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ASSESMENT OF SERUM NOREPHINEPHRINE AND SERUM GLUCOSE LEVEL DURING LAPAROSCOPIC HYSTERECTOMY USING DIFFERENT ANAESTHETIC TECHNIQUES

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ABSTRACT

Background: The use of laparoscopy has revolutionised the surgical field with its advantages of reduced morbidity with early recovery, it is associated with reduced surgical trauma, and therefore with a less acute phase response, as compared with open surgery. Stress response to pneumoperitoneum in laparoscopic activates hypothalamic-pituitary-adrenal axis and the sympathetic nervous system with increase concentration of various stress hormones such as serum norepinephrine and decrease response to insulin.

Material and methods: This is a prospective randomized study conducted at IMS & SUM hospital from January 2017 to December 2017. Patients undergoing elective laparoscopic hysterectomy over the study period were included and divided in two groups, Group A {n=50} received both General and Spinal anesthesia while Group B {n=50} received only General Anesthesia. Neuroendocrine Stress response to laparoscopic hysterectomy was studied by estimation of Serum Noradrenaline and serum glucose. Blood samples were collected at following time interval i.e. in the preoperative room BL, 5 min, 15 min, 30min, 45min and 60 min after pneumoperitoneum.

Result: There was significant increase in serum nor epinephrine and serum glucose level after the onset of pneumoperitoneum,than baseline level .The increase in stress hormones was statistically significant in Group receiving only General anaesthesia than in Group receiving both general anesthesia and subarachnoid block. Group A patients showed more stabilization of intraoperative neuroendocrine stress hormone than Group B.

Conclusion: Subarachnoid block combined with general anaesthesia could significantly reduce the stress reaction induced by pneumoperitoneum, less anaesthesia complications, smooth intraoperative blood flow.

KEYWORDS : Laparoscopic Hysterectomy, Noradrenaline, Glucose, Stress response, subarachnoid block, general anesthesia

INTRODUCTION

Laparoscopic surgery began with the advantage of fewer traumas, safety, less complications, shorter recovery period. It has been developed rapidly 1, 2. In order to meet the requirements of the operation and to eliminate the anxiety and fear, so that patients could stay in good condition, endotracheal intubation general anaesthesia were the traditional anaesthesia methods 3[,4]. A safety, steady and rapid recovery was the key to the process of anaesthesia in operation. The most important development in recently is, understanding the series of physiological changes (stress response) due to anesthesia and surgery.[5] The general stress response is broadly divided into acute phase and flow (hyperdynamic) phase. They involve wide spread endocrinal, metabolic and biochemical reactions throughout the body resulting changes in cardio-vascular, metabolic, fluid and electrolytes etc. It has been shown that the magnitude of stress response is directly related to the magnitude of injury[7], total operating time [8], and the amount of intraoperative blood loss[9] as well as to the degree of postoperative pain[10]. Among these stress responses, activation of hypothalamo-pituitary-adrenal (HPA) axis and resultant stimulation of glucocorticoid secretion seem to be of extreme importance.[16,17]

The stress response leads to secretion of many anabolic and catabolic hormones resulting in hyper metabolism, with the acceleration of most of the biochemical reactions [14.] resulted from decrease in insulin secretion and increase resistance. This results in catabolism of proteins, lipids and rise in blood glucose level. This may be beneficial in early state but when prolonged, may be detrimental to the patients. Increase plasma glucose concentrations are related to the intensity of the surgical injury; and follow closely with the increase in serum catecholamines. The changes are less marked with minor surgery. In laparoscopic hysterectomy plasma glucose concentrations can increase up to 140—200mg/dl and remain elevated for >24 h after surgery. The stress response to surgery initiates a predictable cascade of physiologic and metabolic events through direct activation of the sympathetic and somatic nervous system. The response begins with the initiation of anesthesia and lasts 3 to 4 days postoperatively.[5,6] other key factors induced by stress response are prostaglandins, serotonin, kinines and heat shock protein etc. Currently three main methods are available for modifying the response. 1. Spinal/ epidural anaesthesia for neuronal blockage. 2. Intravenous administration of large doses of potent opiate analgesics to block hypothalamic-pituitary function. 3. Use of agents to inhibit the secretion or action of the catabolic hormones, or by the infusion of anabolic hormones such as insulin.

