THE NEUROENDOCRINE RESPONSE TO GYNAECOLOGICAL SURGERY: COMPARING THE MODULATING EFFECT OF TWO ANAESTHETIC TECHNIQUES

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DECLARATION

I, OYEBOLA OLUBODUN **ADEKOLA,** hereby declare that the contents of this dissertation are the results of work done by me at the Lagos University Teaching Hospital, Lagos, Nigeria. The work has not been presented for any publication, examination or fellowship award.

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CERTIFICATION

We certify that this work was carried out by Dr. Oyebola Olubodun **Adekola** of the Department of Anaesthesia, Lagos University Teaching Hospital, under our supervision.

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DEDICATION

This work is dedicated to all the widows and orphans who were deprived of their rights.

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I give thanks to the Almighty God for the grace to start and complete this work.

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LIST OF ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
ASA	American Society of Anesthesiologists
bpm	Beats per minutes
BMI	Body mass index
BP	Blood pressure
cm	Centimetre
°C	Degree centigrade
CNS	Central nervous system
CSEA	Combined spinal epidural anaesthesia
DOA	Duration of Anaesthesia
DOF	Duration of fasting
DOS	Duration of Surgery

ECG	Electrocardiogram
ELISA	Enzyme linked immunosorbant assay technique
$ETCO_2$	End tidal carbon dioxide
δ	Gamma
G	Gauge
GA	General Anaesthesia
GAR	General anaesthesia relaxant technique
HR	Heart rate
IV	Intravenous
K	Kappa
Kg	Kilogram
Kg/m^2	Kilogram per meter square
kPa	Kilopascal
L_3/L_4	3^{rd} and 4^{th} Lumbar dermatome
L_4/L_5	4^{th} and 5^{th} Lumbar dermatome
m	Metre
MAC	Minimum alveolar concentration

MAP	Mean arterial pressure
mg	Milligram
mg/dL	Milligram per deciliter
mg/m^2	Milligram per square metre
mg/kg	Milligram per kilogram
mins	Minute
ml	Milliliter
mmHg	Millimeter of mercury
mmol/L	Millimoles per liter
MP	Malampatti
nm	Nanometer
%	Percent
p	Probability
PCV	Packed cell volume
pg/ml	Picogram/millilitre
s	Seconds
SBP	Systolic blood pressure

SD	Standard deviation
(SPSS®)	Statistical Package for the Social Sciences
S_5	5^{th} Sacral dermatome
T_4 /T_5	4^{th} and 5^{th} Thoracic dermatome
T_8	8^{th} Thoracic dermatome
T_{10}	10^{th} Thoracic dermatome
µ	mu
uIU/ml	International unit per millimetre
µg	Microgram
µg/dL	Micrograms per deciliter
µg/hr	Microgram per hour
µmol	Micromole
<	Less than
>	Greater than

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SUMMARY

Forty-four healthy patients with the American Society of Anesthesiologists (ASA) physical status I and II scheduled for elective myomectomy and total abdominal hysterectomy were studied. They were randomly allotted by blind balloting to one of two groups of twenty-two; group I patients received balanced general anaesthesia relaxant technique (GAR), and group II patients received combined spinal epidural anaesthesia (CSEA).

Four blood samples were obtained for analysis of glucose, cortisol, insulin, epinephrine and norepinephrine. Blood samples were taken before induction of anaesthesia (preinduction), and at 1, 3 and 4 hours after surgical incision. Serum glucose concentration was measured by the glucose oxidase enzymatic method; the absorbance of glucose was read at 500nm. Plasma cortisol, insulin, epinephrine and norepinephrine concentrations were measured by enzyme linked immunosorbant assay (ELISA) technique; the absorbance of the solution were read within 10 minutes, using a microplate reader set to 450 nm and a reference wavelength between 620 nm and 650 nm.

Three of the forty-four patients enrolled in the study had complications in the perioperative period leaving 41 patients for analysis. In group I (GAR), 1 patient developed postoperative haemorrhage and required a repeat surgery, while in group II (CSEA), 2 patients were excluded on account of severe hypotension with SBP <80 mmHg which required the administration of intravenous ephedrine. Group I (GAR) consisted of 21(51.22%) patients and Group II consisted of 20(48.78%) patients. There were no differences between the two groups regarding age, height, weight, body mass index and packed cell volume ($p>0.05$).

The preinduction glucose concentration was similar in both groups (GAR 4.88 ±0.51 versus CSEA 4.90 ±1.04 mmol/L, p =0.933). The mean glucose was significantly higher in the GAR group than in CSEA group, at 1 hour after incision (6.09 ±1.19 versus 4.58 ±1.31 mmol/L, p <0.001), at 3 hours (6.77±1.39 versus 5.38 ±1.789 mmol/L, p = 0.012), and at 4 hours after incision (GAR 7.28 ±1.44 versus CSEA 6.17 ±1.69 mmol/L, p =0.034).

The mean cortisol was similar in both groups, at preinduction (GAR 13.32 ±6.44 versus CSEA 17.84 ±10.42 µg/dl, p =0.299), and at 1 hour after incision (GAR 30.29 ±14.41 versus CSEA 23.42 ±10.33 µg/dl, p =0.156). The mean cortisol was higher in the GAR group than in CSEA group, at 3 hours after incision (34.16 ±11.88 versus 23.15 ±12.10 µg/dl, p =0.072), but not significant, and at 4 hours after incision (GAR 38.94 ± 10.60 versus CSEA 19.96 ±11.32 µg/dl, p =0.018) which was significant.

The mean insulin concentration was similar in the GAR and CSEA groups, at preinduction (4.63 ±0.49 versus 4.88 ±0.53 uIU/ml, p =0.304), and at 24 hours after incision (GAR 5.04 ±1.06 versus CSEA 4.69 ±2.24 uIU/ml, p =0.403).

The mean epinephrine was similar in the GAR and CSEA groups, at preinduction (19.68 ±13.84 versus 24.36 ±18.03 pg/ml, p =0.641), at 1 hour after incision (GAR 25.44 ±17.91 versus CSEA 26.39 ±19.22 pg/ml, p =0.867), at 3 hours after incision (GAR 20.56 ±17.67 versus CSEA 21.68 ±14.77 pg/ml, p =0.743), and at 4 hours after incision (GAR 22.86 ±11.22 versus CSEA 18.30 ±11.37 pg/ml, p =0.707).

There was no significant difference in mean norepinephrine concentration between GAR and CSEA groups, at preinduction (38.24 ±16.14 versus 65.76 ±23.77 pg/ml, p

=0.480), at 4 hours after incision (GAR 46.56 ±19.51 versus 72.38 ±20.31 pg/ml, p =0.359). The mean norepinephrine, however, was significantly higher in CSEA group than in GAR group, at 1 hour after incision (GAR 54.52 ±19.45 versus CSEA 219.31 ±42.85 pg/ml, p =0.015), and at 3 hours after incision (GAR 27.00 ±18.86 versus CSEA 115.29 ±39.91 pg/ml, p =0.045).

The mean heart rate and mean arterial blood pressure were significantly higher in the general anaesthesia group during the study period.

This study has demonstrated that the mean glucose, cortisol levels, blood pressure and heart rate were significantly lower in patients who received combined spinal epidural anaesthesia than those who received general anaesthesia relaxant technique during major gynaecological surgery. The mean norepinephrine levels, however, were higher in the combined epidural anaesthesia group than in the general anaesthesia group.

INTRODUCTION

The neuroendocrine stress response is the hormonal and metabolic change that follows injury or surgical trauma; these are part of the systemic reaction to injury.[1-3] The magnitude of the stress response to surgery is dependent on the severity, intensity and duration of the stimulus.[4-5] The blood loss, tissue handling and damage, immobilization, the degree of anxiety and pain evoke these hormonal changes. Age, sex, weight, nutritional status of the patient and the environmental temperature have also been implicated.[5-6]

The metabolic response to injury was first described by Sir David Cuthbertson in studies on the effect of trauma to the lower limbs.[1] He introduced the term "ebb and flow" to describe the hypometabolism and hypermetabolism that follow traumatic injury and divided the stress response into ebb and flow phase.[1-3] The ebb or shock phase begins immediately after injury and lasts for a period of 12-24 hours.[4] It is characterised by decrease metabolic rate, enzymatic activity, oxygen consumption and tissue hypoperfusion.[1,4] Catecholamines are released from peripheral nerves as a compensatory mechanism. This process initiates the flow phase; a hyperdynamic phase characterized by activation of the endocrine system and increased metabolic rate.[4]

There are two components of the flow phase, an early phase I, which begins 3-4 hours after injury and lasts for 3-4 days and results in secretion of catecholamines. The delayed phase I peaks 12-24 hours after injury, last for 3-4 days and involves the secretion of glucocorticoids, epinephrine and norepinephrine.[4] Phase II of the flow state commences 24-48 hours after the ebb phase, peaks in 3-4 days and last for 4-5 days. It results in the secretion of glucagon and some glucocorticoids. The outpouring of

counterregulatory hormones such as cortisol, epinephrine, norepinephrine and glucagon results in increase gluconeogenesis, glycolysis and lipolysis. There is pronounced hyperglycaemia and a negative nitrogen balance if the stress response is unabated with untoward sequel.[4-5] This include increased risk of infection, water and electrolyte abnormalities and delayed wound healing.

The anaesthetic technique may stimulate, inhibit or modulate the stress response to surgery. The use of laryngoscopy and tracheal intubation during general anaesthesia stimulates the sympathetic nervous system. Other procedures that cause sympathetic stimulation include skin incision, tissue handling, stretching of the mesentery and light planes of anaesthesia.[5-6] The ability of central neuraxial blockade by either spinal or epidural anaesthesia to suppress some aspect of the stress response was established in the late 1970s.[5-6] Epidural blockade extending from dermatome segment T_4 to S_5, before surgical incision, will prevent the endocrine and metabolic response to surgery in the pelvis and lower limbs.[6-7] Similarly, the attenuation of the stress response by combined spinal epidural anaesthesia was demonstrated in infants and high risk cohorts' patients undergoing gastrointestinal and colorectal surgical procedures.[8-10]

The detrimental effects of the stress response include hyperglycaemia, negative nitrogen balance, increased myocardial oxygen consumption, increased risk of myocardial ischaemia, delayed wound healing, and the risk of infection. It is necessary to reduce the stress response during surgery by using an anaesthetic technique which will inhibit or abolish the stress response.[11] The careful titration of inhalational agents, opioids, the use of cardiostable drugs and the maintenance of the depth of anaesthesia help to attenuate the stress response.[5-6] This study compared the modulating effect of

balanced general anaesthesia with combined spinal epidural anaesthesia on neuroendocrine stress response to major gynaecological surgeries.

AIM OF THE STUDY

To compare the modulating effect of two types of anaesthetic techniques on the stress response to surgical trauma: Balanced general anaesthesia and combined spinal epidural anaesthesia.

OBJECTIVES OF THE STUDY

1. To determine and compare the effect of balanced general anaesthesia and combined spinal epidural anaesthesia on serum glucose levels in response to major gynaecological surgery.
2. To determine and compare the effect of balanced general anaesthesia and combined spinal epidural anaesthesia on plasma cortisol levels in response to major gynaecological surgery.
3. To determine and compare the effect of balanced general anaesthesia and combined spinal epidural anaesthesia on plasma insulin levels in response to major gynaecological surgery.
4. To determine and compare the effect of balanced general anaesthesia and combined spinal epidural anaesthesia on plasma epinephrine and norepinephrine levels in response to major gynaecological surgery.
5. To determine and compare the effect of balanced general anaesthesia and combined spinal epidural anaesthesia on the perioperative blood pressure, and heart rate in response to major gynaecological surgery.

