Journal of Cardiovascular Disease Research

ISSN:0975-3583, 0976-2833 VOL. 13, ISSUE 04, 2022

Effect Of Low Dose Infusion Of Dexmedetomidine On Intra-op Haemodynamic Response, Post-op Analgesia Requirement, And Sedation In Patients Undergoing Laparoscopic Cholecystectomy

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Abstract

BACKGROUND
Dexmedetomidine is α_2 agonist with sedative, sympatholytic, and analgesic properties and hence it can be a very useful adjuvant in anaesthesia as a stress response buster, sedative, and analgesic.

Aims and Objectives
We aimed primarily to evaluate the effect of Dexmedetomidine on hemodynamic parameters during laparoscopic cholecystectomy. The secondary aim was to observe the effect on extubation time, sedation level, post-operative analgesia requirement, and occurrence of adverse effects.

METHODS
62 patients of ASA Grade I and II undergoing laparoscopic cholecystectomy were randomly allocated into two groups, Thirty-one received NS and the rest received Dexmedetomidine infusion at 0.4mcg/kg/hr. Parameters noted were PR, MAP, Post-

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operative sedation level, and analgesic requirement. Student t-test was used to analyse the parametric data, discrete variables were analysed using the X^2 test. Using SPSS22.0 Statistical analysis was executed.

RESULTS
Compared to NS hemodynamic stress response during laparoscopic cholecystectomy due to laryngoscopy, tracheal intubation, creation of pneumoperitoneum was attenuated by infusion of Dexmedetomidine at 0.4 mcg/kg/hr. The postoperative analgesic requirement was much less in the dexmedetomidine group. No significant adverse effects were noted.

CONCLUSION
Dexmedetomidine infusion in the dose of 0.4mcg/kg/hr effectively attenuates hemodynamic stress response during laparoscopic cholecystectomy with a reduction in postoperative analgesic requirement

KEYWORDS
Dexmedetomidine, laparoscopic cholecystectomy, analgesia, sedation, the hemodynamic response

BACKGROUND
The various combinations of pharmacological agents used in the administration of anesthesia for laparoscopic cholecystectomy maintain hemodynamic stability. α_2 – adrenergic agonists provide sedation, anxiolysis, hypnosis, analgesia, and sympatholytic activity, hence serving the role of ideal pharmacological agent for the procedure.[1] Dexmedetomidine has highly selective adrenergic agonistic activity with selectivity $\alpha_2 > \alpha_1$(1600:1).[2] It attenuates a. hemodynamic responses to tracheal intubation and perioperative stress. b. decreases the concentration of plasma catecholamine during surgery. C. decreases the perioperative requirement of anesthetics and analgesia.[3,4]

The Dexmedetomidine administered as pre-medication in various bolus doses has been evaluated and published in different articles. Determining the ideal infusion rate of the drug for maximal anesthetic effect is very difficult due to its adverse effects like hypotension and/or bradycardia.[5,6,7] This study evaluates the efficacy of Dexmedetomidine in the administration of analgesia and anesthetic sparing effects and in maintaining hemodynamic stability during laparoscopic cholecystectomy.

METHODS
The study sample included 62 patients who met the inclusion criteria. It is a hospital-based prospective randomized controlled study conducted between October 2018 to October 2020 in the anesthesia department of MKCG Medical College and Hospital,

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Berhampur. The present study was approved by the Institutional Ethical Committee of MKCG Medical College and Hospital, Berhampur on human subject research. The IEC Number of my study is 745. The sample size was calculated to be 62 based on the pilot study and statistical reports from previous studies, with a power of 90% [assuming a variability(SD of ±10%)and a significant level of 0.05. They were randomly allocated into two groups of 31 each. Group A- normal saline, Group B- Dexmedetomidine infusion at 0.4mcg/kg/hr in patients undergoing laparoscopic cholecystectomy

Inclusion Criteria

1. Patients posted for laparoscopic cholecystectomy under General Anaesthesia.
2. Age group 18-65 years of either sex
3. ASA grade I/II

Exclusion Criteria

1. H/o allergy to Dexmedetomidine / any of the drugs that are planned to be administered.
2. Cardiac disorders
3. Patients taking CCBs/beta-blockers/digoxin
4. Hepatic, renal, hematologic, neuromuscular disorders
5. ASA grade ≥ III
6. Pregnant/lactating female
7. Patients with known h/o substance abuse
8. Patients with airway problems like anticipated or unanticipated difficult airway / obstructive sleep apnea.

