ORIGINAL ARTICLE

The differential impact of two anesthetic techniques on cortisol levels in Nigerian surgical patients

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Abstract

Background: Surgical procedures are associated with a complexity of stress response characterized by neurohumoral, immulogic, and metabolic alterations.

Aim: The aim was to compare the effects on the stress response by isoflurane-based intratracheal general anesthesia (ITGA) and bupivacaine-based epidural anesthesia (EA), using cortisol as a biochemical marker.

Materials and Methods: Following the approval of the Hospital Ethical Board, informed written consent from patients recruited into this study was obtained. One group received general anesthesia with relaxant technique (group A) while the other group had bupicaine epidural anesthesia with catheter placement for top-ups (group B) for their surgeries. Both groups were assessed for plasma cortisol levels – baseline, 30 minutes after skin the start of surgery and at skin closure.

Results: There was no statistically significant difference in the baseline mean heart rate, mean arterial pressure (mean MAP) and the mean duration of surgery between the two groups; the baseline mean plasma cortisol level was 88.70 ± 3.85 ng/ml for group A and 85.55 ± 2.29 ng/ml for group B, *P*=0.148. At 30 minutes after the start of surgery the plasma cortisol level in the GA group was 361.60 ± 31.27 ng/ml while it was 147.45 ± 22.36 ng/ml in the EA group, showing a significant difference, *P*=0.001. At skin closure the mean plasma cortisol value of 384.65 ± 48.04 ng/ml recorded in the GA group was found to be significantly higher than the value of 140.20 ± 10.74 ng/ml in the GA group, *P*<0.002.

Conclusion: Using plasma cortisol as a measure, bupivacaine-based epidural anesthesia significantly reduces the stress response to surgical stimuli when compared with isoflurane-based tracheal general anesthesia.

Key words: Cortisol levels, epidural anesthesia, general anesthesia, surgery

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Introduction

Surgical procedures are associated with a complexity of stress response characterized by neurohumoral, immunologic, and metabolic alterations.[1] During such procedures, hypothalamic activation of the sympathetic autonomic nervous system results in increased secretion of catecholamines from the adrenal medulla and release of norepinephrine from presynaptic nerve terminals.[2] Stimulation of the hypothalamic-pituitary-adrenal axis culminates in the release of both anterior and posterior pituitary as well as adrenocortical hormones.[2] Secretion of cortisol is one of the central features of the neuroendocrine-metabolic response to surgery.[3]

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Research has shown that the magnitude of such stress response is proportional to the magnitude of injury,[4] the operating time[5] as well as the amount of intraoperative blood loss[6] and the degree of postoperative pain.[7] Surgery-related metabolic and endocrine derangements lead to adverse effects, including increased oxygen consumption, catabolism, and impaired immune function.[8] These derangements have been associated with poor postoperative course and clinical outcome.[8,9]

Clinical evidence suggests that the choice of the main anesthetic will be able to influence the stress response by

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inhibiting or modulating the pathophysiologic pathways that induce neurohormonal and immunologic alterations.[10] Attenuating the endocrine metabolic response to surgery, therefore, is of high relevance to the attending anesthetist as this may allow complex operations in high risk patients, such as malnourished, immunocompromised and/or the elderly.[11] Decreasing operative stress may be a pivotal factor in improving outcome and lowering the length of hospital stay as well as the total cost of patient care.[12]

The aim of this study, therefore, is to evaluate the differential impact on the stress response by isoflurane-based intratracheal general anesthesia (ITGA) and bupivacaine-based epidural anesthesia (EA), using cortisol level as a biochemical marker of the degree of stress response.

Materials and Methods

Following institutional Ethical Committee approval and obtaining patient informed consent, patients undergoing elective lower abdominal surgeries were prospectively recruited. Selection was done by simple random sampling. All patients were Class I or II of the American Society of Anesthesiologists (ASA) classification of physical fitness.

Exclusion criteria included age <18 years or >65 years, ASA>II, history of cardiovascular or nervous system diseases, diabetes mellitus, and other endocrine disorders, clotting derangements, obesity (body mass index >30 kg/m^2), medication known to affect the sympathetic response or hormonal secretion, history of substance abuse, patient refusal to participate in the study, allergy to local and/or general anesthetic agents.

