



EFFECT OF DEXMEDETOMIDINE ON INFLAMMATORY CYTOKINES AND STRESS HORMONES IN ADULT PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY

Anaesthesiology

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ABSTRACT

Introduction: Dexmedetomidine may reduce the sympathetic overactivity caused by surgical and anaesthetic stress response in patients undergoing general anaesthesia. We planned a study with an aim to evaluate the effect of dexmedetomidine on the levels of inflammatory cytokines (IL-6, IL-10, TNF- α), C-reactive protein (CRP), stress hormones (Serum cortisol) and glucose in the adult patients undergoing laparoscopic cholecystectomy under general anaesthesia. **Methods:** This prospective, randomized control study included 60 patients fulfilling the criteria of American Society of Anesthesiologists (ASA) Grade 1 and 2, of either sex, aged between 18-65 years undergoing laparoscopic cholecystectomy under general anaesthesia. **GROUP A:** Fentanyl 2 mcg/kg + Dexmedetomidine infusion loading Dose 1.0 mcg/kg in 50 ml of normal saline over 10 minutes after induction of anaesthesia and maintenance dose of 0.5 mcg/kg/hr till the end of surgery. **GROUP B:** Fentanyl 2 mcg/kg + equal volume (50 ml) of normal saline. Haemodynamic parameters HR, SBP, DBP, MAP recorded and blood sample taken for IL-6, IL-10, TNF- α , CRP, serum cortisol and glucose levels at T1- baseline., T2- 4 hours after the surgery and T3- 24 hours after the surgery. **Results:** In our study we observed that IL-6, IL-10 and TNF- α were significantly reduced in the dexmedetomidine group both during 4 hr after surgery and 24 hour after surgery. Cortisol levels were significantly reduced only during 4 hour after surgery in dexmedetomidine group, however CRP glucose and haemodynamic parameters were found to be statistically non-significant among the two groups. **Conclusion:** Thus we conclude that dexmedetomidine leads to significant reduction in release of inflammatory markers-IL-6, IL-10, TNF- α levels, and stress hormones (cortisol) with no difference in CRP and glucose levels. There are no significant haemodynamic alterations and adverse effects associated with use of dexmedetomidine.

KEYWORDS

Dexmedetomidine, inflammatory markers, stress response

INTRODUCTION:

Patients undergoing laparoscopic surgery exhibit stress response due to underlying disease process, tracheal intubation, pneumoperitoneum and general anaesthesia leading to hemodynamic changes, raised cytokine and cortisol levels.^[1] Abnormal stress response can add to the morbidity and mortality of the patient in post-operative period.^[2]

Dexmedetomidine, an alpha-2 receptor agonist, exhibits sympatholytic and anti-inflammatory properties and has been shown to reduce severity of this surgical stress response.^[3] Kang et al conducted a study in 2013 over effect of dexmedetomidine on inflammatory responses in patients undergoing laparoscopic cholecystectomy. They observed effectiveness of dexmedetomidine in reducing release of cytokines intra-operatively and till six hours after surgery. C-reactive protein (CRP) and leucocyte count was found to be reduced at 24 hours of surgery.^[4] However, there is paucity of studies evaluating effect of dexmedetomidine on stress response.

We planned a study with an aim to evaluate the effect of dexmedetomidine on the levels of inflammatory cytokines (IL-6, IL-10, TNF- α), C-reactive protein (CRP), stress hormones (Serum cortisol) and glucose in the adult patients undergoing laparoscopic cholecystectomy under general anaesthesia.

MATERIALS AND METHODS

This prospective randomized study was conducted after obtaining clearance from the ethical committee and written informed consent from patients. Adult patients, 18-65 years of age and either sex belonging to American Society of Anesthesiologists (ASA) Grade 1 and 2, undergoing laparoscopic cholecystectomy under general anaesthesia were included.

A total of 60 patients were randomly allocated to two groups of 30 each by a computer generated table.

Group A (n=30): Patients received fentanyl 2mcg/kg + dexmedetomidine infusion loading dose 1.0 mcg/kg in 50 ml of normal saline over 10 minutes after induction of anaesthesia and maintenance dose of 0.5 mcg/kg/hr till the end of surgery.