LITERATURE REVIEW

The stress response to injury is secondary to stimulation of the hypothalamo-pituitary axis and the sympathetic nervous system. This results in increased secretion of norepinephrine, epinephrine, glucagon and cortisol. The anaesthetic technique can stimulate, inhibit or modulate the metabolic and hormonal changes during surgery.[5-6]

The modulating effects of anaesthesia on glucose level

The blood glucose concentration increases after surgical incision secondary to the release of catabolic hormones. The changes in glucose follow closely the increase in catecholamine**.** Cortisol and other glucocorticoids may stimulate gluconeogenesis by as much as six to ten fold during stress.[5-6] Cortisol causes up to 50% increase in glucose level from preinduction values.[5] In fasting non-diabetic patients undergoing elective intra-abdominal operation, the blood glucose can increase up to a value of 7-10 mmol/L. In cardiac surgery, the glucose level can increase up to a value of 10-12 mmol/L.[11-12] Similar observations have also been reported in paediatric patients, who showed increase in glucose levels following surgical stimulation.[13] An increased incidence of wound infection and mediastinitis was found in diabetics and non-diabetics in whom blood glucose concentrations were >11.11mmol/L after cardiac surgery.[11-12] The increase in glucose concentration during surgery can be modified by different anaesthetic techniques.[14-16]

Christensen et al.[15] compared the effect of anaesthesia on glucose levels in 36 patients undergoing abdominal hysterectomy. They were divided into 3 groups; Group G (general anaesthesia), group E (epidural anaesthesia) and group M (general anaesthesia

with epidural morphine). The blood samples were taken before anaesthesia and hourly for 9 hours after incision. The authors observed that the blood glucose level increased in all the groups during the study; the epidural anaesthesia group, however, had lower glucose concentrations. The mean glucose levels at preinduction were similar in all groups (Group G 5.1 versus Group E 5.2 versus Group M 5.2 mmol/L, $p > 0.05$). The mean glucose level was significantly higher in Group G than Groups E and M, at 1 hour after incision (6.2 versus 5.3 versus 5.7 mmol/L, $p < 0.05$), at 3 hours after incision (Group G 8.0 versus Group E 5.1 versus Group M 5.0 mmol/L, $p < 0.05$), and at 4 hours after incision (Group G 7.8 versus Group E 5.5 versus Group M 5.8 mmol/L, $p < 0.05$). The authors concluded that glucose concentration during hysterectomy was significantly lower in the epidural anaesthesia group (E) than in general anaesthesia (G) only or general anaesthesia with epidural morphine (M) groups. They suggested that unblocked nociceptive pathways from the operation site might have been responsible for the initial increase in glucose level under epidural morphine analgesia.[15]

In the study by Christensen et al.[15] the increase in glucose level after epidural morphine may be due to insufficient dosage, since other researchers have shown that systemic and intrathecal administration of opioids in very high doses can block the increase in glucose secretion during surgery.[16-18] The level of sensory block after injection of morphine was also not indicated; which may suggest that the sensory level was not determined before commencement of general anaesthesia. The migration of the epidural catheter which is not a rare occurrence might have occurred before the injection of morphine. It is suggested that in future studies the level of sensory block should be established before the induction of general anaesthesia. This will ensure that epidural

analgesia was established and that the epidural catheter was still insitu. Pain score was also not determined; however, the authors presumed that the patients were unlikely to have had pain since none requested for additional analgesia. Pain should, however, be taken into cognisance as a major stimulator of the neuroendocrine stress response to surgery.[11,18]

In a similar study Moller et al.[19] compared the effect of three anaesthetic techniques on glucose level in a cohort of 24 patients undergoing abdominal hysterectomy. Group I received general anaesthesia, Group II received general anaesthesia with epidural analgesia 30 minutes after incision, and Group III received general anaesthesia with epidural analgesia 30 minutes before incision. The mean preinduction glucose level was similar in all groups, (Group I 4.7 versus Group II 4.8 versus Group III 5.09 mmol/L, $p > 0.05$). The mean glucose level was significantly higher in Group I than in Groups II and III; at 1 hour after incision (7.5 versus 6.2 versus 5.2 mmol/L, $p < 0.05$), at 3 hours after incision (Group I 8.0 versus Group II 6.3 versus Group III 5.1 mmol/L, $p < 0.05$), and at 4 hours after incision (Group I 8.1 versus Group II 6.0 versus Group III 5.6 mmol/L, $p < 0.05$). The authors concluded that the use of epidural analgesia commenced before skin incision during hysterectomy was associated with lower glucose levels.[19]

The glucose concentration increased at 4 hours after incision, (Group I 72.34% versus Group II 25% versus Group III 10.01%). The percentage increase was more in the general anaesthesia group alone. The higher value recorded in group I may be attributed to a light plane of anaesthesia. Since all patients breathed spontaneously, neuromuscular blocking agent was not administered, and the depth of anaesthesia was not monitored. It

may be that some of the patients were aware during the study period. Awareness during anaesthesia has been associated with pronounced increase in stress response.[6,11] The lower glucose concentrations in groups II and III are probably due to the use of epidural analgesia. Similarly during prostatectomy and colorectal surgery, the use of epidural anaesthesia or analgesia resulted in lower glucose concentrations following surgical stimulation.[20-21]

Lattermann et al.[22] demonstrated in a cohort of 16 elderly patients scheduled for total hip arthroplasty that CSEA prevented the increase in plasma glucose level during surgery, and immediately after the operation compared to general anaesthesia relaxant technique. The mean glucose level was significantly higher in the GAR group than in the CSEA group, at 1 hour after incision (6.2 ±0.7 versus 4.9 ±0.7 mmol/L, $p < 0.05$), and at 24 hours after incision (GAR 7.3±1.1 versus CSEA 5 ±0.9 mmol/L, $p < 0.05$). The authors concluded that the use of CSEA was associated with lower glucose concentration after surgical stimulation.[22] The glucose level during and after surgery in the CSEA group was similar, this may be due to the commencement of CSEA before incision. This is in agreement with previous reports which documented that the administration of local anaesthetic agent into the epidural space before skin incision decreases glucose secretion.[11,19]

Several factors are known to influence the secretion of hormones during surgery; these include patient habitus, blood loss, the duration and intensity of stimuli.[6] The blood glucose levels reported in a cohort of 16 ASA III patients undergoing elective colorectal surgery[21] were higher than values observed in ASA I patients undergoing hysterectomy with shorter duration of surgery.[15,19] The use of glucose containing fluids and longer

duration of preoperative fasting (36 hours) resulted in blood glucose level greater than 10 mmol/L during colorectal surgery.[21] The blood glucose levels were higher than 6.2mmol/L reported in patients that received 0.9% normal saline, and were fasted for 8-10 hours during hysterectomy.[23-24] Prolonged fasting may result in the release of glucagon, cortisol, epinephrine and norepinephrine with subsequent lipid and protein breakdown via lipolysis, glycogenolysis and gluconeogenesis resulting in higher glucose levels.

The deleterious effects of hyperglycaemia include increased risk of infection, impaired wound healing, water and electrolyte loss.[11-12] The prevention of hyperglycaemia and a tight glycaemic control in the perioperative period will therefore reduce the morbidity and mortality associated with surgical injury.

The modulating effects of anaesthesia on cortisol level

The secretion of cortisol from the adrenal cortex increases rapidly as a result of ACTH stimulation. A feedback mechanism operates so that increased levels of circulating cortisol inhibit further secretion of ACTH.[5-6] This control mechanism appears to be ineffective after surgery so that concentration of both hormones remain high. Changes in blood volume produce a very rapid response, and there is some evidence of increased sensitivity of the adrenal cortex during hypovolaemia.[5] Painful stimuli cause increase in cortisol level which may be partly inhibited by balanced general anaesthesia.[11]

Engquist et al.[23] investigated a cohort of 12 patients undergoing hysterectomy under general anaesthesia (group H) and general anaesthesia with epidural analgesia (group HE). There was no significant difference in the preinduction mean cortisol in both groups (Group H 18.32 versus Group HE 24.3 μg/dL, $p > 0.05$). The mean cortisol was

significantly higher in Group H than in Group HE, at 1 hour after incision (51 versus 39 µg/dL, p <0.05), at 3 hours after incision (Group H 82 versus Group HE 63.7 µg/dl, p <0.05), and at 4 hours after incision (Group H 98.38 versus Group HE 65.7 µg/dl, p =0.01). The authors demonstrated that the use of epidural analgesia was associated with lower concentrations of cortisol when compared with general anaesthesia alone.

In the same study, the effect of the type of surgery on cortisol level was investigated, 6 patients had hysterectomy (Group H) and 6 patients had tympanoplasty. There was no significant difference in mean preinduction cortisol in both groups, (Group H 18.32 ±17.1 versus Group TM 30.42 ±5.94 µg/dL, p >0.05). The mean cortisol was significantly higher in Group H than in Group TM, at 2 hours after incision (75.0 ±22.34 versus 47.85 ±10.33 µg/dL, p <0.05), and at 6 hours after incision, (Group H 98.38±59.9 versus Group TM 57.52±11.02 µg/dL, p <0.05). The authors observed that hysterectomy caused a significant increase in cortisol level more than tympanoplasty; therefore they concluded that hysterectomy is a more invasive surgery.[23]

The use of CSEA extending from T_{10} to S_5 was shown to inhibit the secretion of cortisol during hip arthroplasty.[22] The mean cortisol before surgery was similar in both groups (GAR 18.8 ±10.2 versus CSEA 24.2 ±10.2 µg/dL, p >0.05). The authors observed that general anaesthesia caused a significant increase in cortisol concentration during surgery to 65.2 ±5.09 µg/dL whereas CSEA decreased cortisol concentration to 17.5 ±4.6 µg/dL, p <0.05.[22] This is in line with previous reports on the effect of epidural anaesthesia commenced before incision on cortisol levels.[15,23]

In contrast, Breslow et al.[7] in a cohort of 60 patients undergoing lower extremity revascularisation under general anaesthesia (group C) and epidural anaesthesia (group T)

reported that there was no difference in intraoperative urinary cortisol excretion. The mean urinary cortisol was similar in both groups, at baseline (Group C 4 versus group T 5.8 µgm/hr, p >0.05), and at the end of surgery (Group C 10.2 versus Group T 9.4 µgm/hr, p>0.05).[7] This observation may not be unrelated to the anaesthethic technique and the adequacy of pain management, since both groups received continuous postoperative analgesia and the pain score was monitored. The general anaesthesia group received patient controlled intravenous morphine while the epidural anaesthesia group received continuous infusion of epidural fentanyl. It is therefore not surprising that the urinary cortisol was similar between the groups. This is in agreement with previous reports that the use of intravenous or intrathecal opioid, and the absence of pain inhibits the stress hormone secretion.[17-18]

Laparoscopic surgery causes less tissue injury than conventional procedures and it is therefore expected to reduce stress hormone secretion.[5-6] Kim et al.[25] compared the metabolic and hormonal response in a cohort of 24 patients randomly assigned to undergo laparoscopic hysterectomy n = 13, (Group L) or abdominal hysterectomy n =11, (Group AB) under general anaesthesia. They observed that laparoscopic hysterectomy induced less tissue trauma and less inflammatory response than did open abdominal hysterectomy. The mean C-reactive protein level at 24 hours postoperatively was significantly lower in Group L 10.8 mg/L than in Group AB 39.5 mg/L, p <0.05. The cortisol level was, however, similar in both groups during surgery, but decreased after the surgery. It reached its peak level at the end of peritoneum closure in group L, and 1 hour postoperatively in Group AB. The mean baseline cortisol in Group L was 30.4 ±7.7

versus 38.0 ±14.3 µg/dL in Group AB, p >0.05. The mean cortisol after surgery was 1 1.8 ± 3.6 µg/dL in Group L versus 18.1 ± 5.9 µg/dL in Group AB, p>0.05.

The authors concluded that though laparoscopic surgical procedure reduced the inflammatory response to injury it did not affect the stress response to injury. This is in agreement with a previous documentation that hormonal secretion of catecholamine, cortisol and glucose during upper abdominal surgery are not changed greatly by reducing surgical trauma with laparoscopy.[17,27] In the study by Kim et al.[25] the weight, duration of surgery/anaesthesia, and blood loss were similar. It is therefore not surprising that there was no significant difference in the magnitude of evoked stress response.

The modulating effect of anaesthesia on insulin levels

The plasma concentration of insulin during stress is biphasic.[6] There is an initial suppression of insulin after induction of anaesthesia, followed by a period of normal secretion. The period of insulin suppression and normal secretion is known as the state of physiological insulin resistance, during this period the cells of the body fail to respond to insulin, and hyperglycaemia persist.[6] The response of insulin to hyperglycaemia, and the response of glycogen to peripheral glucose are inhibited by the 2^{nd} to 6^{th} thoracic sensory dermatome levels during neuraxial blockade.[6] The 9^{th} to 10^{th} thoracic sensory levels, however, had no influence on insulin secretion.[6]

The insulin levels during hip arthroplasty decreased with both general anaesthesia and CSEA with lower concentrations occurring in patients that received general anaesthesia.[22] The mean insulin level before surgery was similar in groups GAR and CSEA, (5.3 ±3.0 versus 5.3 ±3.2 uIU/ml, p>0.05). The mean insulin level was significantly lower in GAR group than in CSEA group, at 1 hour after incision (2.9 ±1.8

versus 4.4 ±2.6 uIU/ml, p <0.05), and at 24 hours after incision (GAR 6.5 ±3.4 versus CSEA 9.6 ±8.3 uIU/ml, p <0.05). The authors concluded that general anaesthesia and combined spinal epidural anaesthesia decreased insulin level during the surgery but increased insulin level after surgery.[22] The significantly lower values obtained in GAR group is not surprising as propofol and fentanyl have been shown to reduce insulin secretion.[6] The higher level of insulin observed in the combined spinal epidural group may not be unrelated to the level of sensory block established at T_{10} dermatome, since a previous documentation had implicated T_2/T_6 dermatome blockade in the inhibition of insulin secretion during surgery.[6]

In contrast, Buckley et al.[26] studied 13 patients undergoing hysterectomy under general anaesthesia (GA) or general anaesthesia with epidural analgesia (EA). They observed that the insulin concentration was significantly lower in the epidural analgesia group. The epidural blockade extended from T_8 to S_5 dermatome level. The mean preinduction insulin level was similar in both groups (GA 8.5 versus EA 7.8 uIU/L, p >0.05). The mean insulin level in GA group was significantly higher than in EA group, at 1 hour after incision (7.8 versus 5.8 uIU/L, p <0.001), and at 8 hours after incision, (GA 12 versus EA 7.8 uIU/L, p <0.001). The authors concluded that epidural anaesthesia extending from T_8 to S_5 resulted in lower insulin concentration during surgery.[26] The lower concentration of insulin documented in the EA group may not be unrelated to the higher level of sensory block.

