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A Comparative Evaluation of the Efficacy of Dexmedetomidine versus Fentanyl as Anesthetic Adjuvant in Attenuating the Neuroendocrine Stress Response, as Assessed Indirectly, during Laparoscopic Cholecystectomy

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Abstract

Background and Aims: Hyperglycemia and hemodynamic perturbations are the main features of neuroendocrine stress response to surgical trauma and anesthesia. We conducted a study to evaluate and compare dexmedetomidine and fentanyl as anesthetic adjuvants in attenuating neuroendocrine stress response by measuring the changes in the perioperative serial blood glucose levels and monitoring hemodynamic variations during laparoscopic cholecystectomy.

Methodology: Sixty healthy adult patients scheduled for elective laparoscopic cholecystectomy were randomly assigned into two groups (Group D and Group F) of 30 each. Group D patients received dexmedetomidine 1µg/kg/15min whereas group F patients received fentanyl 2µg/kg/15min as loading dose and then the patients were infused with 0.2-0.7µg/kg/h of the respective drug till the end of surgery. Blood glucose levels were measured preoperatively before administration of premedication (baseline) (T_0), at 30 minutes after beginning of surgery (T_1) and 5 minutes postextubation (T_2). Heart rate (HR), oxygen saturation (SpO_2), systolic (SBP), diastolic (DBP) and mean arterial pressures (MAP) were assessed at specific time intervals.

Result: Blood glucose concentration increased in both groups, though group F showed a more obvious increment than group D. T_1 and T_2 mean values in group D (115.57 and 118.80mg/dl respectively) were significantly (p=0.020 and p< 0.001 respectively) lower than that in group F (122.37 and 128.90mg/dl respectively). HR, SBP, DBP and MAP were also significantly lower in group D than group F at various time points.

Conclusion: Dexmedetomidine is a better anesthetic adjuvant than fentanyl in attenuating the neuroendocrine stress response during laparoscopic cholecystectomy.

Keywords: Anesthetic Adjuvant; Dexmedetomidine; Fentanyl; Laparoscopic Cholecystectomy; Neuroendocrine Stress Response.

Introduction

The stress response to surgery and anesthesia is mediated by complex interactions between the neuroendocrine, immunological and hematopoietic systems [1]. Hyperglycemia and hemodynamic variations (hypertension, tachycardia) are the predominant aspects of this neuroendocrine stress response and correlate well with the increased plasma concentrations of cortisol, glucagon and catecholamines. They vary with the extent of surgical trauma and are associated with adverse clinical outcomes especially in patients with compromised organ function; and can be remarkably modulated by appropriate anesthetic technique [2].

Laparoscopic cholecystectomy is associated with multiple postoperative advantages such as minimal degrees of surgical trauma, pain and pulmonary dysfunction, thus permitting faster recovery, early ambulation and shorter hospital stay [3]. Inspite of these benefits, the peritoneal carbondioxide (CO_2) insufflation resulting in increased intraabdominal

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pressure and increased CO_2 absorption; along with reverse Trendelenberg position required in laparoscopic cholecystectomy, induce pathophysiological changes characterized by decrease in cardiac output, increased arterial pressures and increased systemic and pulmonary vascular resistances [4].These hemodynamic changes are mediated by mechanical and neurohumoral factors like increased plasma concentrations of cortisol, adrenaline , noradrenaline and vasopressin; and can be profoundly influenced by various agents like opiods, β-blockers, α_2-agonists, propofol and vasodilators like nitroglycerine, thereby diminishing negative consequences and improving the clinical outcome of laparoscopic cholecystectomy, particularly in patients with diabetes mellitus and cardiovascular compromise [5].

Dexmedetomidine is a highly selective α_2-agonist (α_2:α_1 activity=1620:1). By its action on locus coeruleus in brainstem, it exhibits sedative, anxiolytic, analgesic and thus anesthetic sparing properties without causing respiratory depression. It also produces sympatholysis by diminishing the central sympathetic outflow and the plasma concentrations of noradrenaline and adrenaline [6]. Thus, when used as an anesthetic adjuvant, it provides hemodynamic stability during laryngoscopy, tracheal intubation, pneumoperi-toneum and emergence from anesthesia by obtunding the neuroendocrine stress response [7,8].

