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A COMPARATIVE STUDY OF DEXMEDETOMIDINE AND FENTANYL PREMEDICATION FOR INDIRECT ASSESSMENT OF NEUROENDOCRINE STRESS RESPONSE DURING LAPAROSCOPIC CHOLECYSTECTOMY

Anaesthesiology

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ABSTRACT

Introduction: Hyperglycemia is a characteristic feature of the metabolic response to surgery. A prospective randomized observational study was conducted to compare the efficacy of dexmedetomidineand fentanyl in attenuating the neuroendocrine stress response by measuring serial random blood sugar level in patients undergoing laparoscopic cholecystectomy.

Methodology: 40 patients of ASA physical status I or II of either sex, aged between 35-65 yrs scheduled to undergo laparoscopic cholecystectomy under general anaesthesia were randomly divided by envelope method into one of the 2 groups of 20 patients each (group D and group F). Patients allocated in group D patients (n = 20) were given IV infusion of dexmedetomidine 1µg/kg in 100 ml normal saline and Group F patients (n = 20) were given IV infusion of fentanyl 2 µg/kg in 100 ml normal saline over a 15 min period before the induction of general anaesthesia. Serial random blood sugarestimation was done perioperatively. Heart rate (HR), Oxygen saturation (SPO2), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were recorded at various time intervals.

Results: It was observed that blood glucose concentration increased in both the groups and the increment being more distinct in group F. 5 minutes post extubation, the mean random blood sugar value in group D was clinically lower compared to that in group F and it was statistically significant ($p<0.001$). The heart rate, systolic and diastolic blood pressure and mean arterial pressure was significantly lower in group D when compared to group F.

Conclusion: We conclude that dexmedetomidine is more effective than fentanyl in reducing the neuroendocrine and hemodynamic stress responses during laparoscopic cholecystectomy.

KEYWORDS

Hyperglycemia, neuroendocrine response, hemodynamic stress response, laparoscopic cholecystectomy, dexmedetomidine

I.INTRODUCTION

Pneumoperitoneum and the positions of the patient required for laparoscopic cholecystectomy attribute to the pathophysiologic changes which can complicate the anaesthetic management. It is associated with sympathetic stimulation and stress response with rise in plasma levels of norepinephrine (NE), epinephrine (E) and plasma renin that results in tachycardia and hypertension[1]. Catecholamines evoke changes in carbohydrate metabolism leading to hyperglycemia[2].

There is literature suggesting that blood glucose values reflect the neuroendocrine response to surgical trauma. Glucose values greater than 10 mmol/litre are not uncommon during cardiac surgery and may cause glycosuria[3]. Studies have higher plasma glucose concentrations than preoperative values following laparoscopic and open cholecystectomy[4]. Various pharmacological agents have been used to attenuate the hemodynamic response due to creation of pneumoperitoneum as well as stress response to surgery.

Fentanyl, a potent, synthetic opioid analgesic and dexmedetomidine is a specific, highly selective and potent alpha-2 adrenergic agonist. With emphasis on the multidimensional features of dexmedetomidine and a very reputed drug, fentanyl, we designed a prospective randomized observational study to compare the efficacy of dexmedetomidine and fentanyl premedication in modulating neuroendocrine stress response during laparoscopic cholecystectomy by measuring the changes in the perioperative serial blood glucose levels and monitoring the hemodynamic variables.

II. METHODOLOGY

A prospective randomized observational study was conducted after ethical committee approval and informed consent in 40 patients belonging to ASA physical status I or II of either sex, aged between 35 to 65 yrs scheduled for elective laparoscopic cholecystectomy under general anaesthesia. Thorough pre- anaesthetic evaluation and routine investigation was carried out before taking up the patient for surgery. Patients belonging to ASA physical status III and IV, those with diabetes mellitus and complicated surgeries of more than 2 hours were excluded from the study.

Patients were premedicated with Tab Ranitidine 150 mg at night before surgery and at the morning of the surgery, Tab Lorazepam 1 mg at night before surgery and InjGlycopyrrolate0.2mg IM 1 h before the surgery.

On arrival to operation room, random blood sugar (RBS) estimation of the patient was done using glucometer.Routine, hemodynamic monitoring was performed by automatic blood pressuremeasurements, five-lead ECG monitor, and finger pulse oximetry and baseline readings were recorded. An intravenous (IV) infusion of ringer lactate was started, followed by IV midazolam 1 mg. Group D patients (n = 20) were given IV infusion of dexmedetomidine 1µg/kg in 100 ml normal saline and Group F patients (n = 20) were given IV infusion of fentanyl 2 µg/kg in 100 ml normal saline over a period of 15 minutes (mins) before the induction of general anesthesia.