The modulating effect of anaesthesia on catecholamines levels

The plasma catecholamine concentration increases immediately after injury and peaks in 24-48 hours depending on the severity of the injury. This may cause up to a ten-

fold increase in secretion of epinephrine. Though, urinary catecholamines concentration are raised for days after a major injury, the blood levels of epinephrine and norepinephrine do not necessarily increase concurrently.[23,27] It was observed that after accidental injury, the plasma epinephrine level increased for a short time (about 48 hours) while the norepinephrine levels remained elevated for periods up to 8-10 days.[27] During upper abdominal procedure, the increase in norepinephrine concentrations recorded was relatively greater than that of epinephrine.[27] Hypovolaemia has been shown to be the greatest stimulant of catecholamines secretion, and levels of catecholamines reduce appreciably after restoration of blood volume.[5]

Enquist et al.[23] reported an increase in epinephrine and norepinephrine concentrations in patients scheduled for hysterectomy under general anaesthesia (Group H) and general anaesthesia with epidural analgesia (Group HE). There was no significant difference in the mean preinduction epinephrine concentration in both groups, (Group H 19 ±2 versus Group HE 24 ±3 pg/ml, $p > 0.05$). The mean epinephrine was lower in Group H than in Group HE, at 1 hour after incision (20 ±4 versus 22 ±4 pg/ml, $p > 0.05$), but the difference was not significant. The mean epinephrine was, however, significantly higher in Group H than Group HE, at 3 hours after incision (44 ±5 versus 16 ±0.02 pg/ml, $p<0.05$), and at 4 hours after incision (Group H 39 ±2.0 versus Group HE 24±5 pg/ml, $p <0.05$).

The mean norepinephrine level was similar in both groups, at preinduction (Group H 43 ±5 versus Group HE 46 ±8 pg/ml, $p > 0.05$), and at 1 hour after incision (Group H 30 ±3 versus Group HE 31 ±4 pg/ml, $p > 0.05$). The mean epinephrine level was significantly lower in Group H than in Group HE, at 3 hours after incision (41 ±3 versus

59 ±7 pg/ml, p <0.05), and at 4 hours after incision (Group H 38 ±3 versus Group HE 52 ±6 pg/ml, p <0.05). The authors observed that the epinephrine levels in the Group H were significantly higher than in Group HE (p <0.05). The norepinephrine levels in the Group H were, however, lower than in group HE. They concluded that the use of epidural analgesia during hysterectomy extending from T_4-S_5 dermatome inhibited the secretion of epinephrine and resulted in lower concentrations. The higher norepinephrine level in epidural analgesia group was attributed to the local release of norepinephrine and inadequate vagal blockade.[23]

The significantly lower epinephrine levels in the epidural analgesia group may be attributed to the level of the sensory block established at T_4 as the degree of hormone inhibition has been reported to depend on the level of sensory block.[24]

In another study, the effect of three anaesthetic techniques on plasma epinephrine and norepinephrine level during cystoprostatectomy was investigated.[21] The patients were randomly divided into three groups, group I received fentanyl/midazolam anaesthesia, group II received general anaesthesia with epidural analgesia and group III received isoflurane anaesthesia. The mean epinephrine concentration before surgery was similar in all the groups, (Group I 44 ±11 versus Group II 34 ±3 versus Group III 30 ±4 pg/ml), p >0.05. The mean epinephrine level was significantly higher in Group III compared to Groups I and II, after surgery (237 ±72 versus 174 ±53 versus 36 ±10 pg/ml), p <0.05.

There was no significant difference in the mean norepinephrine level in all the groups before surgery (Group I 234 ±21 versus Group II 240 ±23 versus Group III 336±51 pg/ml), p>0.05. The mean norepinephrine level was significantly higher in Group III compared to Groups I and II, after surgery (692 ±147 versus 471 ±115 versus 190 ±60

pg/ml, p >0.05). The authors concluded that the intraoperative epinephrine, and norepinephrine levels in the epidural group were significantly lower than in the isoflurane or fentanyl/midazolam groups (p <0.05).[21]

The use of fentanyl/midazolam anaesthesia during colorectal surgery did not completely suppress, but blunted, the increase in the intraoperative epinephrine and norepinephrine levels when compared to isoflurane anaesthesia.[21] This may be due to the dosage of midazolam and fentanyl used in the study protocol (general anaesthesia was induced with midazolam 0.15 mg/kg and fentanyl 5-10 µg/kg, and maintained by intermittent boluses of fentanyl and midazolam). This observation was in agreement with a previous study protocol that used similar amount of fentanyl and midazolam during anaesthesia.[17] The increase in epinephrine and norepinephrine is not unexpected as opioids are known to depress the hypothalamic adrenal response to surgery and to depress sympathetic activity in a dose dependent manner.[17,27]

The modulating effect of anaesthesia on HR and BP

The autonomic nervous system is activated by noxious surgical stimuli which increase adrenergic discharge and may counteract the depressant effect of general anaesthetic agents on baroreceptor integrity.[5] The activation of the sympathetic system may be detrimental to the cardiovascular system. It is therefore important to prevent or inhibit the activation of the sympathetic nervous system. The injection of local anaesthetic agents into the epidural and, or subarachnoid space have been shown to inhibit the sympathetic discharge and thus decrease the HR and BP.[23-24]

Engquist et al.[23] documented that the mean blood pressure were significantly lower in patients that received general anaesthesia with epidural analgesia (Group HE) than

those which received general anaesthesia alone (Group H). However, there was no significant difference between the groups in the mean HR. The observation with the HR in both techniques is expected as enflurane (0.5-1.5%) MAC was used for the maintenance of anaesthesia in the general anaesthesia group, and a low MAC of enflurane has been shown to have minimal depressant effect on the heart rate. In the epidural analgesia group (HE), a lower dose of bupivacaine (0.25%) was used, this may account for the HR documented.

The mean baseline BP was similar in both groups, $p > 0.05$. The mean BP was significantly higher in Group H compared to Group HE, at 30 minutes after incision (91.8 ±5.4 versus 61.3±5.0 mmHg, $p < 0.01$), and at 60 minutes after incision (Group H 81.0 ±1.9 versus Group HE 70.7 ±2.1 mmHg, $p < 0.01$). The lower BP documented in the epidural analgesia group (Group HE) may be because the patients also received general anaesthesia. The use of inhalational agent is associated with vasodilatation which may reduce the BP. The addition of epidural analgesia will cause sympathectomy which will also cause vasodilatation. The simultaneous administration of general anaesthesia and epidural analgesia is synergistic; it may cause profound reduction in blood pressure.

Hong et al.[28] monitored haemodynamic variables during laparoscopic hysterectomy in a prospective observational study that involved 50 patients which were randomly divided into 2 groups. Group A had general anesthesia with epidural analgesia, while group G had general anaesthesia alone.

The mean preinduction systolic blood pressure (SBP) was similar in both groups (group A 138 versus group G 137 mmHg, $p > 0.05$). The mean SBP was significantly

lower in group A than group G, after trendelenburg position, (115 versus 128 mmHg, $p<0.05$), during CO2 insufflation, (114 versus 124 mmHg, $p <0.05$), and 20 minutes after pneumoperitoneum (110 versus 119 mmHg, $p <0.05$).

The mean preinduction heart rate (HR) was similar in both groups (group A 80 versus group G 80 bpm, $p >0.05$). Similarly, there was no significant difference in the mean HR at other time intervals; after Trendelenburg position, (group A 79 versus group G 78 bpm, $p>0.05$), during CO2 insufflation, (group A 84 versus group B 84 bpm, $p >0.05$), and at 20 minutes after pneumoperitoneum (group A 82 versus group G 78 bpm, $p >0.05$).[28]

The authors observed that the mean blood pressure of the patients in the group A were significantly lower than in the group G after Trendelenburg position, CO2 insufflation, and at 20 minutes after pneumoperitoneum ($p < 0.05$). The mean heart rate were, however, similar $p>0.05$. The authors concluded that in patients that had general anaesthesia with epidural analgesia the blood pressure was significantly lower, and a great percentage developed hypotension.[28]

The HR remained stable during general anaesthesia and epidural analgesia in the study by Hong,[28] this may be attributed to the technique of anaesthesia used, epidural analgesia was established with 10 ml lidocaine and 2 mg morphine, the level of sensory block was established at T_6. The use of low dose local anaesthetic agent and, or intrathecal or epidural opioid has been reported to have minimal effect on heart rate.[5,18] The decrease in BP is probably due to vasodilatation of the lower extremity vessels, reduction in venous return and cardiac output. The HR in the general anaesthesia group was relatively stable because the researchers aimed at a balanced anaesthesia and

maintained normocapnia. The degree of muscle relaxation and the depth of anaesthesia were monitored, this prevented awareness. The suppression of sympathetic overactivity will further reduce the morbidity and mortality associated with surgical injury.

MATERIALS AND METHODS

The approval of the Research and Ethical Committee of the Lagos University Teaching Hospital was obtained. Written informed consent was obtained from all patients. Forty-four healthy patients with ASA I and II status scheduled for elective myomectomy or total abdominal hysterectomy, aged between 20-60 years and weighing 50-100 kg were recruited for the study. They were randomly allotted by blind balloting to one of two groups.

The sample size calculation was based on the formula.[29]

$p = Z \times \frac{\sigma}{n}$, $pn = Z \times \sigma$, therefore $n = Z \times \frac{\sigma}{p}$

Where p is the probability, σ is the variance, Z is the test statistics and n is sample size. For a normal distribution σ was estimated to be 1, p = 0.05 and Z = 1.96.

$$n = \frac{1.96 \times 1}{0.05}$$

n = 39.2, attrition of 10% was taken into consideration = 39.2 X 10% = 3.9, 39.2 + 3.9 = 43.1. In this study forty-four patients were considered to be adequate.

Patients with poorly controlled hypertension, diabetes mellitus, and history of myocardial infarction in the preceding six months were excluded. Other exclusion criteria were BMI < 19.9 kg/m^2, or class II obesity with BMI > 39.9 kg/m^2. Others included ASA III and IV patients, those with airway assessments of MP III and IV, and those with PCV <30% as well as patients on prolonged steroid therapy for over 2 weeks duration who would require steroid replacement therapy. Patients with contraindication to combined spinal epidural anaesthesia, and known hypersensitivity to lidocaine and bupivacaine.

Anaesthetic procedure

Patients were randomly allocated using 44 sealed envelopes (22 had GAR written while 22 had CSEA written on them), the envelopes were placed inside a box, the patient was asked to pick an envelope, and the type of anaesthesia was determined by what was written inside the sealed envelope. Twenty-two patients received balanced general anaesthesia (group I) and twenty-two patients received CSEA (group II). Baseline investigations for PCV, electrolytes, urea, and creatinine were done for all patients. All patients were fasted from solid food for a minimum of 6 hours prior to surgery. Diazepam 10mg was administered orally at night and 6:00AM on the morning of surgery for anxiolysis. Patients with a pelvic mass greater than 20 weeks gestational size received acid prophylaxis, oral ranitidine 150mg nocte and at 6:00 AM on the morning of the surgery. All operations started between 8:30 and 10:00 AM.

On arrival of the patient in theatre, a non-invasive blood pressure cuff was attached to the upper arm, ECG leads were attached to the chest and limbs, and a pulse oximeter was placed on one of the fingers. The monitoring was through a Multiparameter monitor (Datex Ohmeda Cardiocap 7100). In all patients intravenous access was secured with 16 gauge cannula, 0.9% sodium chloride infusion was given; fluid therapy included correction for preoperative deficit, maintenance fluids and replacement of ongoing losses. Maintenance fluid was given using the Holliday and Segar formular,[30] and blood loss was replaced with colloids.

In group I, all patients were preoxygenated with 100% oxygen for 3-5 minutes. Anaesthesia was induced with IV propofol 2mg/kg and fentanyl 1.5μg/kg. Endotracheal intubation was facilitated with pancuronium 0.1 mg/kg, during the study period because cardiostable drugs such as atracurium and rocuronium were not available in the hospital at the time of the study. The airway was secured with an appropriate sized cuffed endotracheal tube. Anaesthesia was maintained with

isoflurane 1.0-2.5% in oxygen via a closed circuit system, and pancuronium was used for muscle relaxation. All patients were ventilated using intermittent positive pressure ventilation via a Drager Fabius Plus mechanical ventilator. Analgesia was provided by IV fentanyl lμg/kg 30 minutes after induction and 0.5μg/kg at 30 minutes interval for a period of 1 hour. In addition all patients received IV paracetamol 20mg/kg, and diclofenac 1mg/kg. At the end of surgery, residual muscle paralysis was reversed with atropine 0.02mg/kg and neostigmine 0.04mg/kg in all patients. Postoperative analgesia was continued with IV pentazocine 0.5mg/kg 6 hourly and diclofenac 1mg/kg 8 hourly for 24 hours.

In group II patients, 10ml/kg of 0.9% normal saline was infused for 20-30 minutes as preload. The double needle-separate interspace technique was used. Two intervertebral spaces were identified (L_3/L_4) and (L_4/L_5) interspaces. The patient was placed in a sitting position and under aseptic technique; the third and fourth lumbar (L_3/L_4) interspace was identified. The epidural space was localised using the loss of resistance to saline technique via a 16-18G Tuohy needle. The difference in needle size depended on the size of needle supplied with the anaesthetic pack of the patient, this prevented uniformity in the size of needle. The depth of the epidural space was noted, an epidural catheter was inserted into the epidural space leaving 3-4cm in situ. A test dose of 4 mls of preservative free 1% lidocaine in 1:200,000 epinephrine was injected, to confirm correct placement of epidural catheter and thereafter the epidural catheter was secured to the patients' back.

