Estimation of Blood Glucose Levels And Hemodynamic Changes During Laparoscopic Cholecystectomy: A Comparison of Dexmedetomidine and Nalbuphine

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ABSTRACT

Objective: To compare the effect of Dexmedetomidine and Nalbuphine premedication on changes in hemodynamics and neuroendocrine stress response under general anaesthesia by analyzing the variation of perioperative serial blood glucose levels.

Study Design: Prospective comparative study.

Place and Duration of Study: Services Hospital, Lahore Pakistan, from Oct to Dec 2020.

Methodology: Total 90 patients aged between 30-and 65 years were allocated randomly into three groups. Group-D patients (n=30) were administered Dexmedetomidine 0.5 µg/kg in 100 ml normal saline, group-N (n=30) were given Nalbuphine 0.1 mg/kg in 100ml saline, and group-S received saline (100ml) throughout 15 minutes before induction of anaesthesia for laparoscopic cholecystectomy. General Anaesthesia was administered. Intra-abdominal pressure was maintained after abdominal insufflation with carbon dioxide between 12-15 mmHg. Blood glucose levels were analyzed preoperatively, 30 minutes after the beginning of surgery, at extubation and 2.5 hours postoperatively. Hemodynamic changes were recorded after premedication, 15 and 30 minutes after pneumoperitoneum and extubation.

***Results*:** Random mean blood sugar levels were 135.23 mg/dl with Dexmedetomidine and 123.33 mg/dl with Nalbuphine and 122.53 mg/dl in saline group ($p<0.05$). There was a greater decrease in hemodynamic parameters with group-D than with groups N and S ($p<0.01$).

Conclusion: During laparoscopic cholecystectomy, intravenous Dexmedetomidine premedication attenuates the hemodynamic stress response better than Nalbuphine but does not suppress the neuroendocrine response as estimated by a rise in random blood glucose level.

Keywords: Blood glucose level, Dexmedetomidine, Nalbuphine, Neuroendocrine response.

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INTRODUCTION

The hemodynamic changes are characterized by increased systemic and pulmonary vascular resistance, a rise in arterial pressure and heart rate with reduced cardiac output.[1,2] Though better tolerated in ASA I and II patients, these changes can be detrimental in elderly and ASA III patients with compromised cardiovascular physiology.[3,4] Various surgical methods and pharmacological agents were used to decrease the surgical stress of laparoscopic procedures to improve outcome.[5]

Dexmedetomidine, the α2-adrenergic agonist, is useful due to its sympatholytic, hypnotic, sedative, anxiolytic, analgesic, and anaesthetic sparing effects without respiratory depression.[6] It has shown attenuation of the hemodynamic response and prevention of increase in glycogenolysis and gluconeo-genesis, thus inhibiting the rise in glucose levels.[7] Nalbuphine, a partial kappa agonist/mu antagonist opioid, is commonly used to provide analgesia and cardiovascular stability, but little is known about its effect on the neuroendocrine stress response.[8,9] As per our knowledge, there are limited studies in Pakistan comparing Dexmedetomidine with Nalbuphine. Thus, the primary objective of this study was to compare Dexmedetomidine and Nalbuphine premedication on modulation of neuroendocrine stress response during laparoscopic cholecystectomy by analyzing the perio-perative serial blood glucose levels and recording intraoperative hemodynamic changes in our popula-tion.

METHODOLOGY

This prospective comparative study was conducted at Services Hospital Lahore from October to December 2020, after Institutional Review Board approval (IRB/2020/713/SIMS).

The sample size was calculated (n=90), taking the mean blood sugar level in group-D as 119.5 ± 11.95 and group-F as 129.65 ± 10.83 at 30 minutes10 after the

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beginning of surgery, keeping 80% power of the study and alpha error 0.05 from the formula.

$$n = \frac{(Z_{1-\beta} + Z_{1-\alpha/2})^2(\delta_1^2 + \delta_2^2)}{(\mu_{1-}\mu_2)^2}$$

Inclusion Criteria: Patients belonging to ASA physical status I or II of either gender, aged between 30-and 65 years, scheduled for elective laparoscopic cholecystectomy were included in the study.

Exclusion Criteria: Patients belonging to ASA physical status III and IV, those with diabetes, comorbidities, cardiopulmonary, renal, metabolic disorders and allergic to study drugs were excluded from the study.