Patients were categorized into two groups, A and B, by a research assistant using a simple technique of randomization of consecutive numbers. Patients who had odd numbers were categorized under group A and received isoflurane-based tracheal general anesthesia while those who had even numbers were group B and received bupivacaine-based epidural (regional) anesthesia.

Anesthesia and Surgery

All the patients in groups A and B had preanesthetic review in the evening prior to the day of surgery. Assessment of the physical status and airway was done using the ASA and Mallampati classifications respectively. All patients observed an overnight fast (8 hours for solids and 3 hours for clear fluids).

On the day of surgery all the patients had venous access secured with an 18-gauge intravenous cannula and also received intravenous ranitidine 50 mg, ketorolac 30 mg, and metoclopramide 10 mg 1 hour before surgery. All the patients received a preinduction normal saline 10 ml/kg body weight over 10-15 minutes. Subsequently, intravenous fluid administration was done according to the need of each patient. All operations began between 08.30 hours and 09.30 hours, to minimize variations in cortisol level. Baseline vital signs recording of heart rate, peripheral oxygen saturation (SpO_2), temperature, electrocardiograph, and noninvasive blood pressure (NIBP) were recorded just prior to the commencement of anesthesia, and then repeated every 5 minutes. Urine output by urethral catheterization and blood loss was monitored and recorded throughout the intraoperative period.

All group A patients received general anesthesia with the rexalant technique. All the patients were pre-oxygenated for 3 minutes with 100% oxygen at a flow rate of 8 l/min, using Bain's delivery system and then given intravenous fentanyl 1 μg/kg. Anesthesia was induced in supine position in all the patients in this group. Atracurium besylate 0.5 mg/kg was given intravenously while patient continued to breathe 100% oxygen spontaneously. As tidal respiration began to decrease in the patient, intravenous thiopentone sodium 5 mg/kg body weight was immediately administered and gentle intermittent positive pressure ventilation instituted. Adequacy of oxygenation was ensured by the maintenance of SpO_2 value greater than 95%. Following optimal skeletal muscle relaxation, the trachea was intubated with the appropriate size cuffed tracheal tube (TT) and secured. Maintenance of anesthesia was with 1.75% isoflurane in 100% oxygen delivered mechanically via intermittent positive pressure ventilation (IPPV) using the circle-absorber breathing system, and atracurium 0.3 mg/kg body weight for muscle relaxation. Adjustments in the oxygen/isoflurane ratio and IPPV frequency were made as necessary to maintain the patient hemodynamically stable (blood pressure within 15% of the preoperative baseline value and/or heart rate <85 beats/min) during surgical stimulation.

At the last skin suture, isoflurane was discontinued while the administration of 100% oxygen continued. Following adequate reversal of neuromuscular block, using 0.025 mg/kg atropine and 0.05 mg/kg neostigmine, the oropharynx was suctioned dry. The trachea was extubated when the patient was fully awake. Transfer to the recovery room was done when the patient scored 7 and above using the Aldrete scoring system. For postoperative analgesia, the patient received suppository diclofenac sodium 100 mg 12 hourly and pentazocine 30 mg 6 hourly for 48 hours.

Group B patients received epidural anesthesia. All the patients in this group were placed in the sitting position with the neck fully flexed and feet placed on a stool to enhance flexion of the back. A midline approach was used. Using a sterile technique and the iliac crest as a landmark, the skin and underlying tissues over the L3/L4 in each patient was

infiltrated with 3 ml of 1% plain lidocaine. A skin snip was made in the interspace with the tip of a size 15 surgical blade to facilitate the introduction of an 18-G Tuohy epidural needle in the sagittal plane, with its bevel pointing laterally.

With the Tuohy needle passed into the supraspinous ligament, the stilette was then removed and a 10 ml "loss-of-resistance" syringe containing normal saline was attached to the needle. The needle was then advanced slowly with a sustained pressure on the plunger of the syringe filled with saline. The epidural space was located by observing the plunger move freely and emptying the content of the syringe (the loss of resistance to saline). After rotating the Tuohy needle through 90° to direct the tip cranially, a 20-gauge multiorifice epidural catheter (Minipack; Portex Ltd., Kent, UK) was then threaded 3 cm into the epidural space.