The fourth and fifth lumbar (L_4/L_5) interspace was then identified; a 26 gauge spinal needle was inserted via an introducer into the subarachnoid space, as evidenced by free flow of clear colourless cerebrospinal fluid. All patients were injected with 0.2mg/kg of 0.5% heavy bupivacaine with preservative free fentanyl 25μg into the subarachnoid space. The patients were

re-positioned supine and the level of the block was confirmed using the loss of sensation to pin prick. All patients were allowed to lie down flat on the theatre table immediately after administration of local anaesthetic agent until the sensory level progressed to the fifth/sixth thoracic dermatome (T_5-T_6). Epidural anaesthesia was initiated when there was a 2 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 (5ml) with fentanyl 5µg were administered every 30 minutes for 1 hour, and subsequently 3mls of 0.5% bupivacaine combined with fentanyl 3µg every 30 minutes till the end of the surgery. The level of the sensory block was assessed every 20 minutes using the loss of sensation to pin prick till the end of surgery. Postoperative analgesia was continued with injection of 5 mls of 0.125% plain bupivacaine and 5µg of fentanyl 4 hourly for 24 hours.

Haemodynamic monitoring was recorded every 5 minutes, it included the heart rate which was monitored through the electrocardiogram, and noninvasive blood pressure using an automated sphygmomanometer. The oxygen saturation was measured continuously using a pulse oximeter. The $ETCO_2$ was measured in the general anaesthesia group. All patients had ECG monitoring. Postoperatively monitoring was continued, the pulse rate was measured with a pulse oximeter, the blood pressure and oxygen saturation were documented every 5 minutes for 1 hour in the recovery room.

Blood sample analysis

Four blood samples were obtained for analysis of serum glucose, plasma epinephrine and norepinephrine, insulin and cortisol. Baseline sample was taken before induction of anaesthesia; other samples were taken 1, 3 and 4 hours after surgical incision. This evaluated phase I of the

flow phase. Two blood samples were taken for insulin, before induction of anaesthesia and 24 hours after surgical incision. This evaluated phase II of the flow phase.

The blood sample for glucose estimation was taken into a bottle containing sodium fluoride, to prevent a reduction in glucose level from glycolysis. Glucose samples were analysed immediately. Blood samples for cortisol and insulin were collected into a gel vacutainer bottle and that for epinephrine and norepinephrine into an Ethylene diamine tetraacetic acid (EDTA) bottle. The blood sample was kept in the refrigerator in the theatre at 4^0C, and sent to the laboratory immediately after collection of the last sample. The blood sample was centrifuged and was kept in the refrigerator at 2-8^0C in the laboratory for analysis in batches to enable enough pooling of samples. On the day of analysis, the blood samples and reagent were kept for 15-30 minutes to reach room temperature.

Analytical Method

Glucose analysis was performed by enzymatic oxidation in the presence of glucose oxidase. Cortisol, insulin, epinephrine and norepinephrine analysis was done using 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- 5-35uIU/ml; plasma epinephrine concentration- <100pg/ml, and plasma norepinephrine concentration- <600pg/ml (Gateways Medical Corporation Medfield, MA USA).[31-34]

Statistical analysis

Statistical analysis of the study was performed with the Statistical Package for the Social Sciences (SPSS®) for windows 17 computer Software Programme. Demographic and clinical data included age, weight, height, ASA status scale, MP class, type of surgery, duration of fasting, anaesthesia and surgery. Numerical data were presented, as mean ±SD while categorical data was expressed

as frequencies. The differences in means between the two groups was analysed using the student independent t-test.

Definitions

Hypotension- SBP <90 mmHg or a 30% decrease from baseline BP or MAP <70 mmHg.[35] Hypotension was treated with a bolus of 200ml of Isoplasma solution, if the hypotension persisted for greater than 5 minutes, IV ephedrine 0.01mg/kg was given.[35]

Severe bradycardia- HR below 50 bpm which was treated with 0.01 mg/kg atropine.[35]

Adequate regional anaesthesia- The achievement of anaesthesia at sensory dermatome 5th thoracic level that was associated with a pain free Caesarean section.[36]

RESULTS

Forty four patients were recruited for the study, 3 patients were withdrawn on account of perioperative complications, remaining 41 patients for analysis. The GAR group (I) constituted 21 (51.22%) patients, and the CSEA group (II) constituted 20 (48.78%) patients. There was no difference between the two groups in terms of mean age, weight, height, BMI and PCV, the duration of surgery, anaesthesia and fasting ($p > 0.05$) are as shown in table I.

The modulating effect of anaesthesia on glucose concentration

The changes in mean glucose concentrations in groups GAR and CSEA are as shown in table II and figure 1. The preinduction glucose was similar in both groups (GAR 4.88 ±0.51 versus CSEA 4.90 ±1.04 mmol/L, $p = 0.933$). The mean glucose increased significantly in GAR compared to CSEA, at one hour after incision (6.09 ±1.19 versus 4.58 ±1.31 mmol/L, $p < 0.001$), at 3 hours after incision (GAR 6.77 ±1.39 versus 5.38 ±1.79 mmol/L, $p = 0.012$), and at 4 hours after incision (GAR 7.28 ±1.44 versus 6.17 ±1.69 mmol/L, $p = 0.034$). The glucose concentration after the surgical incision was significantly lower in the CSEA group during the 4 hours study period ($p<0.05$).

The modulating effect of anaesthesia on cortisol concentration

The changes in mean cortisol concentrations in groups GAR and CSEA are as shown in table II and figure 2. The preinduction cortisol was similar in both groups (GAR 13.32 ±6.44 versus CSEA 17.84 ±10.42 μg/dl, $p = 0.299$). The mean cortisol level was higher in GAR group than CSEA group, at 1 hour after incision (30.29 ±14.41 versus 23.42 ±10.33 μg/dl, $p = 0.156$), at 3 hours after incision (GAR 34.16 ±11.88 versus

23.15 ±12.10 μg/dl, p =0.072), and at 4 hours after incision (GAR 38.94 ±10.60 versus 19.96 ±11.32 μg/dl, p =0.018). The cortisol concentrations were higher in the GAR group than CSEA group during the 4 hours study period but were only significant at 4 hours after incision.

The modulating effect of anaesthesia on insulin concentration

The changes in mean insulin concentrations in groups GAR and CSEA are as shown in table II and figure 3. The preinduction insulin was similar in both groups (GAR 4.63 ±0.49 versus CSEA 4.88 ±0.53 uIU/ml, p =0.304). The mean insulin increased to 5.04 ±1.06 uIU/ml in GAR group and decreased to 4.69 ±2.24 uIU/ml in CSEA group at 24 hours after incision, p =0.403. The insulin concentration was lower in CSEA group at 24 hours after incision, but the difference was not significant.

The modulating effect of anaesthesia on catecholamine concentration

The changes in mean epinephrine and norepinephrine concentrations in groups GAR and CSEA are as shown in table II and figure 4. The preinduction epinephrine was similar in both groups (GAR 19.68 ±13.84 versus CSEA 24.36 ±18.03 pg/ml, p =0.641). The mean epinephrine increased in both groups, at 1 hour after incision to (GAR 25.44 ±17.91 versus CSEA 26.39 ±19.22 pg/ml, p =0.867), at 3 hours after incision in GAR to 20.56 ±17.67 but decreased in CSEA 21.68 ±14.77 pg/ml, p =0.743), and at 4 hours after incision in GAR to 22.86 ±11.22 pg/ml but decreased in CSEA to 18.30 ±11.37 pg/ml, p =0.707).

The preinduction norepinephrine was similar in both groups (GAR 38.24 ±16.14 versus CSEA 65.76 ±23.77 pg/ml, p =0.480. The mean norepinephrine increased

significantly in both groups, at 1 hour after incision (GAR 54.52 ±19.45 versus CSEA 219.31 ±42.85 pg/ml, p =0.015). The mean norepinephrine decreased in both groups, at 3 hours after incision (GAR 27.00 ±18.86 versus CSEA 115.29 ±39.91 pg/ml, p =0.045), and at 4 hours after incision (GAR 46.56 ±19.51 versus 72.38 ±20.31 pg/ml, p =0.359).

The modulating effects of anaesthesia on intraoperative MAP and heart rate

The changes in mean intraoperative MAP in groups GAR and CSEA are as shown in figure 5. The pre-induction MAP in both groups was similar (GAR 99.80 ±13.88 versus CSEA 94.47 ±7.72 mmHg, p =0.168). The MAP in CSEA was significantly lower than GAR during the study except for an occasional transient increase in GAR group. The changes in intraoperative HR in groups GAR and CSEA are as shown in figure 6. The mean pre-induction HR was similar in both groups (GAR 88.75 ±16.78 versus CSEA 87.06 ±12.42 bpm, p =0.220). The mean HR increased in GAR group but decreased in CSEA group. The mean HR in group CSEA was lower than in group GAR during the study.

The modulating effects of anaesthesia on postoperative MAP and heart rate

The changes in MAP in the postoperative period in groups GAR and CSEA are as shown in figure 7. The mean MAP in GAR group was significantly higher than in CSEA group on arrival in the recovery room (96.70 ±12.82 versus 86.29 ±8.99 mmHg, p =0.008). The mean MAP decreased in both groups during the postoperative period. The changes in mean postoperative HR in groups GAR and CSEA are as shown in figure 8. The mean HR on arrival in GAR group was significantly higher than in CSEA group

(91.45 ±16.45 versus 84.06 ±10.75 bpm, p = 0.122). The mean HR in group GAR was higher than CSEA group during the study.

Table I. The Demographic and Clinical Characteristics of Patients

	GAR Group I Mean ±SD n = 21	**CSEA Group II Mean ±SD n = 20**	**p value**
Age (yrs)	37.38 ± 6.49	39.50 ±9.13	0.392^{NS}
Weight (kg)	63.46 ± 10.84	67.51 ±10.47	0.233^{NS}
Height (m)	1.60 ± 0.72	1.63 ± 0.70	0.153^{NS}
BMI (kg/m^2)	24.71 ± 3.79	24.93 ± 3.73	0.855^{NS}
PCV (%)	34.05 ± 3.4	33.99 ± 2.35	0.957^{NS}
DOA (mins)	185.65 ± 37.14	178.23 ± 34.68	0.166^{NS}
DOS (mins)	167.81 ± 37.09	151.21 ± 38.15	0.617^{NS}
DOF (mins)	458.9 ±44.34	467.6±34.87	0.829^{NS}

Data represents mean ±SD, and p value for age, weight, height, BMI, and PCV.

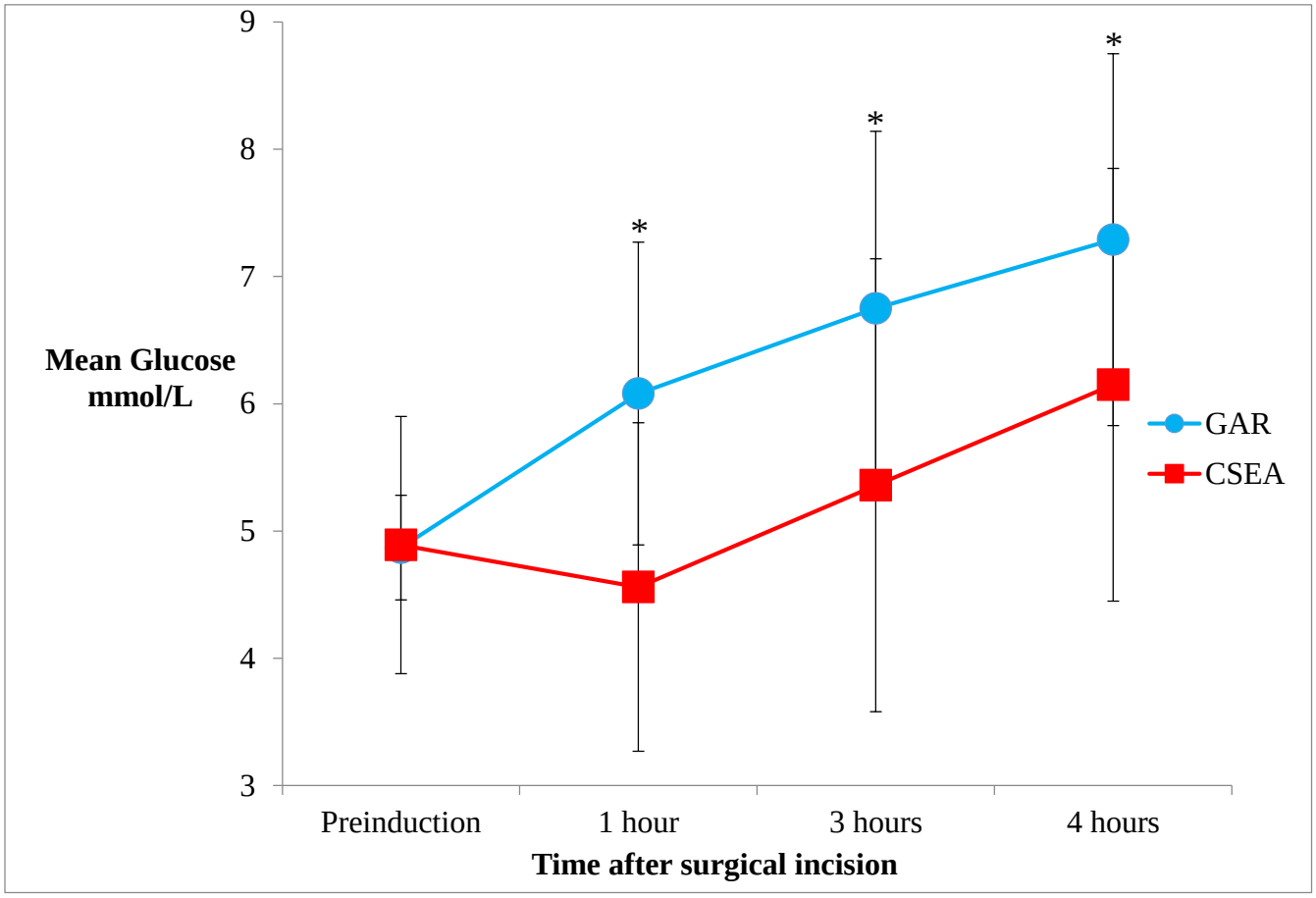
(DOA- duration of anaesthesia, DOS- duration of surgery, DOF- duration of fasting, NS- non significant)