Written informed consent was obtained from all the patients after explaining the study protocol. Patients were randomly divided into three groups of 30 each by lottery method. On arrival in the operation room, random blood sugar (RBS) estimation was done using a glucometer and pulse oximetry, electrocar-diogram, and non-invasive blood pressure were monitored to record baseline values. All patients were given intravenous Midazolam 2mg to relieve anxiety. Group-D patients (n=30) were administered Dexmede-tomidine 0.5 µg/kg in 100 ml normal saline, group-N patients (n=30) Nalbuphine 0.1 mg/kg in 100ml saline, and group-S were given 100 ml normal saline over 15 minutes before induction of general anaesthesia. After pre-oxygenation for 3 min, propo fol (2 mg/kg) induced anaesthesia, followed by tracheal intubation with Atracurium 0.5 mg/kg. Maintenance of anaesthesia was with Isoflurane 1-1.5% and 60% Nitrous Oxide in oxygen. IV Paracetamol l5mg/kg was given at the beginning of surgery. Patients were ventilated in volume -controlled mode. After abdominal insufflation by carbon dioxide, an end-tidal carbon dioxide value of 35-40 mm Hg was maintained, and intra-abdominal pressure was kept between 12 and 15 mm Hg.

All the patients were assessed for changes in hemodynamic parameters of heart rate (HR), systolic (SBP) and diastolic blood pressure (DBP) prior to premedication, after premedication, after intubation, and after pneumoperitoneum, followed every 5 min for 30 min, after that every 15 min till the end of surgery and after extubation. Neostigmine 0.05 mg/kg with Atropine 0.02 mg/kg was administered to reverse the neuromuscular block. In the post-anaesthesia care unit, patients were observed for any adverse effects such as respiratory depression (respiratory rate <8 breaths/min), hypoxemia (SpO2 <94%), and sedation and were managed accordingly. Blood glucose levels were analyzed by glucometer preoperatively, at 30 min after the beginning of surgery, and at 2.5 h postopera-tively.

Statistical package for the social sciences (SPSS) version 25.00 was used for statistical analysis. Quantitative variables were presented as mean ± SD. Mean blood sugar levels and hemodynamic parameters were analyzed by one way ANOVA, and qualitative variables such as respiratory depression, hypoxemia and sedation with chi-square. The *p*-value of ≤0.05 was considered statistically significant.

RESULTS

All the patients in the three groups analyzed intraoperative hemodynamics and random blood sugar levels (n=90). All the patients in the three groups demonstrated a significant rise in mean blood sugar level (*p*=0.01). A decrease in mean blood pressure was seen in the Dexmedetomidine group compared to the Nalbuphine and saline group (*p*<0.05). The Dexmedetomidine group had 5 (16%) males while there were 25 (83%) females with the mean age of 47.50 ± 8.58 years. Group Nalbuphine had 7 (23%) males and 23 (82%) females with the mean age of 47.87 ± 9.87 years. The number of males in the Saline group was 10 (33%) while females were 20 (66%), with the mean age of 44.07 ± 11.19 years. There was no significant difference among groups in weight (*p*=0.35) and the mean time of duration of surgery (*p*=0.23) (Table-I).

Table-I: Demographic data.

Parameters	Group D (n=30)	Group N (n=30)	Group S (n=30)	*p*-value
Age (Years ± SD)	47.50 ± 8.58	47.87 ± 9.87	44.07 ± 11.19	0.01
Weight (Kg ± SD)	68.53 ± 8.52	70.97 ± 6.79	68.23 ± 8.74	0.35
Duration of Surgery (Min) (Mean ± SD)	95.00 ± 36.07	91.33 ± 3.63	82.5 ± 25.24	0.23
Male	5 (16%)	7 (23%)	10 (33%)	-
Female	25 (83%)	23 (82%)	20 (66%)	-

Table-II: Intergroup Comparison of Random Blood Sugar Level.

Parameters	Group D vs Group N	Group D vs Group S	Group N vs Group S
30 Minutes After Beginning of Surgery	0.01	0.02	0.87
10 Minutes Post Extubation	0.001	0.002	0.76
150 Minutes Post Extubation	0.001	0.00	0.98

A rise in mean random blood sugar levels occurred in all the three groups. The increase was significant in Dexmedetomidine (135.23 ± 21.63 mg/dl) when compared to Nalbuphine (122.53 ± 13.37 mg/dl) at 30 minutes after surgery and 150 min after extubation (143.40 ± 23.61 vs 115.17 ± 14.47 mg/dl) (Table-II). The comparison with saline also showed a significant rise in the Dexmedetomidine group at 30 minutes (135.23 ± 21.63 vs 123.33 ± 16.86 mg/dl) after surgery and after extubation. No significant difference could be seen between the Nalbuphine and saline groups (122.53 ± 13.37 vs 123.33 ± 16.86 mg/dl) (Table-II).

