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Clinical Science

Cortisol and Insulin Levels during Major Gynaecological Operations: The influence of Two Anaesthetic Techniques

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Key words: Gyneacological Surgery; Combined spinal epidural Anaesthesia; General Anaesthesia; Cortisol; Insulin; Glucose.

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Abstract

BACKGROUND: Metabolic and hormonal changes are noticed within the first few hours after surgical injury. These changes are influenced by the intensity, duration, type of injury, and the anaesthetic techniques.

AIM: To investigate the effects of anaesthesia on cortisol, insulin and glucose concentrations during major gynaecological surgeries.

METHODS: Forty patients were randomly allotted to receive either balanced general anaesthesia (n=20) or combined spinal epidural anaesthesia extending from T5 to S5 (n=20). Blood samples were collected for cortisol and glucose at preinduction, 1, 3 and 4 hours, and for insulin at preinduction and 24 hours after incision.

RESULTS: The mean cortisol concentration was significantly lower 4 hours after incision with combined spinal epidural anaesthesia (19.96 ± 11.32) µg/dl than with balanced general anaesthesia (38.94 ± 10.6) µg/dl, $p = 0.018$. The mean insulin concentration, 24 hours after incision decreased with combined spinal epidural anaesthesia, but increased with balanced general anaesthesia $p = 0.403$. The mean glucose concentrations were significantly lower with combined spinal epidural anaesthesia than with balanced general anaesthesia during the 4 hour study period $p \leq 0.05$.

CONCLUSION: combined spinal epidural anaesthesia extending from T5 to S5 resulted in lower cortisol, insulin and glucose concentrations during major gynaecological surgeries. This may be of benefit in patients scheduled for surgical operations below the umbilicus.

Introduction

The stress response is a result of hormonal and metabolic changes after injury [1]. Cortisol is secreted by the adrenal cortex secondary to stimulation by adrenocorticotrophic hormone (ACTH), a feedback mechanism operates so that increased levels of circulating cortisol inhibit further secretion of ACTH [2, 3]. However, this control mechanism appears to be ineffective after injury so that concentration of both hormones remains high [1, 2]. There is an initial suppression of insulin after induction of anaesthesia, which is followed by a period of increase secretion, during this period the cells of the body fail to respond to insulin, and hyperglycaemia persists [2]. The blood glucose concentration increases after surgical incision secondary to the release of counter-regulatory hormones such as cortisol, glucagon, epinephrine, and norepinephrine [1].

In fasting non-diabetic patients undergoing elective intra-abdominal operation, the blood glucose can increase up to a value of 7-10 mmol/L, and in cardiac operation, up to a value of 10-12 mmol/L [3,4]. Balanced general anaesthesia, which is achievable by the careful titration of inhalational agents and opioids, use of cardiostable drugs and the maintenance of adequate depth of anaesthesia help to attenuate the stress response [2]. Spinal and, or, epidural blockade extending from dermatome segment T_4 to S_5, before surgical incision has been reported to prevent the endocrine and metabolic response to surgical operation in the pelvis and lower limbs [2, 5].

The use of combined spinal epidural anaesthesia as a technique of choice for major gynaecological operation is on the increase because of the advantage of a rapid, dense block with the spinal anaesthesia, while the epidural anaesthesia offers prolongation of duration of anaesthesia and postoperative analgesia via the epidural catheter. The use of combined spinal epidural in patients with huge fibromyoma is not routinely done at our institution. The size of the fibroid may prolong the duration of operation, and thus increase the stress response. There is also erratic supply of long acting opioids in our country, which limits its use for perioperative analgesia. The administration of opioids has been reported to minimise the secretion of hormones during operation.

We compared the modulating effect of balanced general anaesthesia and combined spinal epidural anaesthesia on stress response to major gynaecological surgeries in female Nigerians with huge fibromyoma greater than 20 weeks gestation.