Table II. The modulating effects of GAR versus CSEA on glucose, cortisol, insulin, epinephrine and norepinephrine concentrations

Time of blood collection after incision (hr)	Group I GAR (mean ±SD) n = 21	Group II CSEA (mean ±SD) n = 20	p value
Glucose mmol/L			
Baseline	4.88 ± 0.51	4.90 ± 1.04	0.933^{NS}
1 hour after incision	6.09 ± 1.19	4.58 ± 1.31	0.001^{S}
3 hours after incision	6.77 ± 1.39	5.38 ± 1.79	0.012^{S}
4 hours after incision	7.28 ± 1.44	6.17 ± 1.69	0.034^{S}
Cortisol μg/dl			
Baseline	13.32 ± 6.44	17.84 ± 10.42	0.299^{NS}
1 hour after incision	30.29 ± 14.41	23.42 ± 10.33	0.156^{NS}
3 hours after incision	34.16 ± 11.88	23.15 ± 12.10	0.072^{NS}
4 hours after incision	38.94 ± 10.60	19.96 ± 11.32	0.018^{S}
Insulin uIU/ml			
Baseline	4.63 ± 0.49	4.88 ± 0.53	0.304^{NS}
24 hours after incision	5.04 ± 1.06	4.69 ± 2.24	0.403^{NS}
Epinephrine pg/ml			
Baseline	19.68 ±13.84	24.36 ±18.03	0.641^{NS}
1 hour after incision	25.44 ±17.91	26.39 ±19.22	0.867^{NS}
3 hours after incision	20.56 ±17.67	21.68 ±14.77	0.743^{NS}
4 hours after incision	22.86 ±11.22	18.30 ±11.37	0.707^{NS}
Norepinephrine pg/ml			
Baseline	38.24 ± 16.14	65.76 ± 23.77	0.480^{NS}
1 hour after incision	54.52 ± 19.45	219.31 ± 42.85	0.015^{S}
3 hours after incision	27.00 ± 18.86	115.29 ± 39.91	0.045^{S}
4 hours after incision	46.56 ± 19.51	72.38 ± 20.31	0.359^{NS}

Data represents mean ±SD, p value and the degree of significance for glucose, cortisol and insulin, epinephrine and norepinephrine concentrations. S- indicates that the difference between the means of GAR and CSEA was significant at $p < 0.05$, NS- non significant.

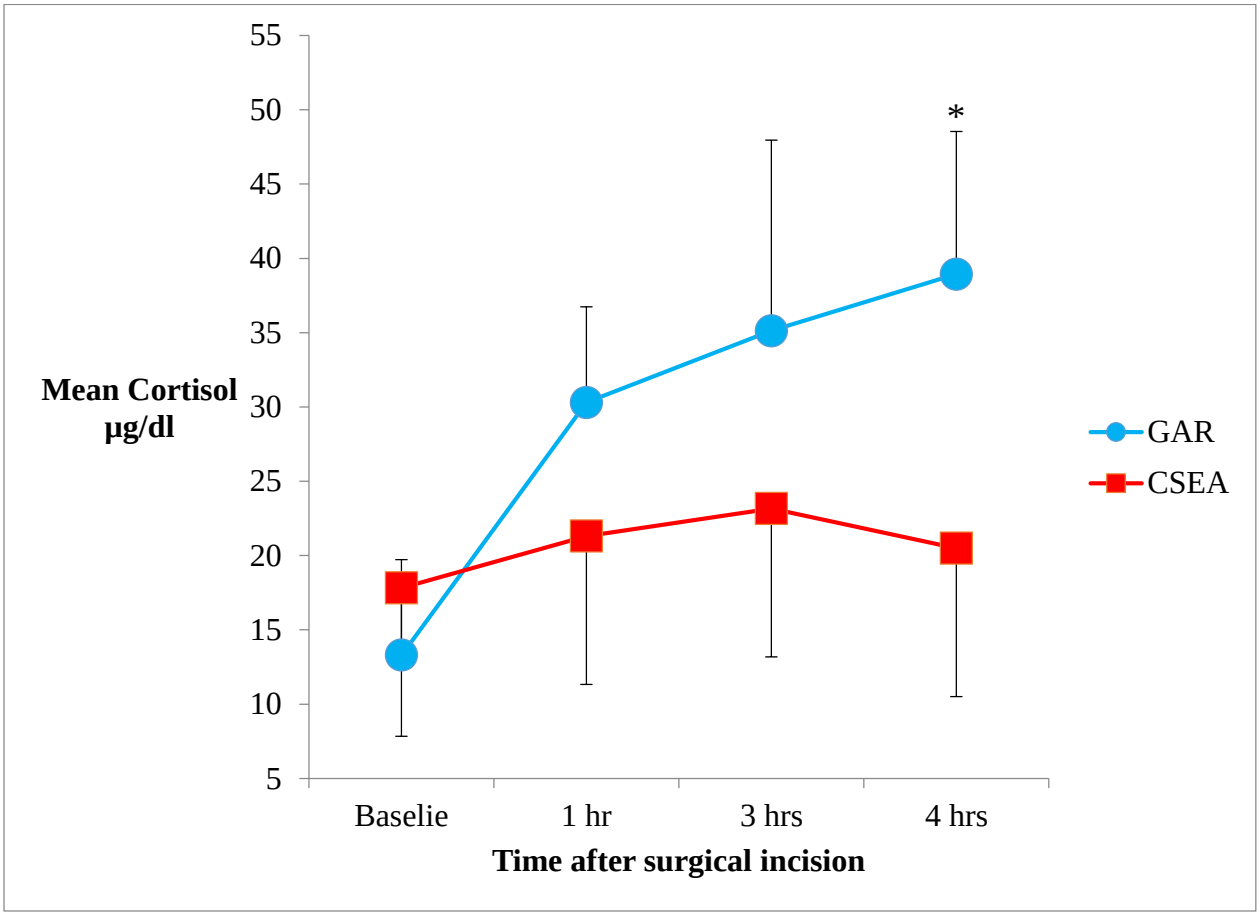
Figure 1. The Modulating Effects of GAR versus CSEA on Mean Glucose Concentrations



This figure shows changes in glucose concentrations from preinduction values to 4 hours after surgical incision. Values are mean ±SD. *Indicates that the difference in the mean glucose concentrations between GAR and CSEA was significant at $p < 0.05$.

Key GAR- General Anaesthesia relaxant technique CSEA – Combined spinal epidural anaesthesia

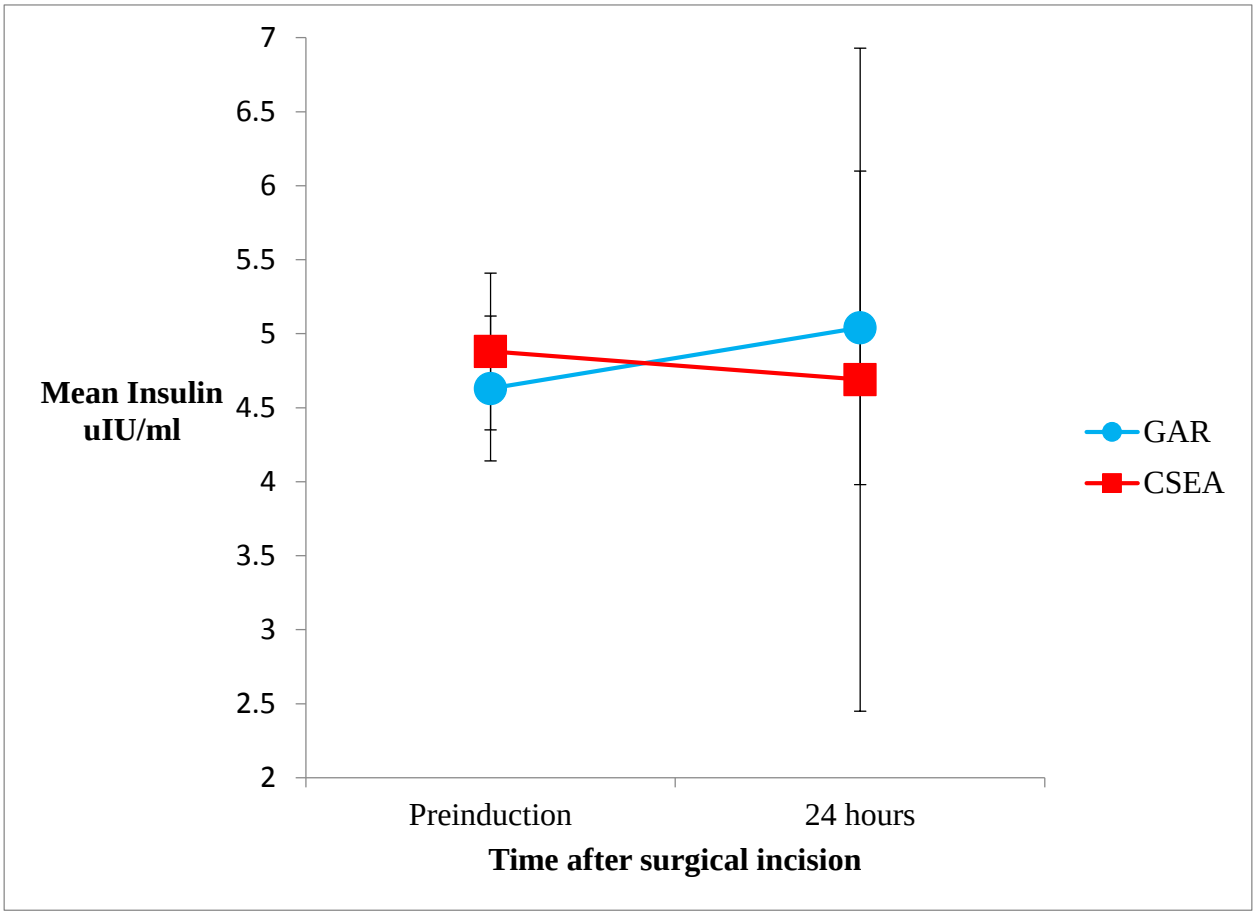
Figure 2. The Modulating Effects of GAR versus CSEA on Mean Cortisol concentrations



This figure shows changes in cortisol concentrations from preinduction values to 4 hours after surgical incision. Values are mean ±SD. *Indicates that the difference in the mean cortisol concentrations between GAR and CSEA was significant at $p < 0.05$.