Group B (n=30): Patients received fentanyl 2 mcg/kg + equal volume (50 ml) of normal saline.

Patients having known hypersensitivity to dexmedetomidine, BMI >35 kg/m², pregnant, nursing females and patients having systemic infections, cardiopulmonary, neurological, hepatic disease and positive viral markers were excluded.

After a detailed pre anaesthetic checkup, premedicated, adequately fasted patients were taken to the pre-operative room and baseline haemodynamic parameters and blood samples taken.

Patients pre oxygenated and induced with fentanyl citrate 2 mcg/kg and propofol 1% solution, 1.5-2 mg/kg body weight intravenously till loss of consciousness. Vecuronium bromide 0.1 mg/kg body weight administered intravenously after ensuring check ventilation. Patients ventilated with mixture of oxygen + N₂O 50:50 for 4 min and endotracheal intubation performed with cuffed endo-tracheal tube. After confirming for bilateral equal air entry, the endotracheal tube fixed and normocapnic ventilation established with monitoring of ECG, NIBP, EtCO₂ and SpO₂.

According to group allocation either dexmedetomidine infusion loading dose 1.0 mcg/kg in 50 ml of normal saline (group a) or 50 ml of normal saline (group b) was given over 10 minutes. the maintenance dose of dexmedetomidine 0.5 mcg/kg/hr in 50 ml of normal saline (group a) or equal amount of normal saline (group b) was given till the end of surgery.

Anaesthesia was maintained with O₂ + N₂O (50:50) and isoflurane (MAC-0.8).

Haemodynamic parameters - heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP) monitored continuously. Additional doses of muscle relaxant i.e. inj. vecuronium bromide and analgesic inj. fentanyl were given according to duration of surgery. Inj. Ondansetron was given before the end of surgery.

During the surgery any adverse event like bradycardia, tachycardia, or arrhythmia recorded and appropriate management was done. At the end of surgery, neuromuscular blockade reversed by inj. neostigmine 50 ug/kg and inj. glycopyrrolate 10 ug/kg. Extubation was performed after adequate recovery from neuromuscular blockade observed and patient was shifted to post anaesthetic recovery room.

Haemodynamic parameters HR, SBP, DBP, MAP recorded and blood samples taken for IL-6, IL-10, TNF- α , CRP, serum cortisol and glucose levels at the below mentioned timelines. All sample analysis done in the department of pathology except CRP levels, which was carried out in the department of microbiology.

T₁- baseline (before induction of anaesthesia) .T₂- 4 hours after the surgery.T₃-24 hours after the surgery.

Statistical Analysis

The study by Li B, et al observed that mean differences [95% CI] in the changes from baseline between dexmedetomidine treated and controls of -25.14 [-35.29, -15.00 (for IL-6), -20.30 [-30.93, -9.67]; (for TNF- α) immediately after surgery.^[5] Taking these values as reference, and assuming standard deviation of 25, the minimum required sample size with 80% power of study and 5% level of significance is 24 patients in each study group. Taking lost to follow up as 20%, total sample size taken was 60 (30 patients per group).

Categorical variables were presented in number and percentage (%) and continuous variables as mean \pm SD and median. Normality of data was tested by Kolmogorov-Smirnov test. Statistical tests was applied as follows-

1. Quantitative variables was compared using unpaired t-test/Mann-Whitney Test (when the data sets were not normally distributed) between the two groups.
2. Qualitative variables were compared using Chi-Square test /Fisher's exact test.

A p value of < 0.05 was considered statistically significant. The data was recorded and analysis done using appropriate Statistical Package for Social Sciences (SPSS) version.

RESULTS:

There was no statistical difference observed in the mean age, mean weight and ASA grade distribution and gender wise distribution of the patients in both the groups. It was observed that more number of female patients was enrolled in both the groups. (Table 1).