Patients and Methods

The approval of the Human Research and Ethics Committee of the Lagos University Teaching Hospital, and written informed consents were obtained. A sample of 20 patients in each group was required to detect a difference between the two groups using a power of 80% and $\alpha = 0.05$. This was based on a randomized trial comparing intraoperative cortisol changes during general anaesthesia and combined spinal epidural anaesthesia [6]. Forty ASA I and II status patients, aged between 20-60 years scheduled for elective myomectomy or total abdominal hysterectomy were recruited. Randomization was performed using the sealed envelope technique. Exclusion criteria included BMI <19.9 kg/m^2 or >39.9 kg/m^2, and history of endocrine, renal, cardiac or neurological diseases. In addition, patients on adrenergic blockers or corticosteroid therapy, hypersensitivity to lidocaine and bupivacaine or contraindications to central neuraxial anaesthesia were excluded. All patients received premedication (oral diazepam 10 mg and ranitidine 150 mg) nocte, and on call to the theatre. All operations commenced between 8:30 and 10:00 hours.

In the combined spinal epidural anaesthesia group, all patients were preload with 0.9% normal saline (10 ml/kg) over 20 minutes. With the patient in the sitting position, the epidural catheter was inserted into the lumbar third/fourth (L_3/L_4) interspace using the loss of resistance to saline technique via a 16 G Tuohy needle. After the depth of the epidural space was noted, 3-4 cm of epidural catheter was inserted. A test dose of 4 mls of preservative free 1% lidocaine in 1:200,000 epinephrine (Rotex Medica, Trittau Germany) was injected to exclude intrathecal or intravenous catheter insertion. Spinal anaesthesia was then induced with 0.2 mg/kg of 0.5% heavy bupivacaine (Marcain Astra Zeneca UK), the preservative free fentanyl 25 μg into the subarachnoid space in the lumbar fourth/fifth (L_4-L_5) interspace using a 26 gauge pencil point spinal needle via an introducer. The patients were re-positioned supine and the level of the block was confirmed using the loss of sensation to pin prick. All patients remained in the recumbent position until the sensory level progressed to the fifth/sixth thoracic dermatome (T_5-T_6).

Epidural anaesthesia was initiated when there was a two segmental regression of sensory block with the injection of 5mls of 0.5% plain bupivacaine into the epidural space after negative aspiration for blood and cerebrospinal fluid. Thereafter, boluses of 0.5% plain bupivacaine (5 ml) with fentanyl 15 μg were administered every 30 minutes for 1 hour, and subsequently 3 mls of 0.5% bupivacaine combined with fentanyl 3 μg every 30 minutes till the end of the operation. The level of the sensory block was assessed every 15 minutes till the end of operation, however; if the sensory level was still at T_5/T_6 dermatome, the epidural dose was missed. Postoperative analgesia was continued with injection of 5 mls of 0.125% plain bupivacaine and 5 μg of fentanyl 4 hourly for 24 hours.

In the balanced general anaesthesia group, all patients were preoxygenated with 100% oxygen for 3-5 minutes. Anaesthesia was induced with IV propofol 2 mg/kg and fentanyl 1.5 μg/kg, and endotracheal intubation was facilitated with pancuronium 0.1 mg/kg. Anaesthesia was maintained with isoflurane 1.0-2.5% in 100% oxygen via a closed circuit system. All patients were ventilated using intermittent positive pressure ventilation via a Drager Fabius Plus mechanical ventilator.

Analgesia was provided with IV fentanyl 1 μg/kg 30 minutes after induction and 0.5 μg/kg at 30 minute intervals for one hour. In addition, all patients received IV paracetamol 15 mg/kg, and diclofenac 1 mg/kg. At the end of operation, residual muscle paralysis was reversed with atropine 0.02 mg/kg and neostigmine 0.04 mg/kg. Postoperative analgesia was continued with IV pentazocine 0.5 mg/kg 6 hourly, and diclofenac 1 mg/kg 8 hourly for 48 hours.