Patient Data Collection and Evaluation

Those patients who are fit during PAC are to be taken up for surgery after receiving informed and written consent from the patient he/she may be shifted to the pre-operative room. Infusion is prepared according to the group allotted in separate OT.

To prepare the infusion dexmedetomidine 1ml containing 100mcg of the drug is withdrawn in a syringe and is diluted with normal saline of 49ml saline resulting in a final concentration of 2mcg/ml. Dexmedetomidine or normal saline infusion may be given through the INFUSA 101-P syringe infusion pump. Depending on the weight of the patient the pump may be adjusted to deliver the targeted infusion rate (0.4 mcg /kg/hr). The accessor and the patient are unaware of the group. Decoding of blinding to accessor is done only at the time of tabulation and results in analysis. After taking the patient to the OT a multipara monitor is attached and the baseline PR, MAP and are noted. A wide bore cannula is inserted for giving the intravenous fluids and another line is given for the infusion pump. An infusion pump containing either Normal Saline or Dexmedetomidine is started 10 minutes before giving premedication. Premedication

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is administered 05 mins before induction to all patients in form of Inj. Glycopyrrolate 0.005mg/Kg and inj. Midazolam 0.03mg/Kg, 4mg ondansetron, inj. tramadol 1mg/Kg I.V as per institutional protocol. Patients will be pre-oxygenated for 3 minutes. Patients will be induced with Propofol 2mg/kg iv followed by Inj. Succinylcholine 1.5mg/Kg I.V. Tracheal intubation will be done with an appropriate sized cuffed endotracheal tube. Anaesthesia will be maintained with N20:02 2:1, Isoflurane, and Vecuronium. Isoflurane is started with 0.5 MAC in both groups and titrated according to hemodynamic parameters (PR, MAP). MAP is maintained between 80-130mm Hg., BIS between 40-60 with isoflurane concentration up to 1.5%. Any further increase in MAP is maintained by inj. Nitro-glycerine i.v. Throughout the laparoscopic procedure, Intrabdominal pressure was maintained between 12 and 14 mmHg. The patient will be mechanically ventilated using a circle system to keep ETCO2 between 35 to 45mm Hg. Any increase in Blood Pressure over 130mmHg is treated with Inj Nitroglycerin I.V Drug infusion and an anesthetic agent will be stopped after removal of the laparoscopic port. The reversal will be carried out as also extubation by conventional methods with neostigmine and glycopyrrolate combination

Study Variable

1. The patient will be observed for isoflurane concentration in both groups to a maximum of 130 SBP and HR of a maximum of 110.
2. All patients will be observed for vital parameters like PR, and MAP at regular intervals in the pre-operative room, pre-induction, induction, after intubation, and after pneumoperitoneum at 5 minutes intervals during surgery.
3. Patients will also be observed at the time of extubation and after extubation.
4. Postoperative sedation level by RAMSAY SEDATION SCORE.
   Score 1 - Agitated and uncomfortable,
   Score 2 - Co-operative and oriented,
   Score 3 - Can follow simple directions
   Score 4 - Asleep but strong response to stimulations
   Score 5 - asleep and slow response to stimulation,
   Score 6 - Asleep and no response to stimulation.
5. Time to first rescue analgesia requirement. (pain reported by the patient when VAS≥4. (Visual analog scale)will be noted.
6. The total amount of analgesic drug required during the first 24 hours post-operatively will be observed. Injection of diclofenac sodium 1.5mg/kg/iv will be used a as rescue analgesic and thereafter when every VAS score ≥4 is observed.
7. Throughout the study, the patient was observed for any adverse event like bradycardia, Ramsay sedation score>4, and dryness of mouth, and will be managed conventionally.[8]