Table 1: Demographic Data

Parameter	Group A (n=30) Mean \pm SD [min-max]	Group B (n=30) Mean \pm SD [min-max]	p-value
Age in years	38.78 \pm 9.31 [18-47]	40.73 \pm 13.69 [18-65]	0.521
Weight in Kg	59.60 \pm 10.40 [40-79]	61.17 \pm 12.96 [40-95]	0.923
Gender distribution M:F	4:26 (6.67%:43.33%)	7:23 (11.67%:38.33%)	0.506
ASA distribution I II	24(40%) 6(10%)	21(35%) 9(15%)	0.317

Baseline values of IL-6, IL-10 and TNF- α levels were similar with no statistical difference among the two groups. The difference was statistically significant for cytokines (IL-6, IL-10 and TNF- α levels) both at T2 and T3 i.e. 4 and 24 hours after surgery. (Table 2)

Table 2: Comparison Of IL6, IL 10 and TNF-alpha Values Between Two Groups.

Time point	Test parameter (pg/ml)	Group A (n=30) [mean \pm SD]	Group B(n=30) [mean \pm SD]	p-value
T1 (baseline)	IL6	14.31 \pm 3.66	12.75 \pm 3.71	0.066
	IL10	18.82 \pm 4.89	17.26 \pm 4.74	0.357
	TNF- α	12.60 \pm 4.40	13.88 \pm 4.04	0.245
T2 (4 hours after surgery)	IL6	25.00 \pm 5.02	27.76 \pm 4.05	0.022
	IL10	27.38 \pm 4.57	32.46 \pm 5.73	<0.001
	TNF- α	20.83 \pm 6.55	26.17 \pm 4.81	<0.001
T3 (24 hours after surgery)	IL6	32.06 \pm 5.02	41.16 \pm 5.45	<0.001
	IL10	37.09 \pm 3.66	42.80 \pm 4.28	<0.001
	TNF- α	28.59 \pm 6.07	41.45 \pm 8.55	<0.001

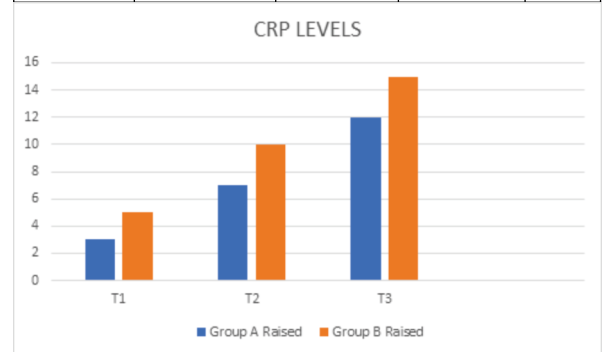
Cortisol levels were reduced in dexmedetomidine group (group A) at T2. CRP and Glucose levels were found to be statistically non significant among both the groups at all observed time periods (T1, T2 and T3) (Table 3) and Figure 1.

On comparison of hemodynamic parameters HR, SBP, DBP and MAP

in group A and B at time interval T1, T2 and T3, the values were found to be non-significant. (Table 4)

Table 3: Comparison Of Serum Cortisol And Plasma Glucose Values Between Two Groups.

Time point	Test parameter	Group A (n=30) [mean \pm SD]	Group B(n=30) [mean \pm SD]	p-value
T1 (baseline)	Serum cortisol (μ g/dl)	8.42 \pm 6.10	6.10 \pm 3.31	0.052
	Plasma glucose (mg/dl)	108.80 \pm 8.73	112.50 \pm 10.66	0.092
T2 (4 hours after surgery)	Serum cortisol (μ g/dl)	10.88 \pm 2.11	12.46 \pm 5.03	0.046
	Plasma glucose (mg/dl)	139.90 \pm 33.44	149.10 \pm 41.32	0.549
T3 (24 hours after surgery)	Serum cortisol (μ g/dl)	13.46 \pm 2.23	17.81 \pm 6.88	0.088
	Plasma glucose (mg/dl)	119.53 \pm 16.59	120.37 \pm 14.50	0.750