Mean heart rate showed a significant decrease from baseline in group D and N compared to control at all times of measurement (Table-III). Compared to Nalbuphine, there was a greater decrease in HR in Dexmedetomidine (72.73 ± 5.39 vs 77.13 ± 7.39 per minute) 15 minutes after pneumo-peritoneum. After pneumoperitoneum, a significant reduction was seen in group-D (70.60 ± 7.32 per minute) and group-N (73.73 ± 7.94 per minute) groups when compared to saline (84.90 ± 10.52 per minute) 30 minutes after pneumo-peritoneum. In comparison to saline (83.66 ± 8.48 per minute), group-N showed a significant decrease (75.50 ± 6.80 per minute) (Table-III).

Table–III: Intergroup comparison heart rate (per minute).

Parameters	Group D vs Group N	Group D vs Group S	Group N vs Group S
After Premedication	p=0.00	p=0.002	p=0.01
After Intubation	0.01	0.01	0.05
15 Min After Pneumoperitoneum	0.00	0.00	0.00
30 Minutes After Pneumoperitoneum	0.01	0.02	0.00
60 Minutes After Pneumoperitoneum	0.00	0.002	0.00
After Extubation	0.00	0.000	0.4

A significant drop in mean systolic blood pressure (SBP) from baseline was seen after pneumo-peritoneum in group-D (110.17 ± 7.98 mmHg) and group-N (115.17 ± 7.76 mmHg), whereas there was a rise in group-S (127.90 ± 9.88 mmHg). The reduction in mean systolic blood pressure was significant in group -D (110.67 ± 6.84 mmHg) 30 minutes after pneumo-peritoneum as compared to group-N (115.60 ± 5.39mmHg) and group-S (130.13 ± 8.88mmHg) Significant difference was seen among the groups at 60 minutes of pneuzmoperitoneum and after extubation (Table-IV). In group-D, only one patient was given phenylephrine for a greater fall in systolic blood pressure.

Mean diastolic blood pressure (DBP) was significantly lower in group-D (68.23 ± 5.07) as compared to group-N (82.23 ± 5.06) and group-S (79.20 ± 7.58) after premedication (p=0.03). Sixty minutes after pneumoperitoneum, diastolic blood pressure was significantly lower in group-D (72.76±5.54) in comparison to group-N (80.97 ± 5.70) and group-S (80.27 ± 6.63). No significant difference was seen between group-N (80.97 ± 5.70) and group-S (80.97 ± 5.70) in diastolic pressures at all times of measurement (Table-V).

Table-IV: Intergroup comparison mean systolic blood pressure (mmHg)

Parameters	Group D vs Group N	Group D vs Group S	Group N vs Group S
After Premedication	p=0.00	p=0.002	p=0.02
After Intubation	0.01	0.01	0.18
15 Min After Pneumoperitoneum	0.00	0.00	0.00
30 Minutes After Pneumoperitoneum	0.01	0.00	0.00
60 Minutes After Pneumoperitoneum	0.00	0.002	0.00
After Extubation	0.00	0.00	0.02

Table-V: Intergroup Comparison Mean Diastolic Blood Pressure (mmHg).

Parameters	Group D vs Group N	Group D vs Group S	Group N vs Group S
After Premedication	p=0.03	p=0.02	p=0.06
After Intubation	0.003	0.01	0.06
15 Min After Pneumoperitoneum	0.00	0.00	0.78
30 Minutes After Pneumoperitoneum	0.002	0.00	0.91
60 Minutes After Pneumoperitoneum	0.02	0.002	0.08
After Extubation	0.02	0.00	0.77

Postoperatively there was no drop in saturation and no significant difference in respiratory depression among the three groups (p=0.1). In the Nalbuphine group, respiratory depression was seen in 2 (6.6%) patients. None of the patients in the Saline group showed respiratory depression. The difference in sedation was statistically significant in the Nalbuphine group (36.6%) vs (10%) in the Dexmedetomidine group. (p<0.01).

DISCUSSION

In our study, intravenous Dexmedetomidine premedication was better than Nalbuphine to attenuate the hemodynamic stress response, but it did not modulate the neuroendocrine response when measured with random blood sugar levels during pneumoperitoneum and after extubation.