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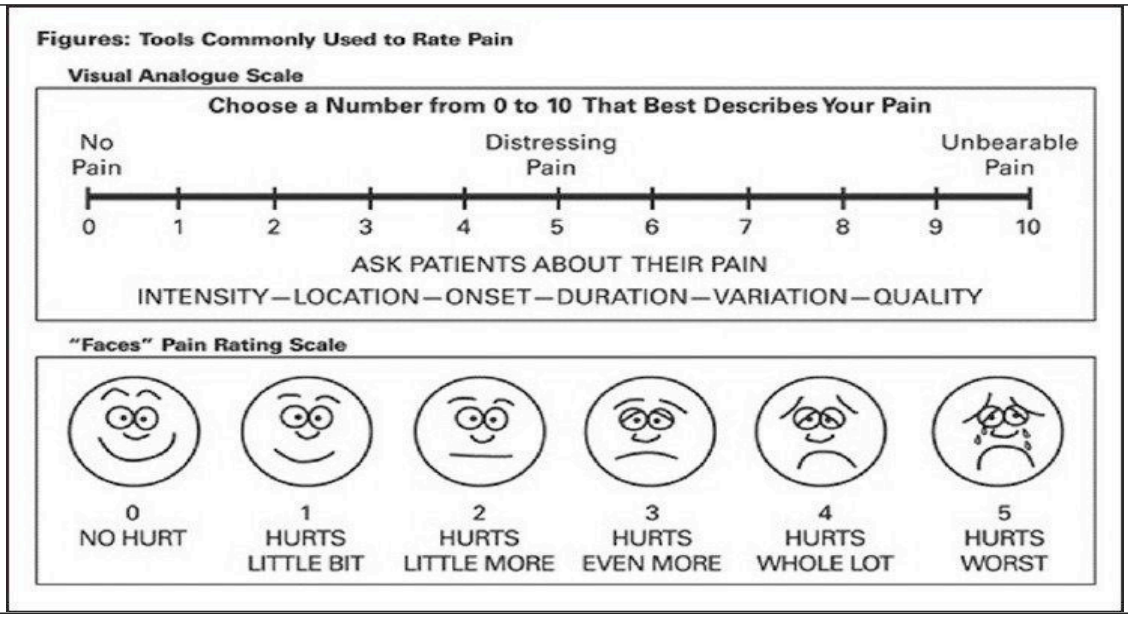

Visual Analog Scale

Statistical Analysis

Student t-test was used to analyse the parametric data and discrete (categorical) variables were analysed using the X^2 test, with a $P<0.05$ considered statistically significant. The statistical analysis was carried out using the statistical software package SPSS22.0.

OBSERVATION

At the end of the collection of the data, all the variables are examined for outliers and non-formal distributions. The categorical variables are expressed as frequency and percentage. The quantitative variables are expressed as mean and standard deviation. Descriptive statistics are used to evaluate baseline characteristics.

	Group A	Group B	P-Value
Age	34.06±10.80	33.51±10.86	0.836
Weight	58.75±6.02	59.21±5.995	0.537
Duration Of Surgery	96.54±22.07	100.01±14.13	0.135

Table-1. Comparison of Mean Age, Weight and Mean duration of Surgery between Group A And Group B

The mean age of patients in Group A and Group B was 34.06 years and 33.51 years respectively. The mean weight of patients in Group A and Group B was 58.75Kg and 59.21Kg respectively. The mean duration of surgery in Group A and Group B was 96.54 minutes and 100.01 minutes respectively.

On analyzing the data statistically, the p-value was calculated as p=0.836, p=0.537, and p=0.135 for age, weight, and duration of surgery respectively. All these values

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were>0.05, hence the difference was statistically insignificant between the two groups in terms of age, weight, and duration of surgery, and the two groups were therefore comparable.

Gender	Group A	Group B	P-value
Male	5	6	1.001
Female	26	25	1.001

Table 2. Comparison of Gender Distribution between Group A and Group B

The total number of males in Group A and Group B was 5 and 6 respectively. The total number of females in Group A and Group B was 26 and 25 respectively.

On analyzing the data statistically, the p-value was calculated as p=1.001 for both males and females between the two groups respectively. All these values were>0.05, hence the difference was statistically insignificant between the two groups in terms of gender distribution, and the two groups were therefore comparable.