*p value non-significant at all time points

Figure 1: CRP levels

Table 4: Comparison Of Hemodynamic Parameters Of Patients Between Two Groups

Time point	Hemodynamic parameter	Group A (n=30) [mean \pm SD]	Group B (n=30) [mean \pm SD]	p-value
T1 (baseline)	HR	76.27 \pm 13.21	78.10 \pm 13.26	0.594
	SBP	121.10 \pm 11.48	122.23 \pm 18.33	0.775
	DBP	69.83 \pm 8.87	69.00 \pm 10.12	0.736
	MAP	88.96 \pm 9.95	89.71 \pm 12.92	0.804
T2 (4 hours after surgery)	HR	79.20 \pm 16.63	75.20 \pm 12.86	0.302
	SBP	115.27 \pm 11.84	119.70 \pm 16.85	0.243
	DBP	93.50 \pm 12.12	71.53 \pm 9.39	0.353
	MAP	85.67 \pm 8.88	87.21 \pm 11.12	0.353
T3 (24 hours after surgery)	HR	79.00 \pm 13.94	76.43 \pm 10.87	0.430
	SBP	117.73 \pm 12.79	118.73 \pm 10.51	0.742
	DBP	72.57 \pm 6.93	72.87 \pm 5.19	0.850
	MAP	87.37 \pm 7.55	87.63 \pm 5.91	0.884

Incidence of bradycardia was observed to be 23.3% and 20% in group A and B. The difference was statistically non-significant . Also, incidence of episodes of hypotension (20% versus 16.7%) was statistically non-significant. (Table 5)

Table 5: Adverse Effects

Parameter	Group A (n=30)	Group B (n=30)	p-value
HYPOTENSION (YES/NO)	6/24 (20%/80%)	5/25 (16.7%/83.3%)	0.758
BRADYCARDIA (YES/NO)	7/23 (23.3%/76.7%)	6/24 (20%/80%)	0.758

DISCUSSION

Laparoscopic cholecystectomy, a routine day care procedure induces neuro endocrine and inflammatory stress response due to pneumoperitoneum and physiological alterations. This stress response is body's mechanism to counteract tissue injury and promote wound healing and recovery. Stress response involves activation of sympathetic system, hypothalamic-pituitary-adrenal axis. There is release of cytokines (IL-6, IL-10, TNF-alpha) which further direct

formation of acute phase reactants like CRP.

All these mediators are beneficial, however when in excess can lead to cellular injury and organ damage. That is why it is imperative to tailor our management so as to minimize their adverse impact on patient outcome.

Dexmedetomidine is an alpha-2 receptor agonist, which acts on locus ceruleus to produce sympatholytic effect and causes decrease of epinephrine and nor-epinephrine and has been found to reduce this stress and inflammatory response in various studies.^[3,4]

In our study, we observed beneficial effect of dexmedetomidine in reducing inflammatory markers and cortisol level with no effect on CRP and glucose levels.

Proposed mechanisms of dexmedetomidine are its sympatholytic properties and stimulation of cholinergic anti-inflammatory pathways. In addition to being anxiolytic, sedative and hypnotic, it has analgesic properties that are particularly helpful in reducing stress response as pain per se leads to initiation of inflammatory response.^[5,6,7,8]

Effect on inflammatory cytokines

We observed significant reduction in IL-6, IL-10, TNF-alpha level in patients receiving dexmedetomidine (group A) versus control group (group B) at 4 and 24 hours after surgery.

Our results are consistent with Yacout et al, who studied effects of intravenous dexmedetomidine infusion on pro inflammatory cytokines, stress hormones and recovery profile in major abdominal surgery. They observed levels of glucose, IL-6 and cortisol at first day postoperatively and found an increase in both groups but the increase was significantly lower value in group D relative to group P.^[9]

Our study results are consistent with meta analysis by Li et al on anti-inflammatory effects of perioperative dexmedetomidine use with general anesthesia. Dexmedetomidine administration significantly decreased IL-6 levels on first postoperative day after surgery and TNF- α immediately after surgery and one day after surgery.^[3]

No significant differences were noted with regards to CRP levels in this meta-analysis, as observed in our study.