Key GAR – General anaesthesia relaxant technique CSEA – Combined spinal epidural anaesthesia

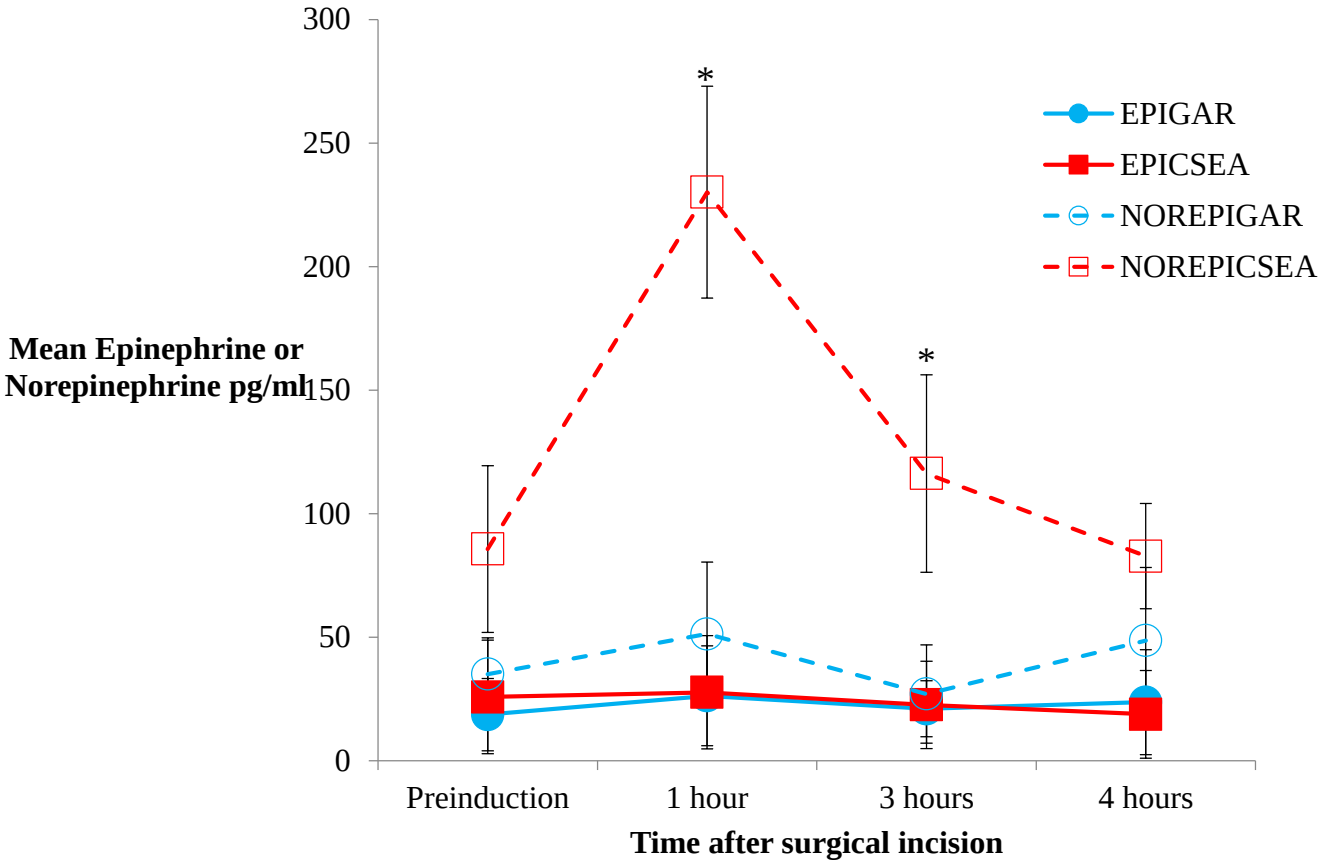
Figure 3. The Modulating Effects of GAR versus CSEA on Mean Insulin Concentrations



This figure shows changes in insulin concentration from preinduction values to 24 hours after surgical incision. Values are mean ± SD.

Key GAR – General anaesthesia relaxant technique CSEA - Combined spinal epidural anaesthesia

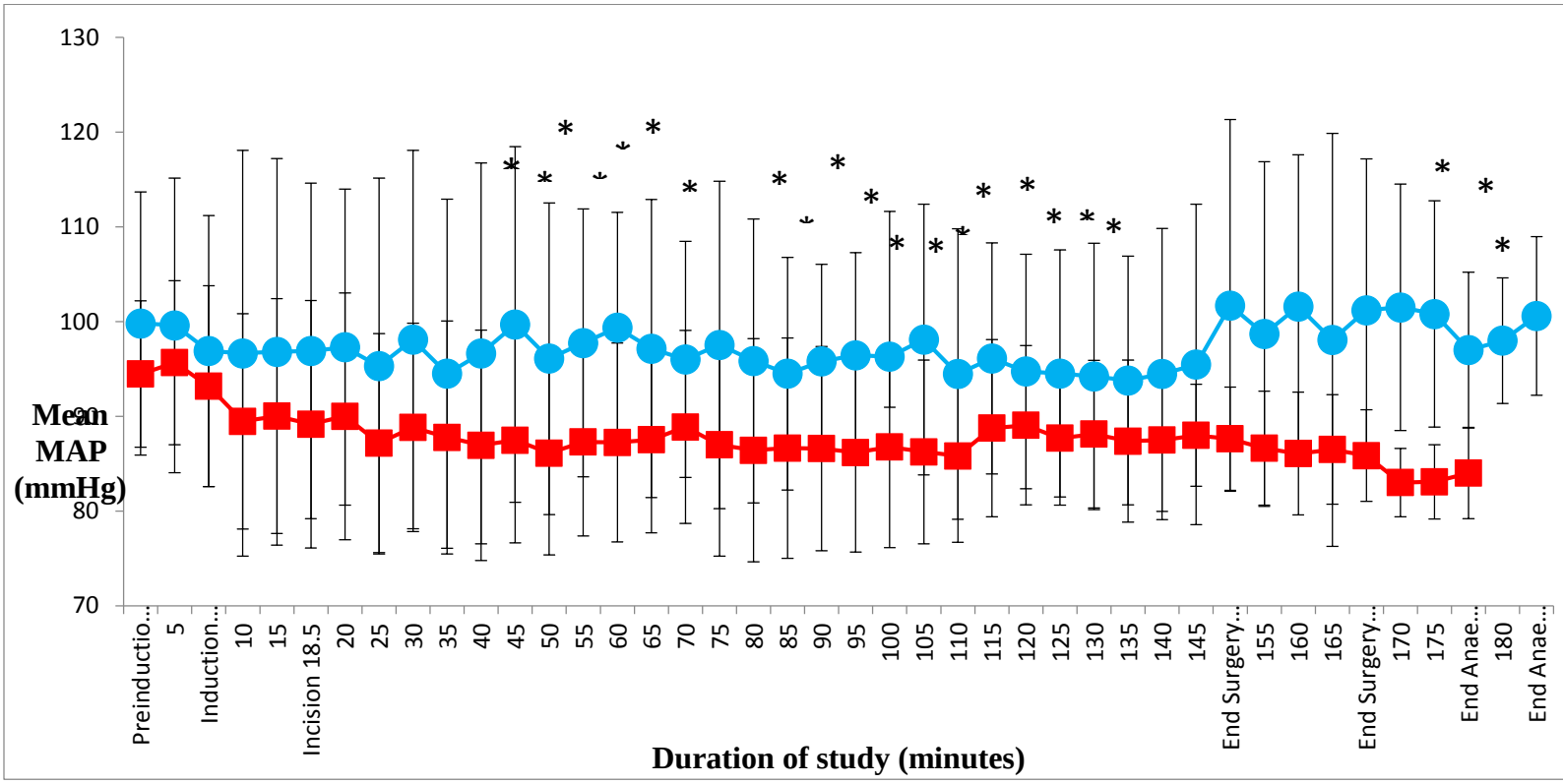
Figure 4. The Modulating Effects of GAR versus CSEA on Mean Epinephrine and Norepinephrine Concentrations



This figure shows changes in epinephrine and norepinephrine concentrations from preinduction values to 4 hours after surgical incision. Values are mean ±SD. *Indicates that the difference in the mean norepinephrine concentrations between GAR and CSEA was significant at $p < 0.05$.

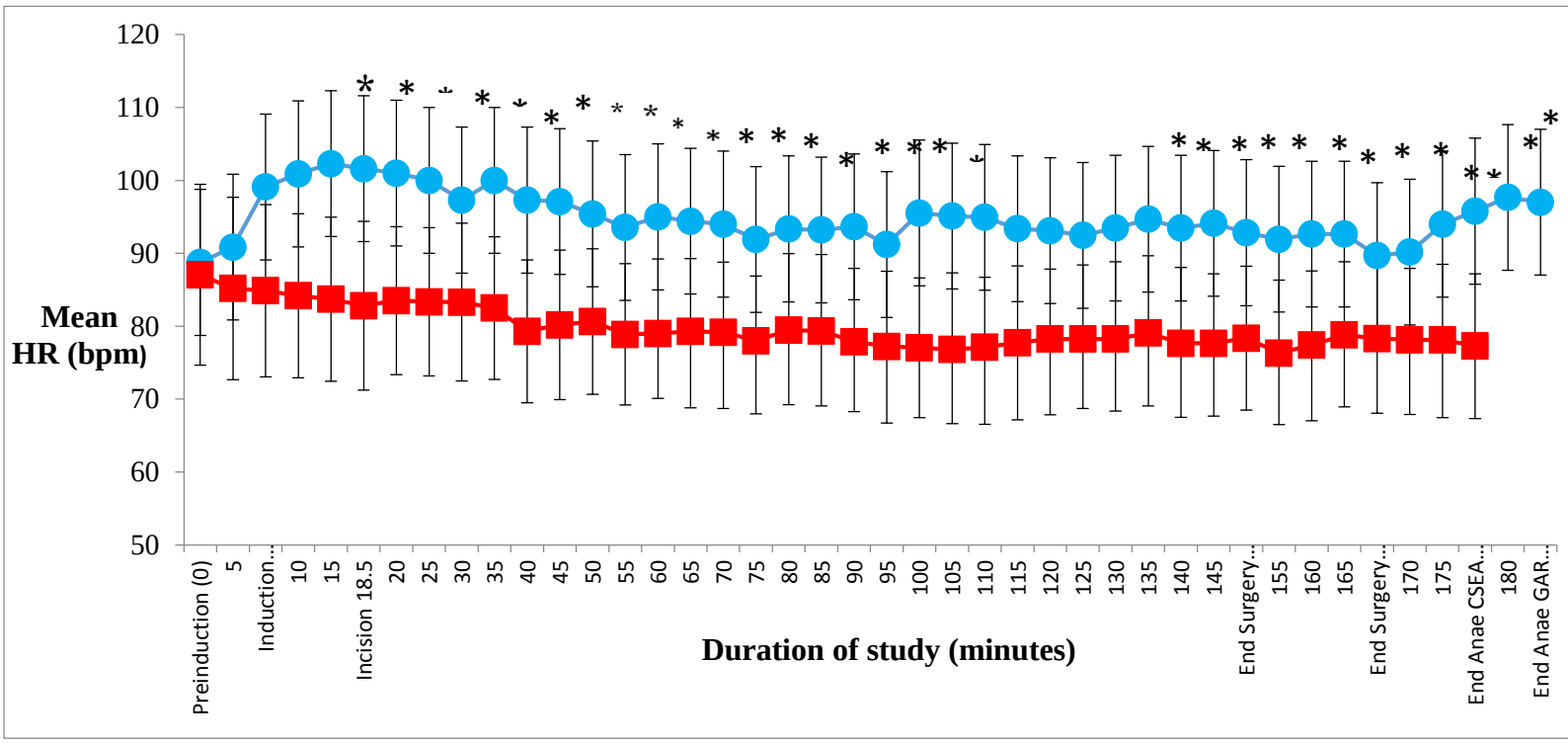
Key EPIGAR- Epinephrine General Anaesthesia relaxant technique; EPICSEA- Epinephrine Combined Spinal Epidural Anaesthesia. NOREPIGAR- Norepinephrine General Anaesthesia relaxant technique, NOREPICSEA- Norepinephrine Combined Spinal Epidural Anaesthesia

Figure 5. The Modulating Effects of GAR versus CSEA on Intraoperative Mean MAP (mmHg)



This figure shows changes in intraoperative MAP from preinduction (0 min) to 185 minutes. Values are mean ±SD. *Indicates that the difference between the means of GAR and CSEA was significant at $p < 0.05$. Key GAR- General Anaesthesia Relaxant Technique CSEA- Combined Spinal Epidural Anaesthesia

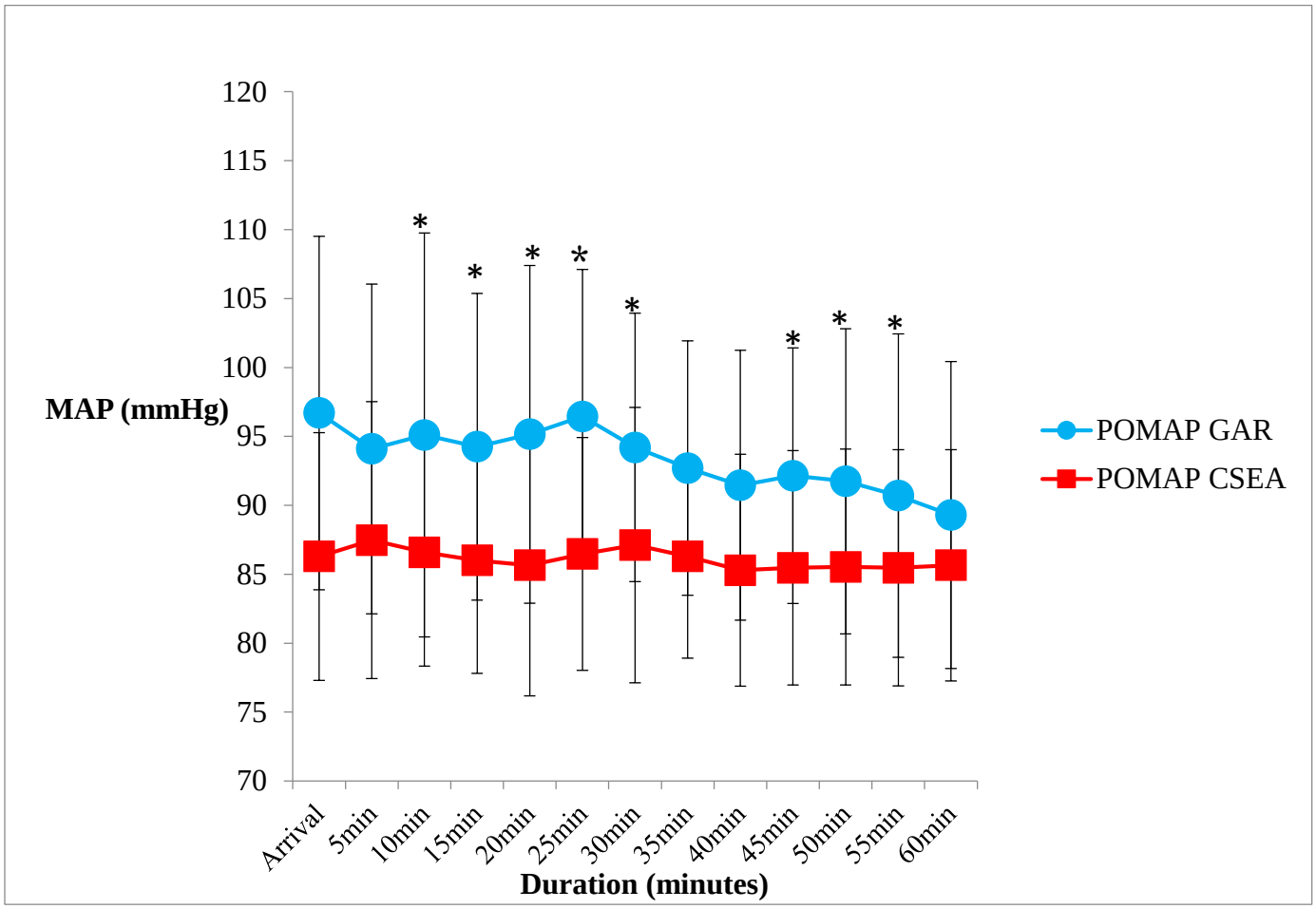
Figure 6. The Modulating Effects of GAR versus CSEA on Intraoperative Mean Heart Rate



