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Original Article

Anaesthesia Section

Monitoring Blood Glucose as a Perioperative Stress Response Marker and the Effect of Dexmedetomidine Premedication in Laparoscopic Surgery Patients: A Randomised Controlled Study

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ABSTRACT

Introduction: Perioperative stress increases cortisol levels, which in turn elevates glucose production. Thus, regular monitoring of glucose during the perioperative period can predict intraoperative stress and the depth of anaesthesia. Dexmedetomidine (Dex) is used as an adjunct during anaesthesia to attenuate the pressor response during tracheal intubation.

Aim: To assess sequential blood sugar values in Dex-mediated attenuation of the perioperative neuroendocrine stress response.

Materials and Methods: A randomised, controlled, double-blinded study was conducted at the Department of Anaesthesiology, M.K.C.G Medical College and Hospital, Berhampur, Odisha, India on 80 patients undergoing laparoscopic surgery, divided into two groups (n=40). Group-I was administered 50 mL of Normal saline i.v. over 10 minutes, whereas Group-II received Dex 1 mcg/kg in 0.9% normal saline diluted to 50 mL over 10 minutes i.v. Blood glucose levels and haemodynamic parameters such as Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP), and Heart Rate (HR) were evaluated in the preoperative room, 30 minutes after surgical incision, after extubation, one hour after surgery, and 2.5 hours following surgery. Unpaired Student's t-test was used to compare the variables at different time points.

Results: There was no significant difference in age (48.58±5.89 and 46.25±6.51 years; p>0.05), weight (57.07±7.84 and 56.8±7.4 kg; p>0.05), and American Society of Anaesthesiologists (ASA) status among the Group-I and Group-II patients. Female preponderance was observed, but it was not significant between Group-I and Group-II patients (27 vs 31; p>0.05). In Group-II, Dex-administered patients, the mean blood sugar levels at 30 minutes past surgical incision, after extubation, one hour, and 2.5 hours following surgery were 104.35±13.58, 97.15±5.86, 98.4±7.45, 94.08±7.37 mg/dL, respectively. This was lower when compared to Group-I saline-treated patients, 135.95±14.4, 137.38±7.93, 138.08±8.84, and 137.70±15.13 mg/dL, and was found to be significant (p<0.05).

Conclusion: Serial blood glucose estimation can be a useful marker to evaluate the perioperative neuroendocrine response. Dex premedication has effectively modulated the neuroendocrine stress response during anaesthesia.

Keywords: Cortisol, Mean arterial pressure, Saline

INTRODUCTION

Anxiety and excitability are more frequent in patients undergoing anaesthesia during surgery. The fear among the patient during this event is associated with several factors and mediates the stress. During surgery, there exists a complex stress response mediated by alteration in metabolic, neurohumoral, and immunological activity [1]. Surgery induces a state of hyperglycaemia due to the metabolic response, which depends on various factors such as the patient's age, mode of anaesthesia, extent of tissue damage, surgery type and duration, blood loss during surgery, and postoperative pain [2].

Laryngoscopy, endotracheal intubation, as well as extubation stimulate the sympathetic nervous system, leading to exaggerated haemodynamic changes. Surgical procedures induce further complex stress responses, manifested by metabolic, neurohumoral, and immunological changes. Within minutes of the start of the surgical procedure, the plasma concentration of Adrenocorticotropic Hormone (ACTH) and cortisol increases [3,4]. Cortisol promotes protein breakdown, lipolysis, and gluconeogenesis and inhibits cellular glucose utilisation. Thus, the blood glucose concentration rises synchronously with an increase in the level of serum cortisol [5]. All these contribute towards perioperative neuroendocrine response. Therefore, the level of glucose in the blood is directly influenced by cortisol levels. Meanwhile, blood glucose measurement is a simple, reliable method and involves low cost for the evaluation of stress response.

The choices of premedication, anaesthetic agents, and techniques modulate the pathophysiological pathways and influence this neurohormonal stress response. Dex, an alpha 2 agonist, initially used for Intensive Care Unit (ICU) sedation, is being used as an anaesthetic adjuvant in different doses and by different routes. Studies have shown that there is a reduction of dose requirement of the induction agent as well as opioids and prevention of perioperative stress-induced haemodynamic changes with the use of Dex [6,7].