However, Kang et al on the effects of dexmedetomidine on inflammatory responses in patients undergoing laparoscopic cholecystectomy, found that the CRP level on post operative day 1 was significantly lower in group D than in group S.^[4]

The participants of our study were patients undergoing laparoscopic cholecystectomy which is a minimal incision surgery resulting less chance of inflammation and post-operative pain. Ramanathan et al found lower values of CRP in laparoscopic surgery compared to open surgery in the postoperative days which support our study.^[10]

Pepys et al found circulating concentration of CRP is determined by its rate of synthesis reflecting the intensity of the pathological process, and hence it is a good indicator of severity of inflammation.^[11]

In both the groups we are using fentanyl as pre-medication agent before induction of anaesthesia. As opioid it also attenuates the stress response in the patients undergoing laparoscopic cholecystectomy surgery. This could be possible explanation for the difference in results of our study with regard to CRP as compared to study by Kang et al.^[4]

Xiao et al found the administration of midazolam alone or in combination with fentanyl markedly down regulated the expression of CRP, indicating inhibition of the inflammatory response in sepsis.^[12]

Effect On Stress Hormones And Glucose Levels

In our study, we observed no difference between the groups with regard to plasma glucose levels at different time points. On comparison of cortisol levels in group A and B at T1 T2 and T3, there was significant difference observed in two groups at T2 (4 hrs after surgery), with decreased level of cortisol in group A.

Yacout et al found no statistically significant difference between the two groups as regards the basal level of blood level of cortisol and

glucose. After complete recovery and at first day postoperatively, they increased in both groups but with significantly lower value in group D relative to group P.^[9]

On the contrary, Aantaa et al. measured cortisol level in patients undergoing minor gynecological surgery and found that it was equally increased in saline and dexmedetomidine group.^[13]

Haemodynamic Parameters

We observed no statistical difference on comparison of haemodynamic parameters (HR SBP DBP and MAP) in group A and B at time interval T1, T2 and T3.

Kang et al conducted to study the effects of dexmedetomidine on inflammatory responses in patients undergoing laparoscopic cholecystectomy. They found both HR and MAP at the end of surgery were lower in group D than in group S.^[4]

Yacout et al found that intra operatively; the HR and MAP were significantly lower in group D relative to group P after intubation and during most of the intra and post operative periods in patients undergoing abdominal hysterectomy.^[9]

The reasons for difference in the observations may be due to the fact that we did not compare hemodynamic parameters at frequent intervals during the surgery and we used balanced anesthesia technique in both the study groups.

Adverse effects

One patient in group B had an arrhythmia (supra ventricular tachycardia-spontaneous remission). No such event happened in dexmedetomidine group. Aho et al studied the adverse effects of dexmedetomidine include hypotension, hypertension, nausea, bradycardia, aerial fibrillation, and hypoxia.^[14] Overdose may cause first-degree or second-degree atrioventricular block. Most of the adverse events associated with dexmedetomidine use occur during or briefly after loading of the drug and can be reduced by omitting or reducing the loading dose.^[15]

Bradycardia and hypotension was observed in few patients in both the groups at the time of insufflation of carbon dioxide (statistically non-significant).

Findings of our studies match the observations of Dabush-Elisha et al, who conducted a retrospective cohort study in 9915 patients undergoing laparoscopic surgery. They observed Intraoperative bradycardia occurred in 1540 (15.5%) patients, in the majority (945, 61.3%) heart rate decreased to <45 beats/min. The majority of events were related to CO₂ insufflation and bolus opioid administration.^[16]

Limitations of our study include not including the post-operative recovery time and infection rate of the patients. Study was done in ASA 1 and 2 patients, high risk patients may exhibit different stress response and adverse effects due to dexmedetomidine. So the results can not be generalized to all types of patients undergoing all kinds of surgery. However, our study does show promising effects of dexmedetomidine and further studies can be planned to evaluate its effects in different patient groups and variety of surgeries.

CONCLUSION:

Thus, we conclude that dexmedetomidine leads to significant reduction in release of inflammatory markers-IL-6, IL-10, TNF- α levels, and stress hormones (cortisol) with no difference in CRP and glucose levels. There are no significant haemodynamic alterations and adverse effects associated with use of dexmedetomidine.

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