After preoxygenation (EtCO2 connected), the anesthesia was induced with propofol 2 mg/kg IV and tracheal intubation was facilitated by vecuronium 0.1 mg/kg IV. Anaesthesia was maintained with isoflurane 1-1.5% and 60% nitrous oxide in oxygen). The patient's lungs were initially mechanically ventilated with a tidal volume of 8 ml/kg, a respiratory rate of 12 breaths/min, and I: E ratio of 1:2 in volume controlled mode. Five mins after securing the airway and abdominal insufflations by CO2, the lung mechanics was adjusted to maintain normocapnia (an EtCO2 value of 35-40mmHg) and IAP maintained between 12 and 15 mmHg. Muscle relaxation was supplemented with IV vecuronium bromide. All patients were covered to maintain normothermia.

Blood samples were estimated using glucometer for RBS levels preoperatively, 30 mins after beginning of surgery and5 mins post extubation.

All patients were assessed for changes in hemodynamic parameters by measuringheart rate (HR), Oxygen saturation (SPO2), SBP, DBP and MAP prior to premedication (Baseline), after Premedication/ Pre-Induction, after induction, after intubation, at 5, 20, 40, 60, 80, 100 and 120 mins after pneumoperitoneum and post extubation.

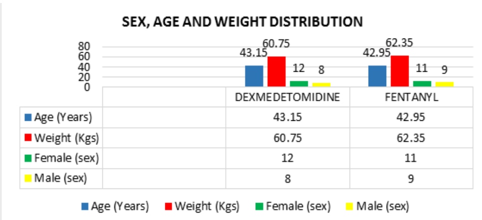
Intraoperatively, patients were monitored for any bradycardia or tachycardia, hypotension or hypertension and it was managed as required. The residual neuromuscular block was reversed with neostigmine 0.05 mg/kg IV and glycopyrrolate 0.01 mg/kg IV and the trachea extubated when respiration was adequate and patient was able to obey simple commands. All patients received Paracetomol 1g intravenously at the end of procedure after RBS estimation. The patients were transferred to PACU and observed for any hemodynamic abnormalities, respiratory depression (respiratory rate <8 breaths/min), or hypoxemia (SPO2 < 94%), shivering, nausea, and vomiting, and managed accordingly.

III. OBSERVATION AND RESULTS

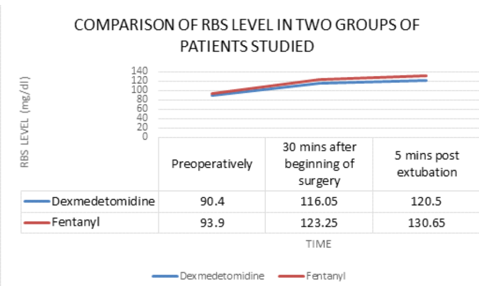
Statistical analysis

For statistical analysis of data within the groups paired 't' test was used while for comparison between groups unpaired 't' test was used. Results were considered statistically significant for p values <0.05. We have taken 20 patients in each group to obtain the power >80%. Qualitative data was analysed by Chi-square test.The Statistical software SPSS 20.0 was used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

Demographic date: Demographic profile of our patients was comparable with respect to mean age, sex and weight and there was statistically insignificant difference among both the groups. (p>0.05).

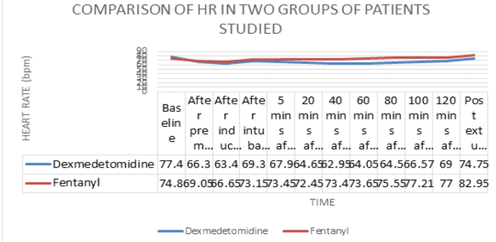


Graph: 1 Sex, age and weight distribution of patients studied



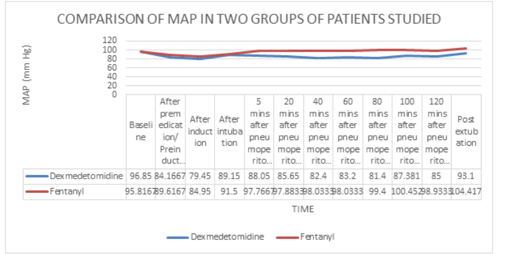
Graph: 2Comparison of RBS level (mg/dl) in two groups of patients studied

RBS level (mg/dl) preoperatively is comparable in both the groups. 30 mins after beginning of surgery, it is clinically lower in Group D. It is clinically and statistically lower in Group D, 5 mins after extubation



Graph: 3 Comparison of HR (bpm) in two groups of patients studied

Basal HR is comparable in both the groups. HR is statistically and clinically lower in group D after intubation; after pneumoperitoneum at 5, 20, 40, 60, 80 and 100 mins; and post extubation compared to Group F.