Time Interval	GROUP A	GROUP B	P-Value
Baseline	85.71	92.84	0.072
Pre induction	84.86	91.03	0.076
Induction	85.41	92.90	0.058
Intubation	101.38	98.77	0.665
After 1 min	90.28	87.33	0.351
5 min	84.32	83.24	0.538
10 min	77.47	81.04	0.533
15 min	78.16	79.21	0.981
20 min	76.27	82.41	0.101
25 min	76.23	80.06	0.401
30 min	76.30	80.31	0.420
40 min	74.25	79.49	0.093
50 min	71.13	76.76	0.092
60 min	73.65	77.26	0.290
70 min	69.44	78.21	0.007
80 min	72.55	77.26	0.093
90 min	73.57	76.10	0.764
100 min	74.73	76.72	0.517
110 min	72.00	75.17	0.605
120 min	70.00	78.50	0.091
130 min	68.50	74.00	0.519

Table 3. Comparison of Heart Rates Group A and Group B

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Following laryngoscopy and endotracheal intubation, there is a maximum increase in heart rates in both groups. The increase in mean heart rate in Group A was 87 to 102 beats per minute while in Group B mean heart rate increased from 91 to 98 beats per minute during endotracheal intubation, but the increase is not statistically significant. None of the groups showed bradycardia during the intra-op and post-op period.

Time Interval	GROUP A	GROUP B	P-VALUE
Baseline	127	133	0.134
Pre induction	127	133	0.169
Induction	110	112	0.501
Intubation	134	137	0.438
After 1 min	111	121	0.291
5 min	106	106	0.772
10 min	112	102	0.003
15 min	114	108	0.261
20 min	116	125	0.120
25 min	124	122	0.623
30 min	127	126	0.516
40 min	126	128	0.728
50 min	124	126	0.574
60 min	118	124	0.378
70 min	118	117	0.980
80 min	120	118	0.357
90 min	123	114	0.074
100 min	120	121	0.902
110 min	126	117	0.245
120 min	118	124	0.647
130 min	115	120	1.001

Table 4. Comparison between Systolic Blood Pressure between Group A & Group B

Following endotracheal intubation, there is a maximum increase in SBP in both groups. The increase in values compared to baseline was found not to be statistically significant.

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Time Interval	GROUP A	GROUP B	P-Value
Baseline	83	84	0.568
Pre induction	82	83	0.193
Induction	72	74	0.687
Intubation	87	91	0.384
1 min	77	81	0.062
5 min	70	73	0.794
10 min	74	67	0.023
15 min	81	78	0.614
20 min	81	83	0.215
25 min	87	85	0.555
30 min	91	88	0.687
40 min	91	87	0.392
50 min	87	86	0.997
60 min	83	86	0.762
70 min	83	81	0.792
80 min	85	78	0.652
90 min	84	77	0.072
100 min	80	81	0.756
110 min	80	75	0.287
120 min	77	82	0.526
130 min	74	76	1.001

Table-5. Comparison between Diastolic Blood Pressure between Group A & Group B

Following endotracheal intubation maximal increase in DBP occurs in both the groups. The increase in value from baseline was found not to be statistically significant.

Time interval	Group A	Group B	P-value
Baseline	97.44	101.6	0.195
Pre induction	97.73	104.2	0.085
Induction	85.17	89.97	0.177
Intubation	106.82	107.23	0.802
After 1 min	91.23	95.75	0.048
5 min	82.73	82.86	0.830
10 min	88.37	79.36	0.006
15 min	90.56	90.12	0.686
20 min	93.27	97,65	0.117
25 min	101.26	99.43	0.933

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30 min	102.64	100.31	0.791
40 min	101.52	99.16	0.721
50 min	98.17	97.74	0.676
60 min	95.29	96.87	0.756
70 min	96.63	92.93	0.640
80 min	96.32	91.86	0.485
90 min	95.34	89.42	0.024
100 min	92.35	93.62	0.928
110 min	92.51	88.01	0.468
120 min	91.00	98.32	0.381
130 min	86.00	83.00	1.000

Table-6. Comparison of MAP (mm Hg) between Group A & Group B

Following endotracheal intubation, there is a maximum increase in MAP occurred. The mean rise in MAP was from 97mmHg to 108 mmHg in Group A while in Group B MAP value increased from 92mm Hg to 98 mmHg. But the values remained within 25% of baseline values and the increase was not statistically significant. 15 patients in Group A and 3 patients in Group B encountered episodes of hypertension (MAP>25% on two consecutive readings taken within 2-3 min) Majority of these episodes were encountered within the first 30 mins of peritoneal insufflation.