Pneumo-peritoneum created for laparoscopic cholecystectomy is associated with metabolic, neuroendocrine and inflammatory stress response.[11,12] This stress response varies according to the intensity, severity and duration of the surgical stimulus. This stress is manifested as sympathetic stimulation that results in a rise in plasma levels of Epinephrine, Norepinephrine and Renin, leading to significant hemodynamic changes. Catecholamines evoke changes in carbohydrate metabolism reflected as an increase in blood sugar levels.[2,10,13] Various drugs have been used to attenuate the stress response in laparoscopic cholecystectomy. Earlier studies have been done with Dexmedetomidine on blood sugar levels compared with fentanyl.[14,15,16] Dexmedetomidine has attenuated hemodynamic response with different doses in laparoscopic cholecystectomy.[17] Nalbuphine, an opioid commonly used as an adjuvant with Dexmede-tomidine, has shown favourable results in controlling pain in laparoscopic cholecystectomy.[18] The present study compared the change in hemodynamics and blood glucose levels with Dexmedetomidine and nalbuphine as an indicator of the stress response. A significant rise in blood glucose level from baseline was observed in all three groups. The increase was significant during surgery and after extubation with Dexmedetomidine compared to Nalbuphine and saline (p<0.01). Premedication with intravenous Dexmede-tomidine and Nalbuphine before induction of anaes-thesia attenuated the hemodynamic response to intubation and pneumo-peritoneum. A significant decrease in heart rate and blood pressure was seen in both groups, but the fall in heart rate (10-12%) and blood pressure (12-15%) was more significant in the Dexmedetomidine group.

In accordance with our results, Gupta *et al*, found a 20% rise in blood sugar levels with Dexmede-tomidine and Fentanyl as pre-medicants during lapar-oscopic surgery. They also found stabilized hemod-ynamic changes (15%) with dexmedetomedine.[9]

Similar results were declared by Singh *et al*, on the estimation of blood glucose levels to assess the attenuation of metabolic and hemodynamic stress responses with Dexmedetomidine infusion during laparoscopic surgery. The increase in blood sugar levels was 20% during and after surgery. The changes in hemodynamic parameters were more stable with Dexmedetomidine as the fall was 15%.[3]

In agreement with our study results, Chandrashekhar *et al*, observed that the blood glucose level increased 30% from the basal value with Dexmedetomidine during and after laparoscopic cholecystectomy. They also observed lower heart rate and meant arterial pressure in the Dexmedetomidine group after premedication, pneumo-peritoneum and post extubation.[10]

Comparable to our study results, Pramod *et al*, also demonstrated an increase in mean random blood sugar value with Dexmedetomidine premedication during laparoscopic appendectomy. They demonstrated a 33% rise with Dexmedetomidine compared to a 39% increase with fentanyl.[11]

In contrast to our study results, Chandrasekaran *et al*, assessed the neuroendocrine response with Dexmedetomidine 1 µg/kg in laparoscopic surgery and found a significant decrease in blood glucose concentration at 30 and sixty minutes after pneumo peritoneum. This difference in results could be due to the dose used as we administered 0.5 µg/kg bolus preoperatively. Hemodynamic effects in their study were similar to our results.[13]

Deepali *et al*, found that Dexmedetomidine significantly reduces heart rate, systolic, diastolic and mean arterial blood pressure. They observed that perioperative use of Dexmedetomidine infusion main-tained better hemodynamic stability than the normal saline in the control group and had a sparing effect on other anaesthetic drugs such as Propofol and Fentanyl. This was similar to our results on hemodynamics.[5]

Abd-Elaziz *et al*, studied the effects of Dexmedetomidine and Nalbuphine as premedication on blood glucose levels and hemodynamics during gynaecological diagnostic laparoscopy.[19] They observed a significant reduction in random blood glucose with Dexmedetomidine and Nalbuphine compared to control. Their results did not agree with our study, as we had seen an increase in blood sugar levels. This difference could be due to variations in dose and methodology. Regarding hemodynamics, they also noted a more significant decrease compared to the results of our study.

LIMITATIONS OF STUDY

There were certain limitations to this study. Stress response includes metabolic, hormonal and immunological responses, but we studied only one portion in the form of random blood glucose measurement. Future studies can measure the cortisol, insulin and catecholamine levels and monitor the depth of anaesthesia.

CONCLUSION

During laparoscopic cholecystectomy, intravenous Dexmedetomidine premedication attenuates the hemodynamic stress response better than Nalbuphine but does not suppress the neuroendocrine response as estimated by a rise in random blood glucose level.

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Conflict of Interest: None.

Authors' Contribution

FEF: Study concept and design, NA: Statistical analysis of data and writing of manuscript, HK: Acquisition of data, ZB: Acquisition of data, NA: Acquisition of data, AS: Revision of manuscript.

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