Thus, we designed a study to compare the efficacy of dexmedetomidine (drug with multidimentional properties) and fentanyl (commonly used opioid) as anesthetic adjuvants in attenuating the neuroendocrine stress response during laparoscopic cholecystectomy by measuring the changes in perioperative serial blood glucose levels and hemodynamic variables. A similar study has been done by Gupta et. al. [9] in which dexmedetomidine and fentanyl are used as premedicants only.

Materials and Methods

Patient Selection

A prospective randomized double blind study was conducted after obtaining approval from the Institutional Ethical Committee and written informed consent was taken from all the patients. Sixty adult nonobese (body mass index <30) patients aged 20-65 years, with physical status of ASA I or II of either sex, posted for elective laparoscopic cholecystectomy under general anesthesia were selected for the study. Patients not willing to give consent, with known allergic reaction especially to the study drugs, with anticipated difficult airways, on chronic medications like opioids, β-blockers, methyl-dopa, steroids, etc. i.e the drugs which affect sympathetic activity or hormonal secretions, with history of cardiorespiratory, hepatic, renal, metabolic or any significant psychiatric or neurological disorders were excluded from the study.

Study Design and Randomization

Thorough preanesthetic evaluation and routine investigations were carried out in all patients on the previous day of surgery. On the day of surgery, after confirming the preanesthetic check-up and fasting status, a multipara monitor was attached to each patient in operation theatre and baseline value of heart rate (HR), oxygen saturation (SpO_2), systolic (SBP), diastolic (DBP) and mean arterial pressures (MAP) was recorded. Baseline blood glucose value was estimated using glucometer before the administration of premedication. Premedications given were tablet alprazolam 0.25 mg and tablet ranitidine 150 mg on the night before surgery, and injection glycopyrrolate 0.2 mg intramuscularly 1h before surgery. An intravenous infusion of ringer lactate was started and then intravenous injections of ondensetron 4mg, metoclopramide 10 mg and midazolam 1 mg were given.

The patients were randomly allocated by envelope method into one of the two groups (group D and group F) of 30 patients each. Group D patients received intravenous dexmedetomidine 1μg/kg over 15 minutes and group F patients received intravenous fentanyl 2μg/kg over 15 minutes before induction of anesthesia and then the patients received continuous infusions of the respective drug @ 0.2-0.7 μg/kg/h till the end of surgery.

The study drug was prepared and the loading dose administered by the resident anesthesiologist who was not a part of data collection and patient management, in a 50 ml syringe with normal saline as a diluent, such that the concentration of dexmedetomidine and fentanyl was 8μg/ml. The patients, attending anesthesiologist and the primary investigators were all blinded to group allocation and the study drug being given to the patient.

Anesthetic Management

Patients were preoxygenated for 3 minutes and then induced with injection propofol 2mg/kg till the loss of response to verbal commands and then tracheal intubation was facilitated by injection vecuronium 0.1mg/kg. Anesthesia was maintained with isoflurane 1-1.5%, 60% nitrous oxide in oxygen and injection vecuronium bromide as a muscle relaxant. The lung mechanics was adjusted to maintain an $ETCO_2$ value of 35-45 mm of Hg and intraabdominal pressure was maintained between 12 and 15 mm of Hg throughout the laparoscopic procedure.

Blood glucose level was estimated using glucometer preoperatively (T_0) before the administration of premedication (baseline), 30 minutes after beginning of surgery (T_1) and 5 minutes post-extubation (T_2).

All the patients were monitored and the changes in hemodynamic parameters of HR, SPO_2, SBP, DBP and MAP were recorded at various time points of baseline/prior to premedication, after loading dose administration, after induction, after intubation, soon after pneumoperitoneum creation, 5, 10, 20, 40, 60, 80, 100 and 120 minutes after pneumoperitoneum and after extubation. Intraoperatively, patients were monitored for any bradycardia or tachycardia, hypotension or hypertension and managed accordingly.

All the patients received intravenous infusion of diclofenac sodium 75mg; and then the study drug infusion and isoflurane were stopped at the end of procedure. The residual neuromuscular blockade was antagonized with injection neostigmine 0.05 mg/kg and injection glycopyrrolate 0.01mg/kg and the endotracheal tube was removed when spontaneous respiration was adequate and regular and the patients obeyed simple verbal commands. The patients were then shifted to postanesthesia care unit for observation and managed accordingly.

Statistical Analysis

Sample size was calculated to detect the difference of atleast 20% in HR and MAP with a power of 0.80 and α error of 0.05. The Statistical Software namely SPSS 18.0, and R environment ver 3.2.2 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables, etc.