(HR)

This figure shows changes in intraoperative heart rate from preinduction (0 min) to 185 minutes. Values are mean ±SD. *Indicates that the difference between the means of CSEA and GAR was significant at $p < 0.05$. Key GAR- General Anaesthesia Relaxant Technique CSEA- Combined Spinal Epidural Anaesthesia

Figure 7. The Modulating Effects of GAR versus CSEA on Postoperative Mean MAP (mmHg)



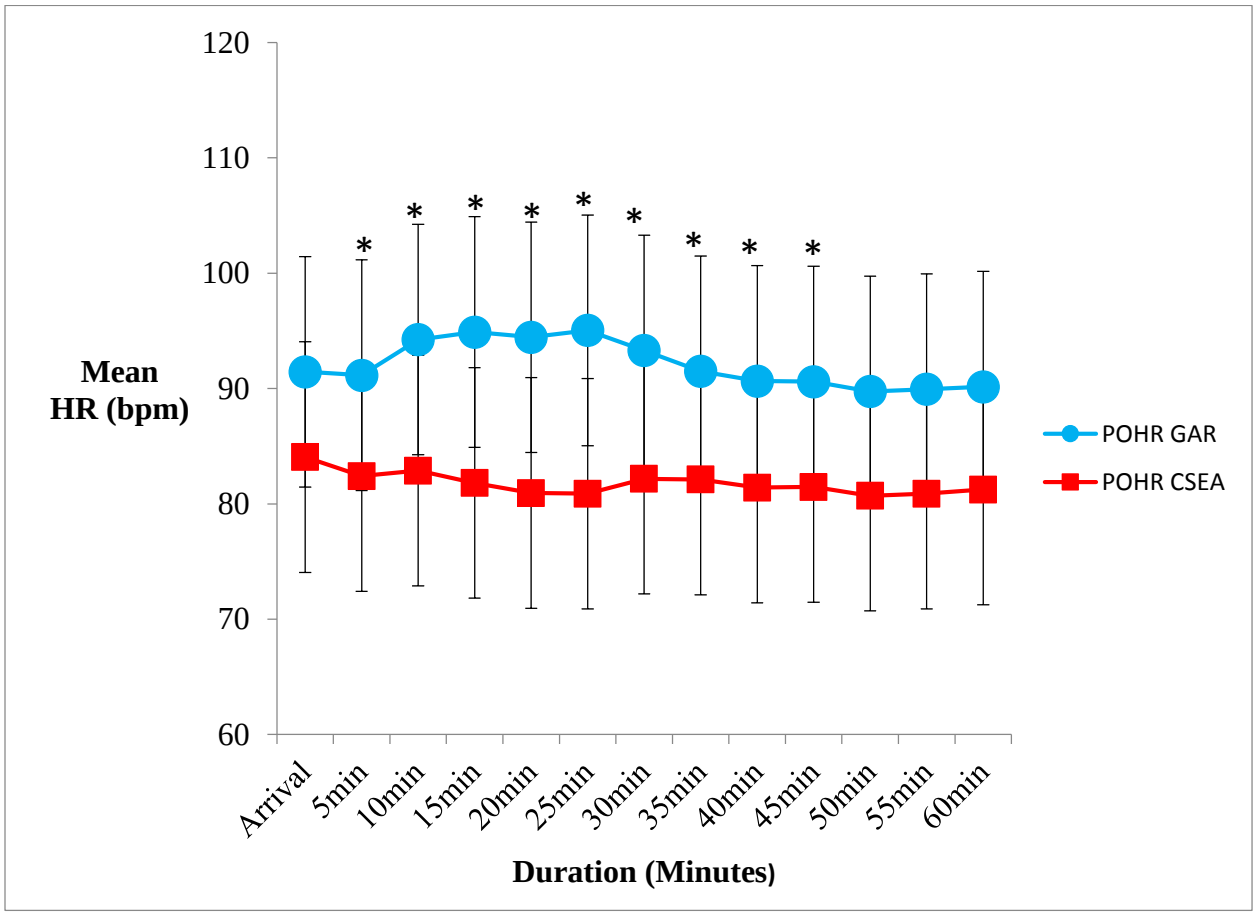
This figure shows changes in postoperative MAP from arrival to 60 minutes. Values are mean ±SD.

*Indicates that the difference between the means of CSEA and GAR was significant at $p < 0.05$.

Key POMAP GAR- Postoperative mean arterial pressure (General Anaesthesia Relaxant Technique)

POMAP CSEA- Post operative mean arterial pressure (Combined Spinal Epidural Anaesthesia).

Figure 8. The Modulating Effects of GAR versus CSEA on Postoperative Mean Heart Rate (HR)



This figure shows changes in postoperative HR from arrival to 60 minutes. Values are mean ±SD. *Indicates that the difference between the means of CSEA and GAR was significant at $p < 0.05$. Key POHR GAR- Postoperative heart rate (General Anaesthesia Relaxant Technique) POHR CSEA- Post operative heart rate (Combined Spinal Epidural Anaesthesia)

DISCUSSION

The stress response to surgery is secondary to activation of the hypothalamic-pituitary-adrenal axis. This leads to the secretion of catabolic hormones from endocrine organs. The response is modulated by the magnitude of injury, pain, the type of surgical procedure and the anaesthetic technique. The degree of stress response may be evaluated by measuring hormonal secretions within few hours of surgical injury.[5-6] This study has demonstrated that CSEA compared with GAR resulted in lower values of glucose, cortisol, MAP and HR in the 4 hour study period from skin incision in patients undergoing major gynaecological operations. The norepinephrine values during CSEA were, however, higher than during GAR.

In patients who had CSEA with intrathecal bupivacaine and fentanyl, the glucose level decreased 1 hour after incision and remained lower than those obtained with balanced general anaesthesia. This is similar to the observations made by Christensen[15] and Moller[19] when intrathecal morphine and bupivacaine were administered before surgical incision. Previous researchers have demonstrated that afferent neurogenic blockade by epidural anaesthesia or analgesia effective before the start of surgical trauma will prevent the endocrine-metabolic response to surgery.[7,22]

In the present study, intrathecal fentanyl was administered in a dose of 1 µ/kg which falls within the stated range for antinociceptive effect. Pain is a known contributing factor to the stress response to surgery.[11,18] The simultaneous administration of intrathecal opioids and local anaesthetic agent was synergistic. It improved the quality of analgesia and reduced the stress response to surgery. This may explain the lower glucose levels obtained with CSEA technique. There are four major subtypes of opioid receptors,

delta (δ) DOP or OP_1, kappa (κ) KOP or OP_2, mu (μ) MOP or OP_3, nociceptin receptor NOP or OP_4 in large concentration in the substantia gelatinosa of the dorsal horn of the spinal cord, a region that is a major site for early integration of nociceptive input.[18]

Intrathecal opioids bind to G-protein-linked presynaptic and postsynaptic opioid receptors in laminae I and II of the dorsal horn. The activation of opioid receptor leads to G-protein mediated potassium channel opening (OP_3 and OP_1) and calcium channel closure (OP_2), with an overall reduction in intracellular calcium. This reduces the release of excitatory transmitters (glutamate and substance P) from presynaptic C fibres with consequent reduction in nociceptive transmission.[18] Fentanyl is the most frequently used intrathecal lipophilic opioid and, when administered in single doses of 10-30μg, it has a rapid onset (10-20 minutes) and short duration of action (4-6 hours) with minimal cephalad spread making it the least likely of all the intrathecal opioids to cause delayed respiratory depression.[18]

The mean glucose level in our study was lower than values reported by Lattermann et al.[21] with a longer duration of surgery, but higher than values reported by Buckley et al.[26] with a shorter duration of surgery. This study involved ASA I and II physical status patients compared to ASA III and IV patients recruited in the study by Lattermann et al.[21] The difference in glucose level is not unexpected as the degree of hormonal secretion has previously been shown to be influenced by the premorbid state of the patient, the duration and intensity of surgical stimuli.[5-6]

A mean glucose level less than 10 mmol/L was reported during the 4 hour study in both groups in this study which may be due to the use of balanced electrolyte glucose free fluid. This is not unexpected as the use of glucose containing fluids had previously

been associated with higher glucose levels.[22] The results of this study also demonstrated that no patient in either group had a fasting blood glucose >7 mmol/L. This may be because patients with diabetes mellitus were exempted from the study. Previous reports have, however, shown an eighteen-fold increase in in-hospital mortality, longer length of stay, and a greater risk of infection in patients with fasting glucose levels >7mmol/L in the surgical wards.[11] In the present study, the infection rate, in-hospital mortality and length of hospital stay were not studied. Hyperglycaemia in the perioperative period has been shown to increase wound infection, cause electrolyte abnormalities, enhanced protein catabolism, and may worsen patients' outcome. It is therefore necessary to preserve perioperative glucose homeostasis.[6,11]

The cortisol concentration increased in both groups in the present study, with lower concentrations documented in CSEA group. The cortisol level in the GAR group doubled 1 hour after incision and increased by threefold 4 hours after incision. A similar study documented a three to four-fold increase in cortisol concentration 4 hours after incision during general anaesthesia and a lower cortisol level during epidural anaesthesia.[19] Other scholars have also reported lower cortisol levels with CSEA.[22]

The cortisol levels observed in this study were higher than other studies.[15,22] This may be because the duration of surgery and anaesthesia was longer than that reported by Christensen.[15] The cortisol concentration during CSEA (T_5) with a higher sensory block level in this study was lower than that documented by Lattermann[22] with block at T_{10}.In another study during cystoprostatectomy with sensory block at T_4,[21] the cortisol level reported was lower than that reported in this study. This is not surprising as other researchers have previously documented that the degree of hormonal inhibition depended

on the level of sensory block.[24] This has further illustrated the effect of different anaesthetic techniques on hormonal secretion.

Enquist et al.[23] also reported a significantly lower cortisol level in patients that had hysterectomy under epidural analgesia. In the same study, the researchers observed that hysterectomy caused a more significant increase in cortisol level compared to tympanoplasty. The authors concluded that hysterectomy was a more invasive surgery.[23] This was unexpected as the mean duration of surgery was longer in tympanoplasty group (174.25 ±35.8) than in hysterectomy group (85.0 ±6.9) minutes. Therefore, it is expected that the mean cortisol 6 hours after incision in tympanoplasty group will be higher than in hysterectomy group. This observation is contrary to previous documentations which showed that the magnitude of the stress response is dependent on the severity, intensity and duration of the stimulus.[5-6]

In contrast, in the present study, the duration of anaesthesia and surgery were similar, despite the similarity, the mean cortisol levels were significantly higher in the general anaesthesia group than the CSEA group. It should be noted that the factors which modulate the secretion of hormones are multiple, and there is interplay of different mechanism. The observation made by Enquist[23] may, however, be due to the small sample size. There is a need for further studies with larger sample size. Alternatively a systematic review of studies that investigated the effect of epidural analgesia on cortisol secretion may be undertaken, as this will overcome the possible effect of a small sample size.

The reduction in cortisol concentration during CSEA may have accounted for the lower glucose level observed in this study. Cortisol has been shown to play an important role in lowering glucose concentration. Physiological hypercortisolaemia results in a

progressive decrease in glucose clearance, and increase in glucose concentration with possible complications arising in the perioperative period.[26] The control of cortisol in the perioperative period with the use of an anaesthetic technique that inhibits its release should be encouraged.

The insulin levels 24 hours after incision increased with balanced general anaesthesia and decreased during CSEA in this study, but this was not statistically significant. This was contrary to a significant decrease in the insulin concentration reported by Buckley et al.[26] during both general anaesthesia and general anaesthesia with epidural analgesia. The difference may be attributed to the difference in time of collection of the blood sample. In the present study, the blood sample was collected 24 hours after incision, while Buckley[26] collected the blood sample at 1 and 8 hours after incision. This will suggest that appropriate timing is important during hormonal study to ensure the hormone will be at the peak concentration. Another reason may be the difference in neuromuscular agents used in both studies. Pancuronium which was used in this study has sympathetic and vagolytic effect, unlike tubocurare a ganglion blocker used by Buckley.[26] The secretion of insulin is decreased by sympathetic stimulation and increased by parasympathetic stimulation. Nevertheless, the factors that influence hormonal secretion are multiple.