A previous report showed that perioperative administration of Dex mitigated the stress response by decreasing the blood levels of epinephrine, norepinephrine, cortisol, and blood glucose in patients undergoing surgery [4]. Dex administration also elicits anti-inflammatory effects by reducing the level of proinflammatory cytokines and C-reactive protein and enhances the activity of B cells and CD4+ cells, as well as the ratio of CD4+:CD8+ and Th1:Th2. Thus, these effects of Dex in patients undergoing surgery are mediated through the hypothalamic pituitary adrenal axis and sympathoadrenal tone [8].

So, the present study was conducted to evaluate the Dex premedication to attenuate the blood glucose level changes, which was the primary outcome, and the secondary outcome was to evaluate the haemodynamic changes before and after administration of Dex at various time intervals.

MATERIALS AND METHODS

It was a randomised controlled, double-blind study conducted at the Department of Anaesthesiology, M.K.C.G Medical College and Hospital, Berhampur, Odisha, India, during the period November 2017 to October 2019. Approval from the hospital Ethical Committee was obtained (vide letter no. 525/Chairman-IEC). Written informed consent was obtained from all patients. Both patients and anaesthesiologists involved in the study were blinded.

Sample size calculation: To calculate the sample size in an Randomised Controlled Trial (RCT), the authors need to consider the power, the effect size, the standard deviation, and the dropout rate. One of the methods to do this is to use the formula for Analysis of Covariance (ANCOVA):

$$n=2\times\{(Z\alpha/2\ Z\beta)^2\times\sigma^2\}/\{(\mu1-\mu2)^2\times(1+r)\}$$

where,

- n is the sample size per group,
- $Z\alpha/2$ is the critical value of the normal distribution at $\alpha/2$ (for a confidence level of 95%, α is 0.05 and the critical value is 1.96),
- $Z\beta$ is the critical value of the normal distribution at β (for a power of 80%, β is 0.20 and the critical value is 0.84),
- σ is the standard deviation of the outcome variable,
- $\mu1$ and $\mu2$ are the means of the outcome variable in the control and intervention groups, respectively, and
- r is the dropout rate.

Plugging in the given values

$n=2\times\{(1.96+0.84)^2\times15^2\}/\{(11)^2\times(1+0.12)\}$

$n=39.6$

Rounding up to the nearest integer, we get n=40 per group.

Inclusion criteria: The study population constituted 80 patients of both sexes belonging to ASA grades I and II in the age group of 18-60 years. All of them were posted for routine laparoscopic surgeries under general anaesthesia.

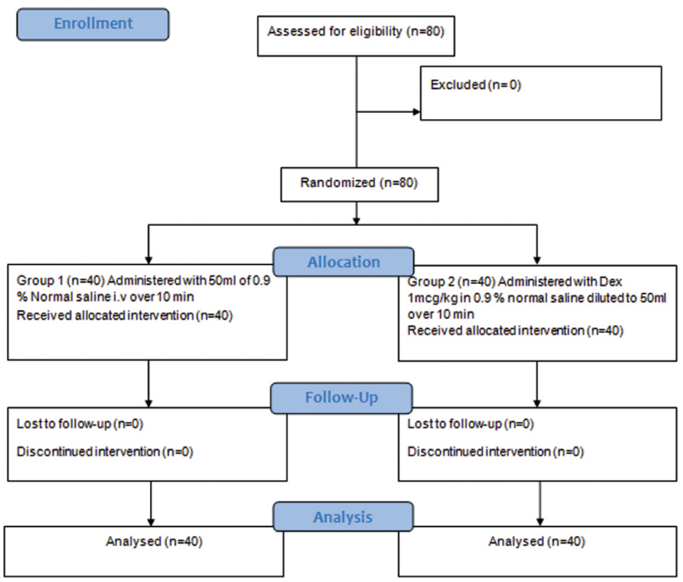
Exclusion criteria: Patients suffering from diabetes, hypertension, renal and other endocrinal diseases, or receiving drugs known to affect sympathetic response or hormonal response were excluded from the study. Cases in which the intubation attempts were more than one and the cases which were converted to open laparotomy were also excluded. Patients with any known hypersensitivity to any of the drugs used were not included in the study.

Study Procedure

All the patients underwent scrutiny, physical examination, and investigation for a complete haemogram, routine examination of urine and stool, blood urea and serum creatinine, blood sugar, cardiological evaluation, and chest X-ray before the operation. They were advised to take Tab Alprazolam (0.25 mg) and Tab Ranitidine (150 mg) the night before surgery and asked to remain fasting after midnight. In order to avoid diurnal variations in hormones affecting our study, these cases were scheduled as the first morning cases.