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented as mean ± standard deviation and results on categorical measurements are presented in number (%). Significance is assessed at 5% level of significance.

To find the significance of study parameters on continuous scale between two groups (intergroup analysis) student unpaired t test has been used, for those within each group (intragroup analysis) student paired t test and for those on categorical scale between the two groups, Chi Square/Fisher Exact test has been used.

Results

Demographic profile such as age, sex and weight of the patients in both groups (D and F) was comparable. The duration of surgery was also comparable in the two groups (Table 1).

Serial Blood Glucose Level

Baseline (T_0) mean blood glucose value in group D (90.93±6.58) was comparable (p=0.276) to that in group F (92.87±7.04).We observed that, T_1 and T_2 mean values in both groups showed statistically significant ($p< 0.001$) increase from the basal value. However, this increase was more striking in group F than group D. This observation is in accordance with that of Gupta et. al. [9]. The increment of T_1 value from the basal value was 27% (group D) and 32% (group F) and that of T_2 was 31% and 39% in group D and group F respectively, and all of them were statistically significant ($p< 0.001$).

In our study, both T_1 and T_2 mean values in group D (115.57 and 118.80 mg/dl respectively) were statistically and significantly (p=0.020 for T_1 and $p < 0.001$ for T_2) lower than that in group F (122.37 and 128.90 mg/dl respectively) (Table II). In comparison, Gupta et. al. [9] found that the mean blood glucose value at 2.5 hours after surgery in dexmedetomidine group was significantly (p=0.043) lower than that of fentanyl group and that at 30 minutes after beginning of surgery did not show significant difference (p=0.53).This difference may be due to the fact that they have used dexmedetomidine and fentanyl as premedicants, whereas we have given the drugs to our patients in the form of loading dose as well as continuous infusions.

Hemodynamic Parameters

The mean basal values of HR, SpO_2, SBP, DBP and MAP were comparable in both groups. In our study, HR, SBP, DBP and MAP in group D were significantly lower than that in group F, but within hemodynamically stable limits.

In group D, the decrease in HR values from baseline was clinically and statistically significant ($p<0.001$) from the time of loading dose administration till 120 minutes after pneumoperitoneum creation, whereas that after extubation was not significant (p=0.051). On the other hand, HR in group F showed significant decrease from baseline after loading dose administration ($p<0.001$), after induction ($p<0.001$) and at 120 minutes after pneumoperitoneum (p= 0.016), whereas that after extubation showed significant increase (p < 0.001) and at all other times there was no significant change from baseline.In intergroup comparison, HR in group D decreased significantly than in group F after induction (p= 0.0430), after intubation (P= 0.005), throughout the pneumoperitoneum (P< 0.001) and after extubation (P= 0.001).(Graph 1).

Significant bradycardia (HR < 50 bpm) was seen in two patients in group D that responded instantly to injection atropine 0.6 mg. This effect of dexmedetomidine is due to decreased central sympathetic outflow, which was also seen in other studies [10,11]. No patients in group F developed bradycardia. There was not much variation in SPO_2 in both the groups throughout the procedure.

In group D, SBP, DBP and MAP mean values showed significant (p< 0.001) decrease from baseline from the time of loading dose administration till after extubation and that in group F, decreased significantly (p<0.001) from baseline after loading dose administration, after induction and after intubation, whereas, that after extubation showed significant increase (p < 0.001), and that throughout the pneumoperitoneum showed no significant change from baseline. MAP values in group D were significantly lower than that in group F after loading dose administration (p=0.001), after induction (p= 0.001), throughout the pneumoperitoneum (p < 0.001) and after extubation (p< 0.001) (Graph 2).

Three patients (10%) in group D developed hypotension (MAP < 20% from baseline) which was treated with faster infusions of intravenous fluids and two patients out of them required vasopressors.