Furthermore, it has been shown that the choice of anaesthetic technique may modulate the extent of such response [11, 12]. Decreasing the stress response to surgery and trauma is of high relevance to the anaesthesiologist, since it may allow complex operations in high risk patients. In upper abdominal surgery it is not possible to prevent pituitary and adrenal hormone response completely even with extensive neuroaxial blockade [14]. Clinical evidence shows that general anaesthesia plus subarachnoid block certainly reduces neuro-endocrine stress responses by stimulating, inhibiting or modulating the patho-physiological pathways which induce neurohumoral and immunologic alterations [14,15].

Material and Methods:

The study design is a prospective study which was undertaken in the IMS &SUM hospital Bhubaneswar Odisha from January 2017 to December 2017. The cases were chosen from the admitted patients in the Gynaecology indoor wards scheduled for elective laparoscopic hysterectomy. After obtaining approval from institutional ethical committee. The purpose and procedure of the study was explained to all patients and written, informed consent for anaesthesia and the procedure was obtained.

Selection of cases

100 adult patients (A.S.A Grade I and II) of either sex, between 40 to 60 years of age, weighing between 42 to 64 kg scheduled for elective upper abdominal surgeries were selected randomly from indoor admittance. The patients selected were randomized into two demographically identical study groups of A, and B (with respect to age, and weight,).

They were assessed preoperatively and suitable cases were prepared for the operation and study. Patients with obesity (BMI >30 kg/m^2) and any history of hypertension, cardiovascular disorder, renal or hepatic dysfunction, endocrine or autonomic dysfunction, neuromuscular or neurological disorder, bleeding disorder, drugs or alcohol abuse, use of medication that affects hormonal or sympathetic response previous spine surgery and contraindicated for subarachnoid block were excluded from the study.

On arrival at preoperative room an 18 G intravenous cannula was inserted into right antecubital vein for obtaining blood sample and another one was inserted into the left cephalic vein near to wrist for administration of fluid and other medications. The patients were next brought to the operating theatre where they underwent anesthesia and surgery. The General anesthetic protocol for **Group B** was strictly maintained in all patients and consisted of an intravenous induction using thiopental sodium 5 mg/kg body weight, vecuronium 0.1 mg/kg body weight and fentanyl 1.5 µg/kg body weight. Once intubated with an endotracheal tube, anesthesia was maintained with inhaled O_2/N_2O (1:2) and appropriate dialling of Isoflurane. Anaesthesia is maintained with Isoflurane as required to ensure adequate depth of anesthesia assessed by BIS score.Vecuronium 0.02 mg/kg body weight every 20 minutes and fentanyl 0.5 µg/kg body weight every 30 minutes is continued until 20 minutes before the anticipated end of surgery. **Group A** patients were first administered subarachnoid block as per the following protocol .Intrathecally, all patients received 2 ml of 0.5% hyperbaric bupivacaine. Spinal anesthesia was performed in the sitting position using a 25-gauge Quincke's needle in the L3–L4 or L4–L5 interspace through midline approach under all aseptic conditions. It was followed by General Anesthesia administered as per the protocol received by Group B. SpO_2, ECG,Blood Pressure, temperature, sweating and tearing is monitored continuously. Temperature was maintained within normal limit. The patients received normal saline with appropriate volume as per 4-2-1 rule. After operation the patients were extubated with intravenous Neostigmine 0.05 mg/kg body weight and Atropine 0.02 mg/kg body weight. The time of introduction of anesthesia, incision, onset of pneumoperitoneum end of surgery and extubation was recorded properly.

The pneumoperitoneum pressure of two groups was kept at 12 mmHg during the operation, T0 (before pneumoperitoneum)T1 (5 min after pneumoperitoneum)T2 (15 min after pneumoperitoneum), T3 (30 min after pneumoperitoneum), T4 (45 min after pneumoperitoneum), and T5 (60 min after pneumoperitoneum) mean arterial pressure (MAP), saturation of pulse oximetry (SpO_2), heart rate (HR) and partial pressure of carbon dioxide in endexpiratory gas (PET CO_2) were continuously monitored before, during and after the operation; and the awakening time and flatus recovery time after the operation were recorded.