Having confirmed a negative aspiration test for blood or cerebrospinal fluid, 3 ml of 2% lidocaine with epinephrine 5 μg/ml was injected through the catheter as a test dose. The patients were observed for any increase in the heart rate that would indicate intravascular injection of epinephrine and were questioned about dizziness, tinnitus, metallic taste in the mouth, or sudden warmth or numbness in the legs. If these responses were negative after 5 minutes, 0.4 ml/kg of 0.5% plain bupivacaine was injected as a bolus single dose via the epidural catheter. The catheter was then fixed to the skin and the patients were returned to the supine position. Intraoperatively, anesthesia was maintained with top-up doses of 0.2 ml/kg body weight of 0.25% plain bupivacaine administered through the epidural catheter.

The attending anesthetist noted any paresthesia during the insertion of the catheter, inability to advance the catheter, and intravenous or subarachnoid canulation. Intravenous or subarachnoid canulation was detected by aspiration of frank blood or cerebrospinal fluid through the catheter. If intravascular or subarachnoid canulation occurred, the catheter was withdrawn 1 cm. If this did not lead to withdrawal from the vein or subarachnoid space, it and the needle were withdrawn together. If it was not possible to thread the catheter, the catheter was removed. The procedure was then repeated; if unsuccessful again, the patient was excluded from the study and general anesthesia administered.

The attending anesthetist assessed the following variables: The onset and extent of sensory block (assessed by pinprick); the existence of unblocked segments; the extent of motor block (assessed by the modified Bromage score); and side effects or complications caused by the epidural anesthesia, including hypotension (systolic blood pressure <100 mmHg or a decrease of $>20\%$ from baseline), postoperative urinary retention, and transient neurological deficits. Complete loss of sensation to cold cotton wool soaked in alcohol up to the sixth thoracic dermatome on both sides was regarded as an appropriate level of block for surgery.

The intra-operative complications from the two anesthetic options were promptly and appropriately treated. Patients converted from one form of anesthesia to the other were excluded. Postoperatively, analgesia was achieved with repeated bolus epidural doses (0.2 ml/kg) of 0.25% plain bupivacaine given 3 to 4 hourly for the first 12 hours. Following catheter removal, the patients had suppository diclofenac sodium 100 mg every 12 hours and pentazocine 60 mg 6 hourly for 48 hours.

Sample collection and analysis

Data collection was done by an anesthetist not involved in the study. Venous blood samples (1.5-2.0 ml) for the cortisol assay were collected from the antecubital vein of each patient in each of the groups at three different times: (a) at 08.00 hours in the ward (time 0); (b) at 30 minutes after skin incision (time 1); and (c) at the last skin suture (time 2). Each sample was transferred in a plain sterile bottle to the Postgraduate Research Laboratory of the hospital within 45 minutes of collection. All the venous specimens were centrifuged to separate the sera which were then stored frozen till the time of analysis. Serum concentrations of cortisol were measured by a commercially available immune-enzymatic colorimetric-based enzyme-linked immunosorbent assay kit (Microwells ELISA, Cortisol; Diagnostics Automation, Inc., USA. REF: 6101Z; LOT: 1602). The reference normal baseline value for serum/plasma cortisol at 08.00 hours was 60-230 ng/ml (6–23 μg/l).

Sample size determination

It was calculated that a sample of 21 patients in each group was required to detect the difference between the two groups using a power of 80% and $\alpha=0.05$. This was based on a prospective randomized clinical study[1] comparing cortisol changes during isoflurane versus sevoflurane-based tracheal general anesthesia in women undergoing pelvic surgery. Sample size estimation was calculated by using NCSS and PASS (Number Cruncher Statistical Systems, Kaysville, UT, USA). All data collected were entered into a master sheet. Differences in mean values between the groups were calculated using the public domain statistical software for epidemiology (Epi-Info) version 2002. Statistical analyses were performed using Student's *t*-test for parametric data and Mann-Whitney *U*-test for nonparametric data. Results were expressed in means and standard deviations, and simple percentages. Statistical significance was set at the $P<0.02$ level.