On the day of surgery, the preoperative baseline blood sugar value was estimated in the preoperating preparation room. In the operating room, baseline HR and blood pressure values were recorded. The study medications were prepared and administered by individuals not associated with data observation and analysis. Laryngoscopy and intubation were performed by an experienced anaesthetist, and cases needing more than two attempts for intubation were excluded from the study.

The patients were divided into two groups as follows, and the Consolidated Standards of Reporting Trials (CONSORT) flow of the study participants was shown in [Table/Fig-1].



[Table/Fig-1]: CONSORT flow diagram.

Group-I (n=40): Administered with 50 mL of 0.9% normal saline i.v. over 10 min [9].

Group-II (n=40): Administered with Dexmedetomidine 1 mcg/kg in 0.9% normal saline diluted to 50 mL over 10 minutes [9].

Patients were premedicated with Inj. Glycopyrrolate (0.2 mg), Inj. Midazolam (0.02 mg/kg), Inj. Butorphanol (0.03 mg/kg) i.v. Anaesthesia was induced with Inj. Thiopentone (5 mg/kg). Oro-tracheal intubation with an appropriate size low-pressure high-volume cuffed PVC endotracheal tube was done under direct laryngoscopy facilitated by Inj. Vecuronium bromide (0.1 mg/kg). Anaesthesia was maintained with an oxygen and nitrous oxide mixture (2:3 ratio) and Isoflurane 1-1.5%, and intermittent i.v. Inj. Vecuronium. Patients were manually ventilated in a closed circuit with carbon dioxide absorption. At the end of surgery, anaesthetics were withdrawn. Residual neuromuscular paralysis was reversed by intravenous Inj. Neostigmine (0.05 mg/kg) mixed with Inj. Glycopyrrolate (0.01 mg/kg). Haemodynamic variations were recorded intraoperatively at regular intervals up to 2.5 hours into the postoperative period.

Following the preoperative baseline evaluation, blood sugar was again estimated 30 minutes after surgical incision, one hour after extubation, and 2.5 hours following surgery. The haemodynamic variables such as SBP, DBP, HR, and MAP were also measured preoperatively, 30 minutes after surgical incision, one hour after extubation, and 2.5 hours following surgery.

STATISTICAL ANALYSIS

The data obtained were statistically analysed using the Statistical Package for the Social Sciences software (version 16.0). As the data were found to be normally distributed, unpaired Student's t-tests were applied for continuous variables, and $p<0.05$ was considered to be statistically significant.

RESULTS

The demographics and clinical characteristics of the patients were similar between the groups and were not significant. The results are shown in [Table/Fig-2]. The mean age of the patients in Group-I and Group-II was 48.58±5.89 and 46.25±6.51 years, respectively,

Parameters	Group-I	Group-II	p-value
Age (years)	48.58±5.89	46.25±6.51	0.09
Weight (kg)	57.07±7.84	56.8±7.4	0.87
Gender (M/F)	13/27	9/31	0.54
ASA status (I/II)	22/18	18/22	0.6

[Table/Fig-2]: Demographics and clinical characteristics between the groups.
ASA: American society of anaesthesiologists; p>0.05 Not significant

and it was not significant. The weight of the patients in Group-I and Group-II was 57.07±7.84 and 56.8±7.4 kg, and it was not significant. The majority of the patients in Group-I had ASA status I (n=22), and in Group-II had ASA status II (n=22), respectively, and it was not significant between the groups.

The comparison of blood glucose levels between the groups is shown in [Table/Fig-3]. There were no marked differences in the baseline blood sugar level between the groups, and it was not significant (p=0.76). However, 30 minutes after surgical incision, one hour, and 2.5 hours following extubation, the blood glucose level was significantly lower in Group-II Dexmedetomidine administered patients compared to Group-I (p<0.001).

Blood glucose levels (mg/dL)	Group-I	Group-II	p-value
Preoperative	86.30±9.74	85.70±8.47	0.76
30 min after surgical incision	135.95±14.4	104.35±13.58	<0.001*
After extubation	137.38±7.93	97.15±5.86	<0.001*
1 hour postop	138.08±8.84	98.4±7.45	<0.001*
2.5 hours postop	137.70±15.13	94.08±7.37	<0.001*

[Table/Fig-3]: Mean blood glucose level between the groups.
Unpaired student's t-test, *denoted p-value <0.05; p>0.05 Non-significant

The SBP and DBP variations between both the groups are shown in [Table/Fig-4]. The mean SBP and DBP were lower in Group-II compared to Group-I. The difference between baseline values was statistically non significant with p-values of 0.888 and 0.188 for SBP, respectively (p>0.05). But in the subsequent comparisons at one minute, five minutes, 15 minutes after intubation, 30 minutes after surgical incision, one hour after extubation, and 2.5 hours following surgery; the p-values were <0.05 (statistically highly significant).