Statistical method

The measurement data was denoted by mean ± standard deviation (x ± s), Statistical analysis was done with student t test, and Chi-square test. All the analyses were done using statistical software SPSS 20.0. The associations were considered statistically significant if the p value < 0.05.

Sample collection

Three samples (5 ml) were collected through right handed cannula with all precautions. The first blood sample was drawn just before T0 (before pneumoperitoneum) T1 (5 min after pneumoperitoneum) T2 (15 min after pneumoperitoneum), T3 (30 min after pneumoperitoneum), T4 (45 min after pneumoperitoneum), and T5 (60 min after pneumoperitoneum. Two ml of blood from each sample was kept in a test tube containing sodium fluoride and potassium oxalate in 1:3 ratios to prevent glycolysis and coagulation and remaining blood was taken in a plain test tube. Both tubes were immediately placed into ice cold water. Serum norepinephrine, and plasma glucose samples were centrifuged at 2500 rpm for 10 minutes and analysed in department of Biochemistry as follows.

Serum concentration of norepinephrine (NE) were estimated by chemiluminescence immuno assay (CLIA) method using Cobas e411 fully autoanalyzer.

Statistical analysis was done with student t test, Fischer test, and Chi-square test. All the analyses were done using statistical software SPSS 20.0. The associations were considered statistically significant if the p value < 0.05.

Results

TABLE 1: Demographic details

		Group A (n=50)	Group B (n=50)	P value
Age (mean ± SD)		52± 6.3	50± 6.8	0.65
Range of age		40 - 60	40 - 60	
Weight (mean ± SD)		54.6± 7.2	52± 7.6	0.43
Range of weight		42 - 64	42 - 64	
ASA	Grade I	32	30	0.88
	Grade II	18	20	

* P value < 0.05 – significant

Table 2: Study of Total Duration of Surgery, baseline MAP, HR and duration of pneumoperitoneum in Different Study Groups

	Group A mean± SD	Group B mean± SD	P value
Total duration of Surgery (min)	70.6± 6.4	71.4± 5.7	0.78
Mean arterial pressure (mm of Hg)	100.4± 4.8	96.44± 10.65	0.6
Heart rate (bpm)	84.65± 4.8	81.43± 7.25	0.93
Pneumoperitoneum (Min) (mean ± SD)	62.3±3.6	61.8±3.3	0.27

* P value < 0.05 – significant

Table 3: Study of Mean Serum NE, and Plasma Glucose Level in Different Study Groups

	Serum Glucose level (mg/dl) – MEAN± S.D		Serum Noradrenaline level (pg/ml) – MEAN± S.D	
Time	Group A(n=50)	Group B(n=50)	Group A(n=50)	Group B(n=50)
T0	98.0± 18.65	96.43± 21.56	465.43± 23.69	478.39± 21.26
T1	104.32± 23.53	108.74± 24.64	496.68± 19.61	567.54± 22.76
T2	108.76± 21.96	118.43± 20.78	532.85± 21.76	596.43± 24.4
T3	114.65± 24.0	126.84± 23.53	585.33± 23.89	624.53± 26.78
T4	122.83± 22.62	132.74± 24.48	602.54± 19.3	689.51± 22.41
T5	125.42± 24.86	138.37± 23.8	632.78± 23.62	708.6± 25.89

Serum norephinephrine and serum glucose level atT0 (before pneumoperitoneum) T1 (5 min pneumoperitoneum) T2 (15 min pneumoperitoneum), T3 (30 min pneumoperitoneum), T4 (45 min pneumoperitoneum), and T5 (60 min pneumoperitoneum.

In total, 100 patients were recruited in the study. The sample size was 50 in each group Patient demographics, [Table 1]. There was no significant difference in patient's demographic profile in two groups. Similarly total duration of surgery, baseline heart rate, mean arterial pressure and duration of pneumoperitoneum in (Table 2) showed no statistical significance P>0.05 in two Groups.

The two groups were compared for serum glucose and serum norephinephrine level recorded at six preset times atT0 (before pneumoperitoneum) T1 (5 min pneumoperitoneum) T2 (15 min pneumoperitoneum), T3 (30 min pneumoperitoneum), T4 (45 min pneumoperitoneum), and T5 (60 min pneumoperitoneum.