Standard haemodynamic monitoring was instituted in all patients with a multiparameter monitor (Datex Ohmeda Cardiocap 7100), monitoring consisted of a non-invasive blood pressure, five-lead electrocardiograph, oxygen saturation, end tidal carbon dioxide and temperature. Fluid therapy included corrections for preoperative deficit, maintenance fluids and replacement of ongoing losses. Maintenance fluid was administered as per standard protocol and blood loss was replaced with colloids (Isoplasma).

Preinduction blood samples were withdrawn between 8:30 and 10:30 hours after an overnight fast.

Other samples were withdrawn 1, 3 and 4 hours after surgical incision, while that for insulin was withdrawn at 24 hours after surgical incision. Blood samples were immediately centrifuged at 4°C (3000 g; 10 minutes), and the obtained plasma stored at -20°C until analysis. On the day of analysis, the blood samples and reagent were kept for 15-30 minutes to reach a temperature of 18-24°C. Glucose analysis was performed by enzymatic oxidation in the presence of glucose oxidase. Cortisol and insulin analysis was done using enzyme-linked immunosorbant assay (ELISA) techniques. The reference interval for serum glucose was 3.9-5.8 mmol/L, plasma cortisol - 3.95-27.23 µg/dl for AM samples and 1.45-10.41 µg/dl for PM samples; fasting plasma insulin concentration 5-35 µIU/ml [7-9].

The primary outcome of the study determined and compared the effect of balanced general anaesthesia and combined spinal epidural anaesthesia on cortisol and insulin levels in response to major gynaecological surgeries. The secondary outcome determined and compared the effect of balanced general anaesthesia and combined spinal epidural anaesthesia on glucose levels in response to major gynaecological surgeries.

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS®) for windows 17 computer Software Program. Results were presented as mean ± SD, frequency and percentage. The differences in means between the two groups were analysed using the Student independent t-test, a p value less than 0.05 was considered significant.

For the purpose of this study, the following definitions were used: Hypotension - SBP <90 mmHg or a 30% decrease from baseline BP or MAP <70 mmHg [10]. Hypotension was treated with a bolus of 200 ml of Isoplasma solution, if the hypotension persisted for greater than 5 minutes, IV ephedrine 0.01 mg/kg was given [10]; Severe bradycardia - HR below 50 bpm, which was treated with 0.01 mg/kg atropine [10].

Results

There was no difference between the two groups in terms of mean age, weight, height, body mass index (BMI) and haematocrit, the duration of operation, anaesthesia and fasting (p >0.05).

Thirty-one patients (77.5%) had myomectomy and nine patients (22.5%) had total abdominal hysterectomy (TAH). The Myomectomy:TAH ratio in combined spinal epidural anaesthesia was 19:1, and in balanced general anaesthesia group was 12:8.

Table 1: The demographic and clinical characteristics of patients. Values presented as mean ± SD.

Variables	Combined Spinal Epidural Anaesthesia Group Mean ± SD, (n=20)	Balanced General Anaesthesia Group Mean ± SD, (n=20)	p value
Age (years)	39.50 ± 9.13	37.38 ± 6.49	0.392
Weight (kg)	67.51 ± 10.47	63.46 ± 10.84	0.233
Height (m)	1.63 ± 0.70	1.60 ± 0.72	0.153
BMI (kg/m^2)	24.93 ± 3.73	24.71 ± 3.79	0.855
Haematocrit (%)	33.99 ± 2.35	34.05 ± 3.4	0.957
Duration of anaesthesia (min)	178.23 ± 34.68	185.65 ± 37.14	0.166
Duration of operation (min)	151.21 ± 38.15	167.81 ± 37.09	0.617
Duration of fasting (min)	467.6 ± 34.87	458.9 ± 44.34	0.829

The mean cortisol concentration, 4 hours after incision was significantly lower in the combined spinal epidural anaesthesia group (19.96 ± 11.32) µg/dl versus balanced general anaesthesia group (38.94 ± 10.6) µg/dl, p = 0.018 (Fig. 1).