Variables	Group-I	Group-II	p-value
SBP (mmHg)			
Preoperative	124.08±3.91	123.95±4.01	0.88
1 min after intubation	137.80±3.18	116.28±5.99	<0.05*
5 min after intubation	131.63±3.31	113.23±7.04	<0.05*
15 min after intubation	128.95±5.17	112.78±5.98	<0.05*
30 min after surgical incision	126.28±5.28	114.68±6.20	<0.05*
After extubation	131.68±3.66	117.80±19.85	<0.05*
1 h post-op	129.97±2.51	118.90±4.66	<0.05*
2.5 h post-op	129.85±3.19	120.17±4.88	<0.05*
DBP (mmHg)			
Preoperative	76.80±4.90	78.30±5.19	0.18
1 min after intubation	99.38±2.47	76.80±4.82	<0.05*
5 min after intubation	99.23±2.50	80.90±4.50	<0.05*
15 min after intubation	96.90±4.13	82.45±5.50	<0.05*
30 min after surgical incision	92.63±5.14	81.05±4.92	<0.05*
After extubation	88.48±3.78	76.78±4.73	<0.05*
1 h postoperative	81.42±4.13	73.82±3.44	<0.05*
2.5 h postoperative	80.85±4.48	71.15±2.66	<0.05*

[Table/Fig-4]: Blood pressure changes between the groups.
Unpaired student's t-test, *denoted p-value <0.05; p>0.05 Non-significant

The MAP variation between both the groups is shown in [Table/Fig-5]. The mean MAP was lower in Group-II compared to Group-I. The difference between baseline values was non-significant between the groups (p=0.56). But in the subsequent comparisons at one minute, five minutes, 15 minutes after intubation, 30 minutes after surgical incision, one hour after extubation, and 2.5 hours following surgery, the MAP values were significantly lower in Group-II Dexmedetomidine-treated patients compared to the group, and it was significant (p<0.05).

There was a significant reduction in HR following the loading dose of Dexmedetomidine, at one minute, five minutes, 15 minutes after intubation, 30 minutes after surgical incision, after extubation, one hour, and 2.5 hours following surgery in Group-II (p<0.05) compared to Group-I, where there was an increase in HR following the various interventions of anaesthesia and surgery. The results are shown in [Table/Fig-6].

MAP (mmHg)	Group-I	Group-II	p-value
Preoperative	92.65±3.40	93.32±3.98	0.56
1 min after intubation	112.07±2.04	89.92±3.65	<0.05*
5 min after intubation	110.02±1.87	91.67±4.14	<0.05*
15 min after intubation	107.52±3.58	92.52±4.00	<0.05*
30 min after surgical incision	103.87±4.21	92.7±3.50	<0.05*
After extubation	102.85±2.87	91.4±4.19	<0.05*
1h postoperative	97.60±3.13	88.85±2.86	<0.05*
2.5h postoperative	97.25±3.44	87.42±2.5	<0.05*

[Table/Fig-5]: Mean arterial changes between the groups.
Unpaired student's t-test, *denoted p-value <0.05; p>0.05 Non-significant

Heart Rate (HR) (bpm)	Group-I	Group-II	p-value
Preoperative	88.45±4.72	88.05±4.96	0.42
1 min after intubation	94.60±4.70	79.98±3.49	<0.05*
5 min after intubation	89.05±4.12	75.10±4.16	<0.05*
15 min after intubation	83.55±3.39	72.28±3.05	<0.05*
30 min after surgical incision	85.55±4.26	74.28±3.64	<0.05*
After extubation	92.98±5.22	81.05±4.92	<0.05*
1 h post-op	91.35±4.74	79.55±4.17	<0.05*
2.5 h post-op	89.85±5.22	73.92±3.47	<0.05*

[Table/Fig-6]: Mean Heart Rate (HR) changes between the groups.
Unpaired student's t-test, *denoted p-value <0.05; p>0.05 Non-significant

DISCUSSION

The neuroendocrine response, or stress response, during surgery is a frequently encountered condition and has significant effects on patient-related outcomes. Blood glucose level is one of the indirect measures that reflect the neuroendocrine response during surgery, and so anaesthesia techniques can be modified or changed accordingly [1]. Increased blood glucose after surgical incision displayed a good correlation with the extent of tissue injury during surgery [10].