Results

A total of 42 patients were approached and recruited for the study. Out of this number, 40 (95.24%) patients

participated throughout the study. Two (4.76%) patients in the epidural group were converted to general anesthesia (GA) and therefore excluded from the study - one due to a patchy block, the other due to inadvertent dural puncture.

Table 1 shows the patients' characteristics. There were no statistical differences in the mean age, body weight, and the ASA physical status between the two groups. Table 2 shows the various indications for surgery in this study. Out of the 40 patients that participated throughout the study, 10 (25.0%) of them were cases of open prostatectomy, with 5 (12.5%) in the EA group and 5 (12.5%) in the GA group. Sixteen (40.0%) patients were cases of abdominal myomectomy with the EA and the GA groups having 8 (20.0%) each. Thirteen (32.5%) patients were cases of total abdominal hysterectomy, 6 (15.0%) and 7 (17.5%) under EA and GA respectively. One (2.5%) patient in the study had myomectomy with ovarian cystectomy under GA.

Table 3 shows the cortisol levels of the patients in the study. The mean baseline cortisol level in the patients in the GA group was 88.70 ± 3.85 ng/ml while those in the EA group was 85.55 ± 2.29 ng/ml, P=0.148. The result showed that there was no statistically significant difference between the two groups in the baseline cortisol levels. Assessment of the cortisol levels at the first 30-minute intraoperative period showed a rise in the plasma cortisol levels in the two groups. The mean plasma cortisol levels in the GA group were 361.60.90 ± 31.27 ng/ml while the mean cortisol level in the EA group was 147.45.95 ± 22.36 ng/ml. The difference was statistically significant, P=0.000. A further rise in the mean cortisol level was observed in the GA group at skin closure. The mean cortisol level in the GA group was 384.65.4 ± 48.04 ng/ml while that in the epidural group was 140.20 ± 10.74 ng/ml. The difference between the two groups was also statistically significant, P=0.0001. The result showed more than fourfold increase above the baseline mean cortisol level in the general anesthesia group.

Table 4 shows the intraoperative condition of the patients. The baseline mean heart rate of patients in the GA group was 78.05 ± 10.01 beats/min while that in the EA group was 71.74 ± 10.43 beats/min, P=0.359. At 30 minutes after the onset of surgery, the mean heart rate was 102.50 ± 15.35 beats/min in the GA group while that for the EA group was 72.68 ± 7.16 beats/min. The difference was statistically significant, P=0.001. At skin closure, a fall in the heart rate was observed in the general anesthesia group. The mean heart rate in the GA group was 99.03 ± 4.38 beats/min and the EA group was 79.11 ± 6.24. This difference also was statistically significant, P=0.001.

The mean arterial pressure (MAP) is also shown in Table 4. In the GA group, it was 71.0 ± 4.33 mmHg while that for the EA group was 67.47 ± 5.29 mmHg. The difference was not significant, P=0.292. At 30 minutes following the onset of surgery, the mean MAP for the GA group was 103.20 ± 4.96 mmHg while that for the EA group was 64.21 ± 4.90 mmHg, showing a significant difference, P=0.001. At skin closure, the mean MAP in the GA group was 89.65 ± 10.86 mmHg while the EA group had 69.37 ± 5.49 mmHg, the difference being significant, P=0.002. The mean duration of surgery however was not statistically different in the two groups of patients.

Table 1: Patients characteristics

Characteristics	GA	EA	*t*-value	*P* (two-tailed)
Age (years)	44.62 ± 9.57	44.43 ± 7.29	0.03	0.976
Body weight (kg)	80.48 ± 5.99	78.71 ± 6.67	0.42	0.682
ASA	1.47 ± 0.23	1.57 ± 0.23	0.62	0.549

Mean±Standard deviation; GA = General anesthesia; EA = epidural anesthesia

Table 2: Types of surgery in the different groups

Type of surgery	EA Number (%)	GA Number (%)
Prostatectomy	5 (12.5)	5 (12.5)
Myomectomy	8 (20.0)	8 (20.0)
Myomectomy with ovarian cystectomy	0 (0.0)	1 (2.5)
Total abdominal hysterectomy	6 (15.0)	7 (17.5)