This study has demonstrated that during general anaesthesia the glucose and insulin levels increased simultaneously after surgical injury. An increase in insulin is expected to cause a decrease in blood glucose level. There is, however, a period of physiological insulin resistance during surgical injury. During this period the cells of the body are unresponsive to plasma insulin concentrations, therefore hyperglycaemia

persists after surgical injury. This may explain why the increase in insulin level was not associated with a concomitant increase in glucose level during general anaesthesia in this study.

Lattermann[22] reported a decrease in blood insulin concentration with both general anaesthesia and CSEA. In addition, the insulin concentration with CSEA in the study by Lattermann[22] was higher than values obtained in this study. This may be because the sensory block was established at T_{10} (a lower sensory dermatome) compared with T_5 in this study. Some researchers have observed that the 2nd to 6th thoracic sensory levels are implicated in mediating the secretion of insulin, but the 9th to 10th thoracic sensory levels have no influence on insulin secretion.[6] It is therefore not unexpected that a sensory blockade established at T_5 sensory level as in this study will cause a reduction in insulin secretion. In addition, the administration of intrathecal local anaesthetic agents and opioid into the spinal, and, or, epidural space has long been recognised to prevent or blunt the neuroendocrine stress response, which will improve the insulin sensitivity to glucose and limit catabolism.[6,11]

The blood epinephrine and norepinephrine levels in this study were lower in the GAR group than in the CSEA group. This observation is unexpected as pancuronium was used for neuromuscular blockade in patients that had general anaesthesia. Pancuronium is known to prevent the re-uptake of norepinephrine at nerve endings, and to augments the release of catecholamines. This therefore should cause an increase in the secretion of plasma epinephrine and norepinephrine, but this was not the observation with GAR in the present study. A neuromuscular blocking agent such as atracurium and rocuronium would have been preferred as they do not augment the release of epinephrine or norepinephrine,

unfortunately atracurium and rocuronium were unavailable in our institution during the study period. In the GAR group, balanced anaesthesia was, however, achieved with the use of opioids, and maintenance of normocarbia. This may have contributed to the suppression of epinephrine and norepinephrine during general anaesthesia.

In patients that had CSEA, there was significant increase in norepinephrine level in our study, this was surprising because in a previous report in patients scheduled for gynaecological surgery, epinephrine was the predominant catecholamine released.[27] Despite, this earlier documentation, in another study during hysterectomy under general anaesthesia with epidural analgesia Enquist et al.[23] also reported predominant increase in norepinephrine levels. They explained that this was probably due to the local release of norepinephrine during manipulation of the peritoneum and diaphragm, and unblocked vagal nerves stimulation during surgery.

It has previously been documented that the analgesic effect of intrathecal fentanyl is restricted to the immediate region of administration, due to minimal cephalad spread.[18] Since the intrathecal injection in this study was sited at L_3-L_4 lumbar interspace, it may have been that the effect of fentanyl was limited to that region while that of bupivacaine achieved the observed sensory level. This may also account for the predominant release of norepinephrine.

The epinephrine and norepinephrine levels observed in this study were higher than that reported by Breslow et al.[7] This may be attributed to the difference in the anaesthetic techniques in the two studies. In the general anaesthesia group in the present study, IV fentanyl was administered at induction of anaesthesia to suppress laryngopressor response, and normocarbia was maintained during surgery at 3.5-4.5 kPa. Similarly,

Breslow et al.[7] maintained normocarbia at 3.5-4.5 kPa but attenuated the laryngopressor response with IV lidocaine in addition to fentanyl. The combination of lidocaine and fentanyl may have a synergistic effect on the suppression of epinephrine and norepinephrine suppression, and may account for the lower catecholamine level reported by Breslow.[7]

The stimulation of cervical sympathetic afferents via the Vagus nerve during laryngoscopy and intubation as well as hypercarbia increase sympathetic discharge with untoward detrimental effects on the cardiovascular system such as hypertension and tachycardia.[5-6] Transient hypertension and tachycardia present low risks to healthy individuals. This may, however, be hazardous to patients with cardiac diseases such as uncontrolled hypertension and coronary artery disease. There are many pharmacological strategies for blunting haemodynamic responses to tracheal intubation. IV lidocaine and opioids particularly fentanyl, remifentanil, sufentanil and alfentanil are widely used. These opioids are used because of their high potency and short half-life.[11] However, the use of thoracic epidural blockade is gaining ground either in the avoidance of intubation or as an adjuvant to suppress sympathetic discharge during intubation.[8-10] It has been demonstrated that preoperative thoracic epidural anaesthesia can inhibit and sometimes completely block the haemodynamic response during laryngoscopy and tracheal intubation.[8-10]

A significant increase in HR with GAR and a decrease with CSEA was observed in this study. Although the intraoperative HR observed in the present study with CSEA was lower than with GAR, the mean value was never below 60bpm. The HR reported during general anaesthesia in our study was higher than that reported by Enquist[23] and

Hong.[27] The use of isoflurane/fentanyl/pancuronium for the maintenance of anaesthesia in our study may have contributed to the observed HR. Isoflurane has been shown to produce a dose dependent increase in HR which occurs at low doses of isoflurane. Pancuronium is known to augments the release of catecholamines, blocks the re-uptake of catecholamines at adrenergic nerve endings, and have vagolytic properties, therefore it may cause an increase in the HR.[36] The use of pancuronium during this study as earlier documented was because cardiostable neuromuscular blockers such as atracurium and rocuronium were unavailable in the institution at the time of the study.

In contrast, Hong[28] used nitrous oxide/enflurane/rocuronium for maintenance of anaesthesia. The administration of nitrous oxide and enflurane are not associated with substantial changes in HR. On the other hand rocuronium is cardiostable at 1-2 X ED_{95} dose though tachycardia, and increase in cardiac index have been reported at higher doses.[36]

The use of CSEA in the present study was associated with a decrease in the HR which was contrary to observation reported by Hong.[28] who documented no change in the HR. The reason for the difference in the observed heart rate may be due to the difference in volume and dose of local anaesthetic agent used during epidural anaesthesia/analgesia in the two studies. In the present study, epidural anaesthesia was established with 0.5% plain bupivacaine (15.5 ± 2.2ml) and fentanyl (25µg), in contrast Hong[28] established epidural analgesia with 1% lidocaine (10ml) and morphine (2mg). The degree of neuronal blockade has been associated with the dosage of local anesthetic agent, as low volume local anaesthetic agents have been reported to be relatively cardiostable.[24]

In this study, though there was an increase in the norepinephrine levels in patients that had CSEA, this was not followed by a concomitant increase in heart rate and blood pressure. This may be because the norepinephrine level during the study was within the stated normal range. Therefore, the increase in norepinephrine reported is not clinically significant, and may not have caused significant increase in the heart rate and blood pressure in patients who received CSEA. It is also important to appreciate that the level of sensory block was aimed at T_5/T_6 dermatome level. Therefore the sympathetic level is expected to be two dermatome levels higher (T_3/T_4) than the sensory level. These are the cardioaccelerator fibers, and when inhibited may result in bradycardia. However, in this study there was no episode of bradycardia. The release of norepinephrine may have augmented the expected drop in heart rate and therefore an equilibrium was established and the heart rate remained essentially within normal range. This may suggest that the stress response is a complex process with interplay of different mechanisms.

The use of combined spinal epidural anaesthetic technique is gaining popularity in obstetric, lower abdominal and orthopaedic surgeries.[22,35] The most common complication encountered with CSEA is hypotension, which is due to sympathetic nervous system blockade.[35] A mild drop in BP is significant in high risk patients such as the elderly and in those with underlying organ dysfunction in whom the auto-regulatory mechanism may be abnormal. However, these cardiovascular effects have been successfully treated with volume expansion and administration of vasopressors.[35] The use of CSEA is associated with reduced haemodynamic demand on the heart, and decreased secretion of catabolic hormones.[22]

When compared to general anaesthesia, CSEA demonstrated early postoperative recovery, no requirements for intubation, reduced overall mortality in 30% of patients undergoing surgical procedures on the lower extremities or pelvis.[9,11] With CSEA technique, epidural analgesia can be provided in the postoperative period for 24-48 hours. These factors were, however not investigated in this study. The anaesthetist should aim at reducing the stress response during surgery by reducing the secretions of catabolic hormones.

CONCLUSIONS

It is concluded from this study, in patients aged 20-60 years, undergoing gynaecological surgery under balanced general anaesthesia with pancuronium and combined spinal epidural anaesthesia that:

1. The blood glucose levels were significantly lower in CSEA group compared with GAR group.
2. The blood cortisol levels were significantly lower in CSEA compared with GAR group.
3. The blood insulin levels increased after incision in GAR group but decreased in CSEA group. The difference, however, was not significant.
4. The blood norepinephrine levels were significantly higher in CSEA group compared with GAR group at 1 and 3 hours. The HR and BP were, however, significantly lower in CSEA group compared with GAR group.

RECOMMENDATIONS

From this study, it can be recommended that

1. CSEA should be employed in patients scheduled for abdomino-pelvic surgery as it has been demonstrated to result in reduce stress response to surgery. This effect

can be continued in the postoperative period with the use of epidural catheter to give analgesia.

2. CSEA should be preferred in patients with diabetes scheduled for abdomino-pelvic surgery as it has been shown to result in better glucose control than GAR.

3. CSEA is recommended for abdomino-pelvic operations as it results in a moderate fall in heart rate and blood pressure.

LIMITATIONS

1. It was difficult to ensure that all patients were exposed to the same duration of starvation.
2. Different type of incision was used; some of the patients had midline incision and others **Pfannenstiel incision.** This may have contributed to difference in tissue handling and therefore tissue injury.
3. The unavailability of cardiostable neuromuscular blockers such as atracurium and rocuronium at the time of this study limited the choice of neuromuscular blocking agent to pancuronium.

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APPENDIX 1

PROFOMA

The Neuroendocrine Response to Gynaecological Surgery: The Modulating Effect of Two Anaesthetic Techniques

Name of patient…… Age…… Date…….

Weight……Height…… BMI…….PCV……ASA Status…….

Duration of Fasting…… Duration of Anaesthesia……

Duration of Surgery……Type of Surgery…… Type of Anaesthesia……

Intraoperative monitoring

Time	HR	SBP	MAP	DBP	SPO_2	$ETCO_2$
Preinduction						
5 min						
10 min						

15 min						
20 min						
25 min						
30 min						
35 min						
40 min						
45 min						
50 min						
55 min						
60 min						

Time	HR	SBP	MAP	DBP	SPO_2	$ETCO_2$
65 min						
70 min						
75 min						
80 min						
85 min						
90 min						
95 min						
100 min						
105 min						
110 min						
115 min						
120 min						
125 min						
130 min						
135 min						
140 min						
145 min						
150 min						
155 min						
160 min						
165 min						
170 min						
175 min						

180 min						
185 min						
190 min						
195 min						
200 min						
205 min						
210 min						
215 min						
220 min						
225 min						
230 min						
235 min						
240 min						

Postoperative monitoring

Time	HR	SBP	DBP	MAP	SPO_2
0 min					
5 min					
10 min					
15 min					
20 min					
25 min					
30 min					
35 min					
40 min					
45 min					
50 min					
55 min					
60 min					

Blood Sample

	Glucose	Cortisol	Epinephrine	Norepinephrine
Preinduction				

1 hour after incision				
3 hours after incision				
4 hours after incision				

Time	Insulin
Preinduction	
24 hours after incision	

APPENDIX II

PATIENT INFORMED CONSENT

Title of study:

The Neuroendocrine Response to Gynaecological Surgery: The Modulating Effect of Two Anaesthetic Techniques.

Introduction

Patient undergoing elective gynaecological surgeries are administered either general anaesthesia or regional anaesthesia so the surgery can be painless. During the administration of anaesthesia, drugs are administered through the vein for patients undergoing general anaesthesia and into a space at the back of the patient for patients undergoing combined spinal epidural anaesthesia. The procedure has some side effects in susceptible patients, however, these are minimal.

Purpose and description of study

The study aims to determine the effect of balanced general anaesthesia or combined spinal epidural anaesthesia on the secretion of hormones during gynaecological surgery. An anaesthetist will visit you on the ward, and explain the study, answer any questions, and ask for a written informed consent. In the operative theatre, an intravenous access will be secured for intravenous fluid and drugs. While under anaesthesia, the blood pressure, heart rate and oxygen level will be monitored. Five mls of blood samples will be taken before anaesthesia, 1, 3 and 4 hours after incision and after surgery. The type of anaesthesia administered depending on the choice you made via a selection of a sealed envelope.

Potential risks

The risk during the study is minimal, all drugs will be given on a weight basis and the maximum safe dose will be administered.

Confidentiality: All information obtained during the study will be held in strict confidence.

Consent Form

You or your relation has the right not to participate in the study. This does not deny your legal right to treatment in the intensive care unit. You or your relation have the right to withdraw from the study at any time you deem fit.

Consent

I have had an opportunity to ask all necessary questions regarding the information on my participation in this study and have received satisfactory answers. I understand that my participation in this study is entirely voluntary

I, the undersigned, accept to participate freely in this research project.

……

Patient's/Relation's Name Patient's/Relation's Signature Date

……

Witness Name Witness Signature Date

For further enquiry please contact

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