A maximal decrease in MAP was observed around 10 minutes following tracheal intubation. Episodes of hypotension (MAP<25% of baseline values for two consecutive readings within 2-3 minutes) occurred in 18 patients in Group B while in Group A only one patient had an episode of hypotension.

	Group A	**Group B**	**P-Value**
Duration to eye-opening	14.42 ±3.12	16.89 ± 1.19	0.001
Sedation score	2.01±0.01	2.18±0.37	0.024

Table-7. Comparison of the Mean Duration to Recovery (Eye-Opening Time) and Post-Operative Sedation Score between Group A and Group B

	GROUP A	**GROUP B**	**P-Value**
Average inspiratory Isoflurane concentration	1.25±0.09	1.02±0.12	0.002

Table-8. Comparison of Average Inspiratory Isofluorane Concentration

The mean average inspiratory isofluorane concentration in Group A and Group B was 1.26 and 1.01 respectively. P value=0.002 was **statistically significant.** Hence the total average inspiratory concentration was significantly **less** in Group B compared to Group A.[9,10]

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GROUP	Time for first rescue analgesic requirement in min	Cumulative analgesia required in 24hr mg
Group A(NS)	55.51	180.01
Group B(Dex 0.4)	248	97.6

Table 9. Postoperative Analgesia Requirements

The rescue analgesia was required early (55 min) in Group A(NS) compared to Group B(Dex 0.4%)(249 min). All the patients in the group in Group A and Group B require rescue analgesia.

DISCUSSION

Dexmedetomidine is a potent analgesic and it reduces the perioperative requirement of other analgesics in humans. The alpha-2 receptors located in the locus ceruleus and the dorsal horn of the spinal cord are implicated in the analgesic action of Dexmedetomidine.Alpha-2 agonists and opioids act by diverse mechanisms and their combination provides a synergistic analgesic effect without increasing the incidence of respiratory depression. In our study, the requirement for analgesics was reduced significantly upon the administration of Dexmedetomidine. Therefore we concluded that Dexmedetomidine at a dose of 0.4 microgram/kg/hr had significant analgesic sparing effects. **Ebert et al[5]** in the year 2000 had studied the hemodynamic responses to Dexmedetomidine and found the same analgesic sparing effects and increases in sedation. The results of this study are analogous to our study.

It was postulated that a central alpha-2 adrenergic C4 isoreceptor may be involved in the anaesthetic sparing effects of Dexmedetomidine. Also, It has a significant anaesthetic sparing effect. **Anta et al[9]** concluded the same with the reduction in the requirement of desflurane & isoflurane in their respective studies. Dexmedetomidine reduces the requirement for volatile anaesthetics.

Endotracheal intubation is associated with a significant increase in arterial pressure, heart rate, and plasma catecholamine concentrations. Dexmedetomidine attenuated the sympathoadrenal response during the tracheal intubation effectively but didn't completely abolish the cardiovascular response. There was an increase in both MAP and heart rate in both the groups after intubation, but the values remained within 25% of the baseline values and the increase found was not statistically significant. **Yildiz et al[11]** showed that a pre-induction intravenous dose of Dexmedetomidine at 1 microgram/kg/hr decreased the need for thiopental and sevoflurane by 39% & 92% respectively and thus effectively blunted the hemodynamic responses to laryngoscopy. Our study protocol does not include a preinduction bolus dose of Dexmedetomidine; however, the stress response was reduced upon the administration of the drug but not completely abolished.

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CONCLUSION

Low dose infusion of dexmedetomidine has analgesic and anaesthetic sparing properties & good sedation & hemodynamic stabilization property, with episodes of transient hypotension, no serious side effects, or adverse reactions.

Hence, it is conclude that Dexmedetomidine administered at an infusion rate of 0.4 microgram/kg/hr may serve as an ideal anaesthetic adjuvant in patients undergoing laparoscopic cholecystectomy.

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