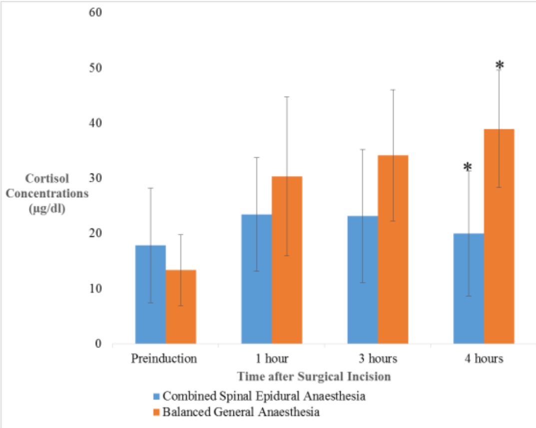

Figure 1: The effects of combined spinal epidural anaesthesia versus balanced general anaesthesia on mean cortisol concentrations during major gynaecological operations. Values presented as mean ±SD (error bars).

The mean insulin concentration, 24 hours after incision decreased in combined spinal epidural anaesthesia group (4.69 ± 2.24), but increased in balanced general anaesthesia group (5.04 ± 1.06) uIU/ml, however, the difference was insignificant, p = 0.403. The mean glucose concentrations were significantly lower in the combined spinal epidural anaesthesia group during the 4 hour study period.

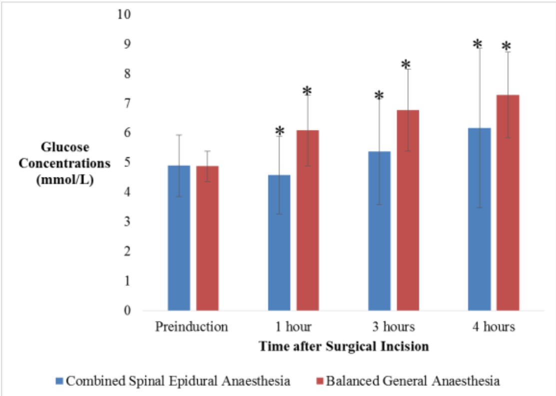

Figure 2: The effects of combined spinal epidural anaesthesia versus balanced general anaesthesia on mean glucose concentrations during major gynaecological pperations. Values presented as mean ± SD (error bars).

Discussion

Surgical injury activates the hypothalamic-pituitary-adrenal axis causing a stress response [1-2]. The degree of stress response may be evaluated by measuring hormonal secretions within few hours of surgical injury [1-2]. This study has demonstrated that combined spinal epidural anaesthesia compared with balanced general anaesthesia resulted in lower concentrations of cortisol, and glucose in the 4 hour study period from skin incision in patients undergoing major gynaecological operations. This observation is similar to previous documentations during hysterectomy and prostatectomy [11-13], as well as during hip arthroplasty [7]. The degree of change in cortisol levels depend on a number of confounding factors. For example the cortisol levels in our study were higher than values observed during hysterectomy and cystoprostatectomy [11-13], which was due to a longer duration of operation and anaesthesia. However, lower levels of cortisol was reported when we compared our values to those obtained in ASA III and IV patients who had colonic operation [14]. Other factors that may influence the secretion of cortisol include blood loss, co-existing medical conditions or the pre-morbid state of the patient and the choice of anaesthesia.

In the balanced general anaesthesia group, the cortisol level doubled 1 hour after incision and increased by threefold 4 hours after incision. This observation is in agreement with previous documentation of a three to four-fold increase in cortisol concentration 4 hours after incision during hysterectomy under general anaesthesia [15]. Surprisingly, the anaesthetic agent used in the two studies differed, our patients were induced with sodium thiopentone/pancuronium, and anaesthesia was maintained with isoflurane/O_2, while Moller [15] induced and maintained anaesthesia with halothane/O_2/N_2O. This may suggest that the mechanism involved in hormonal secretion is complex, and no single variable can exclusively determine the degree of hormonal secretion.

