dexmedetomidine on isoflurane requirements in healthy volunteers 1: Pharmacodynamic and pharmacokinetic interactions. Br J Anesth. 1999;83:372–80.

5. Hall JE, Uhrich TD, Barney JA, *et al.* Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. Anesth Analg. 2000;90:699–705.

6. Haselman MA. Dexmedetomidine: A useful adjunct to consider in some high-risk situations. AANA J. 2008;76:335–39.

7. Langer SZ. Presynaptic regulation of the release of catecholamines. Pharmacol Rev. 1981;32:337–61.

8. Drew GM, Whiting SB. Evidence for two distinct types of postsynaptic alpha-adrenoceptor in vascular smooth muscle in *vivo*. Br J Pharmacol. 1979;67:207–15.

9. Manne GR, Upadhyay MR, Swadia VN. Effects of low dose dexmedetomidine infusion on hemodynamic stress response, sedation and post-operative analgesia requirement in patients undergoing laparoscopic cholecystectomy. Indian J Anesth. 2014;58:726–31.

10. Bhattacharjee DP, Nayek SK, Dawn S, *et al.* Effects of dexmedetomidine on hemodynamics in patients undergoing laparoscopic cholecystectomy: A comparative study. J Anesth Clin. Pharmacology. 2010;26(1):45-48.

11. Gurbet A, Basagan-Mogol E, Turker G, *et al.* Intra-operative infusion of dexmedetomidine reduces peri-operative analgesic requirements. Can J Anesth. 2006;53:646–52.

12. Tufanogullari B, White PF, Peixoto MP, *et al.* Dexmedetomidine infusion during laparoscopic bariatric surgery: The effect on recovery outcome variables. Anesth Analg. 2008;106:1741–748.

13. Abdelmageed WM, Elquesny KM, Shabana RI, *et al.* Analgesic properties of a dexmedetomidine infusion after uvulopalatopharyngoplasty in patients with obstructive sleep apnea. Saudi J Anesth. 2011;5:150–56.

14. Lin TF, Yeh YC, Lin FS, *et al.* Effect of combining dexmedetomidine and morphine for intravenous patient-controlled analgesia. Br J Anesth. 2009;102:117–22.