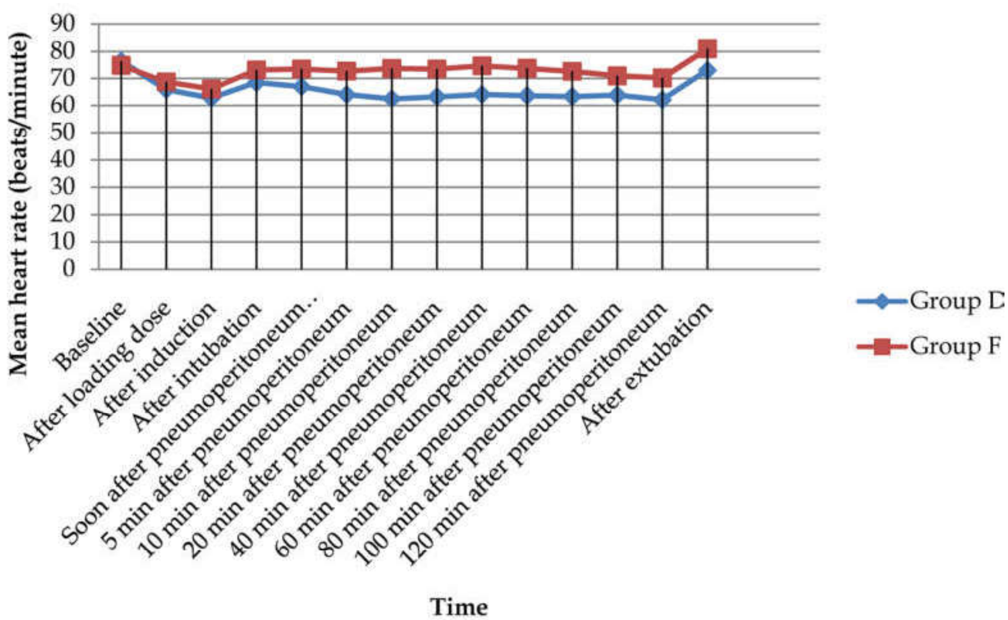
Discussion

Hyperglycemia and hemodynamic perturbations are the main aspects of the neuroendocrine stress response to surgery and anesthesia. Perioperative hyperglycemia is the result of increased hepatic glycogenolysis and gluconeogenesis, due to increased

Table 1: Demographic profile and duration of surgery of patients in group D and F

Parameters	Group D	Group F	P value
Age(years)	43.57±7.97	43.53±7.75	0.987
Gender (M/F)	13/17	14/16	1.000
Weight (Kg)	60.60± 7.70	61.47± 7.68	0.664
Duration of surgery(min)	98.47±12.29	99.47± 11.69	0.748

Values are in mean ± standard deviation.*p<0.05 is considered as significant. Both groups D and F were comparable in age, gender, weight and duration of surgery.

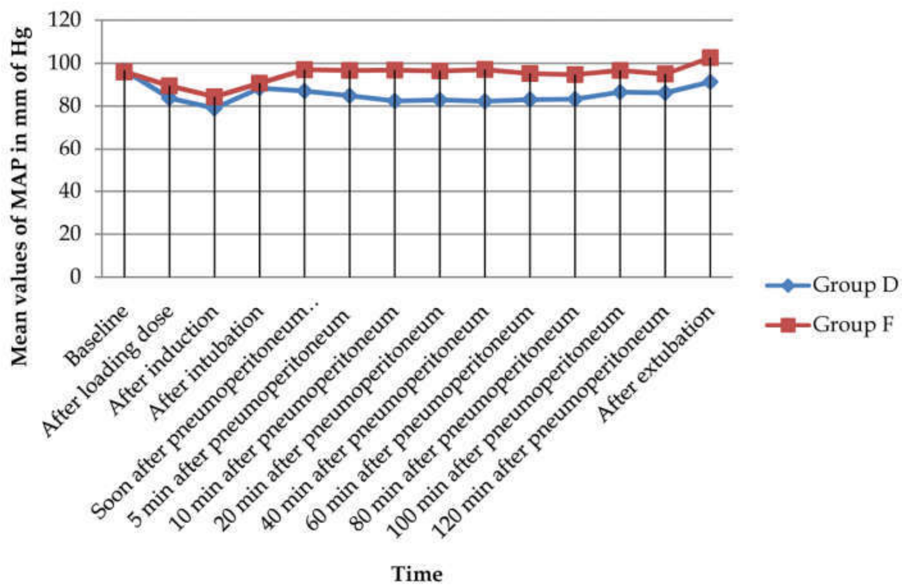


Graph 1: Perioperative variations in heart rate (beats/minute) in both groups

Table 2: Perioperative serial mean blood glucose values in mg/dl in group D and group F.