There was significant increase in serum glucose level p<0.05 after onset of pneumoperitoneum in two groups compared to T0 (before pneumoperitoneum). The increase of serum glucose was more in Group B compared to Group A after the onset of pneumoperitoneum with peak reaching maximum at 60 min pneumoperitoneum. The intragroup as well intergroup comparison of serum glucose level showed a statistically significant with p>0.05.

Similarly serum norephinephrine level were significantly raised p<0.05 after the onset of pneumoperitoneum with peak reaching maximum at 60 min pneumoperitoneum .On inter group comparison the rise of serum norephinephrine is more in Group B than Group A The intragroup as well intergroup comparison of serum norephinephrine level showed a statistically significant rise in Group B than Group A with p>0.05.

Discussion

The combination of general anaesthesia and subarachnoid block may easily adapt the patient to pathological, physiological changes. It could be explained by the subarachnoid block during the operation obstructing the sensory nerve excitation function of cardiac sympathetic nerve and trachea at the related part, weakening the mechanical stimulation to tracheal mucosa in tracheal intubation, and significantly suppressing the rise of plasma β-endorphin levels, catecholamine and other stress hormones [14]. And the subarachnoid block obstructs the efferent impulse of sympathetic-adrenal medulla and suppresses the noxious stimulation, resulting in the excitation of hypothalamic-pituitary-adrenal axis and the decrease of adrenaline, noradrenaline and cortisol secretion.

Rothenberg and Loh-Trivedi documented that laparoscopic surgery elicits a stress response that is directly proportional to the degree of tissue trauma [15]. Another study suggests that the principal mechanism lies with the elevation of sympathetic tone with a consequent release of cortisol and catecholamines during surgery [16]. These hormones, in turn, lead to relative insulin hyposecretion, insulin resistance, and increased protein catabolism. Anesthesia also principally effects glucose metabolism through the modulation of sympathetic tone; however, *in vitro* evidence exists that insulin secretion is suppressed by inhalational agents with consequent increase in serum glucose level.

Normotensive patients can develop sympathetic overactivity during Intraoperative period due to pain, light plane of anesthesia, and hypercapnia. This adrenergic response is caused by nociceptive pathways and humoral mediators originating from the surgical site, which are detrimental in elderly and hemodynamically compromised patients. Numerous surgical and anesthetic techniques have been used to reduce the incidence and severity of these hemodynamic responses. Clinical evidence showed that the choice of the anesthetic techniques influences the stress response by modulating the pathophysiological pathways that induce neurohormonal and immunological alterations[17,18,19]

In ***Aono et tal*** [20]there occur significant increase in catecholamines level in patients receiving general anesthesia only; catecholamines did not increase significantly in patients receiving general anesthesia combined with central neuraxial block, this observation is consistent with our study where serum nor ephinephrine increased significantly in patients receiving only general anesthesia than other group.

In Mikami et tal [21] we found that the plasma concentrations of epinephrine and norepinephrine remained unchanged after the insertion of a Veress needle but increased significantly immediately after creation of pneumoperitoneum at 15 mm Hg of intra-abdominal pressure (IAP) in laparoscopic surgery,this observation is consistent with our study where after the onset of pneumoperitoneum the serum catecholamines and serum glucose were significantly elevated in both groups ,and there occurs significant increase in serum stress hormone level in Group receiving only General anesthesia.

In *Gupta et tal* [22] Blood glucose concentration has shown 20% increase after surgery. The differences between groups were statistically significant as observed by analyzing the variation of serial perioperative blood glucose estimation. Patients who have received both general and central neuraxial block had attenuated the hemodynamic and neuroendocrine stress response of pneumoperitoneum than patients receiving only general anesthesia.This observation is consistent with our study.

CONCLUSION

Patients who have received both general and central neuraxial block has effectively modulated the neuroendocrine stress response induced by surgery and pneumoperitoneum as assessed by analyzing the variation of blood glucose levels and serum noradrenaline level . Modulating the stress response to surgery might enable laparoscopic hysterectomy in obese, hypertensive, and cardiac compromised patients, and may be a key factor in improving outcome of these patients.

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