Number (percentage); GA = General anesthesia; EA = Epidural anesthesia

Table 3: Intraoperative cortisol levels

Time	GA	EA	*t*-value	*P* (two-tailed)
Baseline (time 0)	88.70 ± 3.85	85.55 ± 2.29	1.51	0.148
Time 30 minutes (T1)	361.60 ± 31.27	147.45 ± 22.36	11.95	0.0001
At skin closure (T2)	384.65 ± 48.04	140.20 ± 10.74	10.65	0.0001

Mean±standard deviation; GA = General anesthesia; EA = Epidural anesthesia

Table 4: Intraoperative condition

Characteristics	GA	EA	*t*-value	*P* (two-tailed)
Heart rate (beats/min)				
At time 0	78.05 ± 10.01	71.74 ± 10.43	0.94	0.359
30 minutes	102.5 ± 15.35	72.68 ± 7.16	3.76	0.001
Skin closure	99.3 ± 4.38	79.11 ± 6.24	5.70	0.001
Mean arterial blood pressure				
At time 0 minute	71.0 ± 4.33	67.47 ± 5.29	1.08	0.292
30 minutes	103.2 ± 4.96	64.21 ± 4.90	12.02	0.001
Skin closure	89.65 ± 10.86	69.37 ± 5.49	3.57	0.002
Mean duration of surgery (minutes)	111.85 ± 12.46	117.90 ± 10.0	0.81	0.433
Intraoperative blood loss (ml)	660.0 ± 108.44	481.58 ± 46.27	3.25	0.004
Urine output (ml)	156.0 ± 30.30	228.95 ± 33.41	3.48	0.001

Mean±standard deviation; GA = General anesthesia; EA = Epidural anesthesia

The mean intraoperative blood loss, as shown in Table 4, was 27% higher in the GA group than the EA group. The mean intraoperative blood loss in the GA group was 660.0 ± 108.44 ml while it was 481.58 ± 46.27 ml in the EA group with a significant difference, $P=0.004$. The mean urine output in the intraoperative period was significantly less in the EA group (156.0 ± 30.30 ml) than that in the EA group (228.95 ± 33.41 ml), $P=0.001$.

Discussion

Plasma cortisol level is the most frequently used marker for different kinds of stress-induced reactions such as operative procedures and anesthesia.[13] In our study, we found that, while a minimal rise in cortisol levels was found to be associated with the use of regional anesthesia, more than fourfold increases above the baseline levels were observed in the patients who had surgery under general anesthesia.

Surgery-related metabolic and endocrine derangements lead to adverse effects, including increased oxygen consumption, catabolism, and impaired immune function.[8] These derangements may be associated with poor postoperative course and clinical outcome.[8,9] The categories of surgery studied were myomectomies, prostatectomies, and total abdominal hysterectomies. These forms of surgical procedures are capable of eliciting increases in cortisol level as a response to surgical stimulation. Clinical evidence has shown that the choice of the main anesthetic has an impact on the stress response through the inhibition or modulation of the pathophysiologic pathways that induce neuro- hormonal and immunologic processes.[10]

A fourfold rise in the cortisol level was most marked at 30 minutes following skin incision in the general anesthesia group. Although a minimal rise in the cortisol level was also observed in the epidural anesthesia group, the value obtained did not rise beyond the reference range for this study. The difference between these groups could be explained by the fact that epidural anesthesia attenuates stress response to surgical stimuli.[14]

General anesthesia may limit the perception of sensations due to surgical injury, but does not abolish the response completely as the hypothalamus reacts to the noxious stimuli even in the deeper planes of anesthesia. All the intravenous agents and volatile anesthetics in normal doses have minor influence on the endocrine and metabolic pathways.[15]

Neuraxial blockade has been shown to have direct influence on endocrinal and metabolic response to surgery.[16] The effect of this blockade could be due to the total prevention of the nociceptive signal from the surgical area from reaching the central nervous system. The inhibitory effect of the neural blockade on endocrine and metabolic response to surgery is involved through both afferent and efferent pathways but differ among the individual endocrine glands.[17] The afferent pathway is involved in the release of pituitary hormones whereas adrenocortical hormones release is complex. The cortisol is released through the afferent neural pathway to the pituitary and efferent neural pathway to the adrenal cortex by ACTH.[18]