Time	Group D	Group F	P value
Preoperative/baseline(T_0)	90.93±6.58	92.87± 7.04	0.276
At 30 min after beginning of surgery (T_1)	115.57±11.29	122.37± 10.67	0.020*
At 5 min postextubation (T_2)	118.80± 9.70	128.90± 8.05	< 0.001*

Values are in mean ± Standard deviation. *p value < 0.05 is statistically significant. Baseline mean blood glucose level was comparable in both groups whereas that at 30 minutes after beginning of surgery and at 5 minutes postextubation were significantly lower in group D than that in group F.



Graph 2: Perioperative variations in MAP in mm of Hg in both groups. MAP – mean arterial pressure.

secretion of catabolic hormones like ACTH, cortisol, catecholamines and glucagon; in addition to the relative deficiency of insulin and peripheral insulin resistance [12]; and is linked with potential clinical hazards like increased susceptibility to infection, endothelial dysfunction and impaired wound healing and can be remarkably modulated by appropriate anesthetic technique as shown in several studies [13-16].

In our study, there was statistically significant (p< 0.001) increase in the perioperative blood glucose level from the basal value in both groups, reflecting the neuroendocrine stress response to surgery. Though, the increase was more marked in fentanyl group than in dexmedetomidine group.

In theory, α_2 adrenoreceptor agonists by their action on postsynaptic α_2- adrenergic receptors on pancreatic β-cells can cause hyperglycemia by inhibiting insulin release [6]. But interestingly, in their study, Ahmed et. al. [17] and Yacout et. al. [18] observed that intravenous infusion of dexmedetomidine reduced the hemodynamic and neuroendocrine stress response to cardiopulmonary bypass and major surgeries respectively, as indicated by clinically and statistically significant reduction in heart rate, mean arterial pressure, blood glucose level and plasma levels of cortisol, adrenaline and noradrenaline. Also, Harsoor et. al. [11] found that when dexmedetomidine was given at loading dose of 1μg/kg/10 min followed by continuous infusion of 0.5μg/kg/h till the end of surgery, it was effective in attenuating metabolic stress response to major surgeries as suggested by stable blood glucose levels without affecting intraoperative cardiovascular stability.

Even, Uyar et. al. [19] have shown that a single bolus dose of 1μg/kg/10 min given before induction of anesthesia was effective in blunting the hemodynamic and neuroendocrinal responses to skull-pin insertion in patients undergoing craniotomy, as evidenced by significant lower levels of HR, arterial blood pressures and blood glucose levels as well as that of plasma cortisol and prolactin in dexmedetomidine group as compared to the placebo group. In contrast to our study, Bulow et. al. [20] observed that hyperglycemia was higher in dexmedetomidine group when they compared it with remifentanil in TIVA in patients undergoing gynecologic videolaparoscopic surgery.

Dexmedetomidine, a highly selective α_2-adrenergic agonist possesses sedative, anxiolytic, analgesic, anesthetic sparing and sympatholytic properties without causing respiratory depression; which have enabled it to be used as a highly effective anesthetic adjuvant. Its biphasic cardiovascular response can be overcome by infusing loading dose slowly over 10 or more minutes [6].

Thus, when administered as a continuous infusion, dexmedetomidine exhibits an expected and stable hemodynamic response, even during stressful conditions of laryngoscopy, intubation, pneumoperitoneum and extubation as seen in our study and many other recent studies [8,10,12].

In our study, the mean values of HR and MAP were significantly lower in group D than that in group F at various time points but within hemody-namically stable limits. Also, the rise in HR and MAP in response to creation of pneumo-peritoneum and extubation was more effectively suppressed by dexmedetomidine than fentanyl [9,22,23].

Similarly, Bilgi et. al. [24] observed that dexmedetomidine in comparison to fentanyl diminished the sympathetic response to laryngoscopy and intubation in hypertensive patients, maintained stable hemodynamics intraoperatively as well as during extubation. Also Goyal et. al. [25] found that dexmedetomidine is superior to fentanyl in attenuating pressor responses to laryngoscopy, intubation and extubation and provides better hemodynamic stability in breast cancer surgeries.

Conclusion

We conclude that, dexmedetomidine as an anesthetic adjuvant is more effective than fentanyl in attenuating the neuroendocrine stress response to laryngoscopy, intubation, pnemoperitoneum and extubation; though we suggest that dexmedetomidine be used cautiously, as it can cause bradycardia and hypotension. Further studies involving the use of dexmedetomidine in patients with diabetes mellitus and cardiovascular compromise will enable them to achieve better clinical outcome from laparoscopic surgeries.

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Nil

Conflicts of Interest

There are no conflicts of interest.

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