Graph: 4 Comparison of MAP (mm Hg) in two groups of patients studied

MAP values in both the groups are comparable at baseline. Values are statistically and clinically significantly lower in group D after premedication/ preinduction; after induction; afterpneumoperitoneum at 5, 20, 40, 60, 80 and 100 mins; and post extubation compared to Group F.

IV. DISCUSSION

Random blood glucose level

We observed that the blood glucose level increased during and after surgery from the basal value in both groups which was statistically significant (<0.001), reflecting the neuroendocrine stress response to surgery. However, this increase was more striking in the fentanyl group than dexmedetomidine group.

Preoperative mean RBS level was 93.9 and 94.05 mg/dl which was not statistically significant. The increment from the basal value 30 mins after beginning of surgery was 28% and 31% in Group D and group F respectively both of which were statistically significant (p<0.001). 5 mins following extubation there was 39% increase from the basal value in group F which was clinically and statistically significant (p <0.001) and 33% increase from the basal value in Group D which was also significant statistically (p <0.001).

In comparison, RBS levels at 30 mins after beginning of surgery increased to116.05 mg/dl in group D and 123.25 mg/dl in group F and the difference between the groups was non-significant (p = 0.053). However, 5 mins post extubation, the mean RBS value in group D (120.5 mg/dl) was clinically and statistically lower (p<0.001) compared to the mean RBS value in group F (130.65 mg/dl).

Although in theory, α_2 adrenoceptor agonists can cause hyperglycaemia in humans[5, 6], hyperglycaemia was not found after surgery when oral clonidine was given[7], and this may reflect attenuation of the sympathoadrenal response. Venn *et al.*found no differences in glucose concentrations between the dexmedetomidine and propofol groups, and observed that there was no differences in the requirements for exogenous insulin infusion. The neuroendocrinal effects of dexmedetomidine leading to better perioperative glucose stability may be attributed to the activation of peripheral presynaptic α_2-adrenergic receptors which reduces the release of catecholamines, and hence reduces sympathetic response to surgery[8,9].Dexmedetomidine is an imidazole agent but unlike etomidate, it does not appear to inhibit steroidogenesis when used as an infusion for short-term sedation[8,9].

Observation of our study is in accordance withGupta*et al.* observed that blood concentration of glucose had increased significantly in the fentanyl group, than in thedexmedetomidine group[10].

Interestingly, Yacout *et al* in their study observed that IV infusion of dexmedetomidine reduced stress response to major surgeries as indicated by clinically and statistically significant reduction in blood glucose and cortisol levels[11]. Similarly, studies by Uyar *et al.*and Mukhtar *et al.* foundthat dexmedetomidine did inhibit the hyperglycemic response to surgery significantly more than placebo, and this may reflectattenuation of the sympatho-adrenal response[5,6].

Khalighinejad *et al*. found no significant differences in the mean blood glucose level at any time of the study when they used fentanyl for light sedation in combination with propofol or midazolam in diabetic patients who underwent cataract surgery[12].

The hyperglycaemia of surgery is the resultof an increase in glucose production compared with the rate of utilization. Suppression of insulin secretion is an early response to surgical stimulation and this has led to studies of glucose utilization in the perioperative period.

Ibacache M et al in their study found no significant changesin the intra and postoperative blood glucose levels between the groups (p=0.31), without hyperglycemia and concluded that administration of dexmedetomidine in obese patients with impaired glucose tolerance, undergoing bariatric surgery, does produce a mismatch between theobserved glucose level and the expected insulin secretion pattern but without causing hyperglycemia[13].

In contrast to our present study, Bulow *et al*observed that hyperglycemia was higher in dexmedetomidine group when they compared it withremifentanilin TIVA in patient undergoing gynecologic videolaparoscopy[7]. Venn *et al.* did not find any difference in glucose levels between dexmedetomidine and propofolused for sedation in the intensive care unit in patients following major surgeries[8].