Although the baseline cortisol levels of our patients were statistically the same, they were much higher than the lower limit of the reference range (60-230 ng/ml) used in this study. This finding compares well with the work of Scheer *et al.*[19] These high baseline values may be due to the surgical ward activities such as open conversations, cleaning of the ward, and noise from machines. The World Health Organization recommends that background noise in a patient's hospital room should be no greater than 35 dB during the day, 30 dB at night, with peaks no higher than 40 dB.[20] Noise levels in excess of these guidelines are believed to disturb sleep and contribute to stress.[21] This could explain the higher baseline values of the cortisol levels in our patients.

The activation of the sympathetic neural and autonomic humoral pathways causes changes in heart rates, blood pressure, and blood circulation.[22] In this study, there was no significant difference in the baseline values of the pulse rate between the two groups. However, following induction of anesthesia and commencement of surgical stimulation, a rise in the heart rate was observed in the general anesthesia group. Heart rate variability is well known to follow laryngoscopy and tracheal intubation. This necessitated the use of intravenous fentanyl to obtund hemodynamic changes that followed airway manipulation as suggested by Kautto.[23] The heart rate of the patients in the epidural anesthesia group did not change significantly from the baseline as a result of neural blockade which inhibits transmission of nociceptive stimuli.

Although the surgeries were carried out by different surgeons, the mean duration of surgery did not differ statistically between the two groups of patients. The duration of surgery is important as this could influence the release of neuro-endocrine hormones from tissue injury during surgical incision and prolong tissue handling.[24] The magnitude, duration, and severity of the surgical tissue handling have direct relationship with the manifestation of the host defense. The quantity of the mediators and spill over of these mediators affect neuro-endocrine reflexes.[17]

One interesting finding in this study was the tendency to more intraoperative blood loss in the general anesthesia group than the epidural anesthesia group. This finding also compares with the work of Fyneface-Ogan and Eke.[25] The use of very high concentrations of volatile anesthetic agents during anesthesia causes direct myocardial depression and a lowered peripheral resistance from direct central vasomotor depression,[26,27] This effect, however, is quite minimal on

the post-arteriolar and small venules which bear the bulk of the blood volume.

The reduction in blood loss observed in the epidural group may be due to a fall in arterial blood pressure[28] from vasodilatation at the post-arteriolar capillaries and small venules. Total peripheral resistance decreases by 18% following complete regional block.[27] This block leads to the dilatation of post-arteriolar capillaries and smaller venules both, somatic and visceral, when the anterior roots are paralyzed, along with their sympathetic vasomotor fibers. The resultant effect is pooling of blood in the lower extremities and organs resulting in a less hemorrhagic surgical field. When the arterial blood pressure is low, hemorrhage is expected to be minimal.[29] This could explain the reduced blood loss found in the epidural anesthesia group compared to that in the general anesthesia group.

Decreased urine production is frequently associated with stress response to noxious stimulus.[30] In this study, the urine output in the patients that received general anesthesia was significantly lower than that in the epidural anesthesia group. Surgical stimuli provoke the release of antidiuretic hormone (ADH) which reduces renal blood flow and hence, glomerular filtration.[31] However it has been found that regional anesthesia increases perioperative water excretion.[32] General anesthesia may limit the perception of sensations due to surgical injury, but does not abolish the response completely as the hypothalamus reacts to the noxious stimuli even in the deeper planes of anesthesia.[15,33] However, the neural blockade by regional anesthesia with local anesthetics has direct influence on endocrinal and metabolic response.[34] Therefore, total prevention of nociceptive signals from the surgical area reaching the central nervous system could be the basic mechanism of neural blockade on stress response to surgery, which mechanism is lacking in general anesthetics. More elaborate studies, however, may be needed to find out whether this holds true.

Conclusion

Surgical handling of tissues may produce neurohumoral, immunologic, and metabolic activities. Anesthetic care provided can reduce the impact of surgical stimulation on the release of the stress hormones. Bupivacaine-based epidural anesthesia has been demonstrated in our study to provide a better inhibition in the production of plasma cortisol usually triggered by surgical stimulation during lower abdominal surgery.

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