The anaesthetic technique may modulate, stimulate, or inhibit the stress response to surgical injury [2, 5]. The insulin concentration increased 24 hours after incision in our balanced general anaesthesia group, but decreased in the combined spinal epidural anaesthesia group, the difference was, however, insignificant. In contrast, a significant decrease in the insulin concentration during general anaesthesia alone and general anaesthesia with epidural analgesia during revascularization of the lower limb was reported [16]. The difference in the secretion of insulin in the two studies may be due to the variation in the time of blood collection. Blood sample for insulin analysis was collected 24 hours after incision in our study, compared to 1 and 8 hours after incision by Buckley et al [16]. This may suggest that appropriate timing is important during hormonal studies to ensure the hormone is at its peak level. This is because insulin secretion is maximum during phase II of the flow phase, which commences 24 hours after injury, and peaks 3-7 days thereafter [1]. Dermatome sensory block extending from S_5 to T_5 during combined spinal epidural anaesthesia in our study resulted in a lower insulin concentration than dermatome sensory block extending from T_{10} to S_5 dermatome level during hip arthroplasty [6]. The control of insulin secretion is mediated by the 2^{nd} to 6^{th} thoracic sensory levels [2], therefore, a sensory blockade established at T_5 sensory level my result in profound reduction of insulin secretion when compared to a lower sensory level (T_{10}).

Glucose and insulin concentrations during balanced general anaesthesia in our study increased simultaneously, which was attributed to changes in insulin concentration in the flow phase. During this phase, there is insulin resistance, as such, the cells of the body are unresponsive to plasma insulin concentrations, therefore, and the high levels of insulin fail to suppress glucose production [2-3]. There is also a reduction in glycogen storage, lipolysis and fat oxidation; therefore hyperglycaemia persists during this phase [17, 18]. A significantly lower glucose concentration was noticed in the combined spinal epidural anaesthesia group than the balanced general anaesthesia group. This is likely due to the reduced cortisol concentration observed in combined spinal epidural anaesthesia group, because an increase in cortisol level has been associated with a 50% increase in glucose level from preinduction values [3]. Physiological hypercortisolaemia in the perioperative period has been reported to cause progressive decrease in glucose clearance, and increase in glucose concentration [15]. Therefore, judicious control of cortisol secretion in the perioperative period will have a positive influence on glucose release. The addition of intrathecal fentanyl might have suppressed cortisol secretion, because afferent neurogenic blockade effective before the start of surgical trauma has been reported to prevent the endocrine-metabolic response to surgical procedures [11, 13, 15].

A similar observation was made with intrathecal morphine [3, 15]. The simultaneous administration of intrathecal opioids and local anaesthetic agent may have a synergistic effect on pain reduction, improve the quality of analgesia, because pain is a known potent stimulator of hormonal secretion [2, 3]. The administration of pentazocine an agonist-antagonist may have counteracted the analgesic (or anti-nociceptive) effect of initial fentanyl, which may result in a more pronounced stress response in the balanced general anaesthesia group. Pentazocine was administered because long acting opioids were unavailable in our institution during the study period.

The mean glucose level was less than 10 mmol/L during the 4 hour study period, which may be due to the use of balanced electrolyte glucose free fluid. The infusion of glucose containing fluids in the perioperative period has resulted in higher glucose concentrations [15]. The untoward effects of perioperative hyperglycaemia include increase wound infection, electrolyte abnormalities, enhanced protein catabolism, and worsened patients' outcome. It is therefore necessary to preserve perioperative glucose homeostasis [3]. Factors which may impair glucose metabolism include the outpouring of counter-regulatory hormones such as cortisol, epinephrine, norepinephrine and glucagon increase gluconeogenesis, glycolysis and lipolysis in the perioperative period. It is therefore necessary to reduce the stress response during surgical operation by using an anaesthetic technique which will inhibit or minimise the response [2, 3]. It is concluded that combined spinal epidural anaesthesia extending from T_5 to S_5 resulted in lower cortisol, insulin and glucose concentrations during major gynaecological surgical operations in a sample of Nigeria women. This may be of benefit in patients scheduled for surgical procedures below the umbilicus.

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