Hemodynamic parameters

There was statistically significant difference in HR between the twogroups at various time intervals. In group D, the mean HR decreased significantly (p<0.001) from the baseline after premedication and it remained low till post extubation. It decreased by 14% after IV infusion with dexmedetomidine and 18% after induction. During the intraoperative period it was lower than the baseline by 12% after creation of pneumoperitoneum and by 19% at 120 mins after pneumoperitoneum. However, post extubation the decrease was 3% and not statistically significant. On the other hand in group F, there was decrease in mean HR from the baseline after administration of premedication and induction of anaesthesia by 7% and 10% respectively. There was minimal increase in the HR from the basal value after creation of pneumoperitoneum. But, the increase was 5% at 120 mins after pneumoperitoneum and 10% post extubation which was significant.

The mean HR was lower in group D after intubation, after pneumoperitoneum at 5, 20, 40, 60, 80 and 100 mins and post extubationthan compared to group F which was clinically and statistically significant.

Significant bradycardia of less than 50bpm was observed in 2 patients (10%) in group D that responded to injection atropine IV. No patients in group F developedsignificant bradycardia.There was not much variation in SPO_2 in both the groups throughout the procedure.

There was statistically significant difference in SBP, DBP and MAP at variousintervals between the two groups. In group D, it was observed that SBP decreased remarkably from the baseline by 13% and 16% respectively after premedication and induction of anaesthesia (p<0.001). The decrease ranged from 9 to 14% intraoperatively and postextubation was found to be significantly lower than the baseline by 5%. DBP also showed significant decrease (p<0.001) after premedication and induction of anaesthesia by 14% and 18% respectively. The decrease ranging from 8 to 14% during the intraoperative period. But post extubation, the decrease was 2% and not statistically significant. The MAP was significantly lower in comparison to the baseline. The respective decrease was 13% (p<0.001), 17% (p<0.001), 9% (p<0.001) 15% (p<0.001), 11% (p= 0.006) and 3% (p= 0.02) after premedication, induction of anaesthesia, at 5, 80 and 120 mins after pneumoperitoneum and postextubation respectively.

In group F, it was found that SBP was significantly lower (p<0.001) than the baseline by 5%, 10% and 8% after premedication, induction of anaesthesia and post extubation respectively. Intraoperatively, after pneumoperitoeum it was lower by 2-6% which was significant. The DBP was significantly lower than the baseline by 6% (p<0.001), 10% (p<0.001), 4% (p=0.026), 3% (p=0.038), 10% (p<0.001) after premediction, after induction, after intubation, at 5 mins after pneumoperitoneum and post extubation respectively. Intraoperatively, however, there was decrease from the baseline by 2-5% which was not statistically significant. The MAP showed significant decrease from the basal value by 6% (p<0.001), 11% (p<0.001), 4% (p=0.005), 4% (p=0.048) and 9 % (p<0.001) after premedication, after induction, after intubation, at 80 mins after pneumoperitoneum and post extubation respectively.

In comparison, the SBP values were statistically and clinically lower in Group D after pneumoperitoneum at 5, 20, 40, 60, 80, 100 and 120 mins; and post extubation compared to Group F. DBP values were statistically and clinically lower in group D after premedication/ preinduction; after induction; after pneumoperitoneum at 5, 20, 40, 60, and 80 mins; and post extubation compared to Group F. Similarly, MAP values were lower in group D after premedication/ preinduction; after induction; after pneumoperitoneum at 5, 20, 40, 60, 80 and 100 mins; and post extubation compared to Group F which was clinically and statistically significant.

2 patients (10%) in Group D developed hypotension, which was treated with intravenous fluids and one patient out of them was managed with vasopressors.

The rise in BP and HR due to creation of pneumoperitoneum was suppressed by dexmedetomidine more efficiently than fentanyl. In agreement with our study, Gupta[10]*et al.* found that dexmedetomidine did blunt the hemodynamic stress response to pneumoperitoneum more effectively with fentanyl. Similarly, Bhattacharjee[14] et al., Ghodki[15]*et al.* and Waindeskar[16]*et al*observed in their studies that dexmedetomidine effectively attenuates the stress response of laryngoscopy and intubation and the sympathoadrenal responseoccurring with pneumoperitoneum.

V. CONCLUSION

In conclusion, our study demonstrates that both dexmedetomidine and fentanyl premedication attenuate the neuroendocrine and hemodynamic stress responses during laparoscopic cholecystectomy. However, dexmedetomidine as a premedicant is more effective than fentanyl with respect to modulating the neuroendocrine responses and also blunting the hemodynamic stress response to pneumoperitomeum. Although it is very efficient in obtunding the stress response, we suggest the use of dexmedetomidine with caution as it leads to bradycardia and hypotension. Further, studies on the use of dexmedetomidine in patients with diabetes and cardiac dysfunction could help these patients to avail benefit from laparoscopic surgeries.

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