Earlier reports showed that the clinical utility of an α2-adrenergic receptor agonist decreases this response, but the activation of α2-adrenergic receptors leads to the inhibition of insulin release [11,12]. Dexmedetomidine (Dex) is a selective α2-adrenergic receptor agonist with a greater affinity towards the α2 receptor and thus elicits a potential effect on glucose levels [13]. Previous reports showed that perioperative administration of Dex could attenuate stress and also decrease the levels of stress inducers such as catecholamines and cortisol [14,15]. In spine and abdominal surgery, Dex treatment reduces the incidence of hyperglycaemia and also minimises the variation in glucose levels [16]. Therefore, the present study was carried out to find the effect of Dex on blood glucose levels and haemodynamic parameters during the perioperative period in patients undergoing laparoscopic surgeries under general anaesthesia.

In the present study, there was a significant decrease in blood glucose levels following Dex infusion in Group-II patients at 30 minutes after surgery, after extubation, and 1.5 and 2 hours after extubation when compared to Group-II patients infused with saline. Similar to the present study report, Li CJ et al., reported that the glycaemic variation in dexmedetomidine was slightly lower as compared to the control group, and it was significant (p=0.03)[17]. In another study done by Mostafa RH et al., in patients undergoing laparoscopic bariatric surgery, Dex at a dose of 1 μg/kg reduced the blood glucose level at 30 minutes after the initiation of surgery (88.77±14.46 vs 95.3±14.2; p=0.08) but was not significant when compared to the control group [18]. However, at one hour

(84.27±20.1 vs 101.3±14.6 mg/dL; p<0.001), two hours (81.57±19.3 vs 103.6±14.36 mg/dL; p<0.001), and six hours (82.53±12.95 vs 106.97±15.2 mg/dL; p<0.001), there was a significant decrease in blood glucose level in the Dex group compared to the control group, and it was significant. In Kameshwar YV and Upadhyay MR study, Dex administration showed a significant decrease in blood glucose level 30 minutes after laryngoscopy and intubation (117.3 vs 156.3 mg/dL; p<0.001), one hour postoperative (103.8 vs 136.7 mg/dL; p<0.001) and 2nd hour postoperative (106 vs 119.9 mg/dL; p<0.001) when compared to placebo [19]. In Harsoor SS et al., study Dex administration showed a significant decrease in blood glucose level at 1 hour postoperative when compared to placebo (118.2±16.24 vs 136.95±19.76; p<0.0001) [20].

The haemodynamic stress response is a common complication during laparoscopic cholecystectomy, laparoscopic hysterectomy, or laparoscopic nephrectomy surgeries [21]. Mounting studies showed that Dex attenuates the intraoperative stress response and maintains haemodynamic stability during laparoscopic surgeries [22,23]. Likewise, in the present study, Dex infusion significantly reduced the SBP, DBP, MAP, and HR at 1, 5, and 15 minutes after intubation, 30 minutes after surgical incision, after extubation and 1.5 and 2.5 postoperatively when compared to saline-infused patients (p<0.05). In Zheng L et al., study Dex significantly decreased the HR and blood pressure during the perioperative period as compared to remifentanil and sufentanyl in patients undergoing radical gastrectomy for cancer [24]. Likewise, in Mostafa RH et al., study Dex administration significantly reduced the HR and MAP starting from postinduction till 120 minutes of the surgery period (p<0.001) [18].

Limitation(s)

The major limitation of the study was that simultaneous serum cortisol estimation to correlate with perioperative hyperglycaemia was not measured. Additionally, intraoperative Bispectral Index (BIS) monitoring for the depth of anaesthesia would have helped to assess the stress level and provided better results.

CONCLUSION(S)

Dexmedetomidine administration significantly maintained the blood glucose level until the end of the postoperative period and thus attenuated the stress response. Additionally, it affected the haemodynamic variables such as SBP, DBP, MAP, and HR, respectively. Therefore, Dex will be a suitable agent to reduce the stress response in patients undergoing laparoscopic surgery, and in addition, it also maintained the blunting of the laparoscopic-mediated haemodynamic changes.

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