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Effect of ascorbic acid on surgical stress response in gynecologic surgery

L. PIRBUDAK,[1] Ö. BALAT,[2] M. ÇEKMEN,[3] M.G. UGUR,[2] S. AYGÜN,[1] Ü. ÖNER[1]
Department of Anesthesiology,[1] Department of Obstetrics and Gynecology,[2] Department of Clinical Biochemistry,[3] University of Gaziantep, Sahinbey Medical Center, Gaziantep, Turkey

SUMMARY

Surgical stress may cause neural, endocrine, metabolic and humoral responses depending on the severity of the procedure. In this study, we aimed to study the effect of the preoperatively given ascorbic acid (AA), which is an antioxidant, and its role in the biosynthesis of neuropituitary hormones on the surgical stress response. Twenty-two American Society of Anaesthesiologists I and II patients ageing between 18 and 40, who have no endocrine and metabolic disease, and undergoing abdominal operation for non-malignant diseases were allocated to the study. These non-premedicated patients were divided into two groups in random: Group I, etomidate group; and Group II, AA plus etomidate group. AA was given to patients in Group II 20 min before etomidate injection. After monitoring the patient, anaesthetic induction was applied by giving 0.3 mg/kg of etomidate, 2 μg/kg of fentanyl and 0.1 mg/kg of vecuronium. Anaesthesia was continued with 1–0.7% isoflurane and N_2O/O_2 (67 and 37%, respectively). Tramadol was given for the management of post-operative analgesia. Blood samples were obtained from all patients before the operation and at second, sixth, twelfth and twenty-forth hours after the beginning of operation for cortisol, adrenocorticotropic hormone (ACTH), osteocalcin, insulin and blood glucose level analyses. There was no statistically significant difference in cortisol, osteocalcin, insulin and glucose levels in both groups, when compared to the control levels. Whereas, patients in Group II had higher levels of cortisol than the control group at sixth hour, which were in normal limits, and there was no decrease in osteocalcin concentration. ACTH level was increased at the second and sixth hours, which was statistically significant, but at twelfth and twenty-forth hours, they were close to control group levels. As a result, we conclude that AA given before anaesthesia achieved by etomidate is not sufficient for the prevention of surgical stress response and that AA induction before anaesthesia should be preferred, particularly for the prevention of decrease in osteocalcin levels.

Keywords: Surgical stress; cortisol; general anaesthesia; ascorbic acid

INTRODUCTION

As a result of endocrine and metabolic stress response in surgery, the plasma concentration of cortisol, antidiuretic hormone, β-endorphin, lactate, catecholamine, glucose, other hormones and metabolites increases. If the case that causes stress is minimal, the effects of physiological response would be useful. But, particularly after a major trauma or surgical operation, the response may turn out to reveal negative results. Hypertension, tachycardia, increase in myocardial load, tissue hypoxia and acidosis resulting from vasoconstriction are some of these negative results (1). Hormonal response can depress both inflammatory and immune mechanisms that can ruin the tissue recovery. It has been alleged that the free radicals are formed as a result of the auto-oxidation of excessively secreted catecholamines (2). While the prohibitive enzymatic systems (superoxide, dismutase and catalase) are secondarily activated against oxidative stress, non-enzymatic anti-oxidative systems [tocoferole, ascorbic acid (AA) and selenium] decrease pointing out the emerging needs (3). AA is a potent reductant and the most important anti-oxidant in extracellular fluid; furthermore, it is the cofactor in 11β-hydroxylase enzyme which takes part in steroid production. Ethmoidale inhibits re-synthesis of AA and reversibly blocks the production of endogen cortisol (4,5).

Consequently, suppressing the response of surgical endocrine and metabolic stress may decrease the post-operative morbidity and mortality (6). The reason for our study on the effects of AA on gynaecological surgery stress response was the previous contradictional studies concerning the effects of AA on surgical stress response.

Correspondence to:
Lutfiye Pirbudak, MD, Universite PTT şubesi, P.K. 43, 27310 Gaziantep, Turkey
Tel: +90 342 360 39 10
Fax: +90 342 360 22 44
Email: lutfiyep@hotmail.com

METHODS

The study was approved by the Local Ethics and Research Committee. We studied 22 premenopausal women undergoing elective abdominal hysterectomy for a non-malignant disease, who have been shown to have American Society of Anaesthesiologists (ASA) physical status I and II. They were healthy with no disorder of the bone or mineral metabolism, no haemochromatosis, no endocrine disease and were not receiving drugs known to affect bone function. Patients who have body mass index below 20 kg/m^2 and above 30 kg/m^2 have all been excluded from our study. All patients were well informed and gave written consent to the study. Patients were allocated in random to receive etomidate or AA plus etomidate for induction of anaesthesia.

No premedication was given. Surgery started between 8:00 and 11:00 PM. On arrival at the anaesthetic room, an intravenous cannula was inserted for administration of drugs and fluids, and a central venous catheter was inserted into the antecubital fossa for collection of blood samples. Routine monitorisation including blood pressure, heart rate, end-tidal CO_2 and SpO_2 measurements were performed for each patient. After the baseline blood sample was obtained, anaesthesia was induced with fentanyl 1–2 μg/kg and etomidate 0.3–0.4 mg/kg (etomidate group) or AA 500 mg, fentanyl 1–2 μg/kg and etomidate 0.3–0.4 mg/kg (AA + etomidate group) and the lungs ventilated with isoflurane and nitrous oxide in oxygen (67 and 37%, respectively) after administration of vecuronium 0.1 mg/kg.

Routine monitoring was undertaken during surgery. Sodium chloride 0.9% solution was infused at 5 ml/kg/h during operation and at 2 ml/kg/h after the operation. Measured blood loss did not exceed 400 ml and was replaced with equivalent volume of Gelofusine. Further increments in vecuronium were given as required, and additional fentanyl to a total dose of 3 μg/kg was administered. Analgesia was provided after surgery by patient-controlled analgesia tramadole, and an initial bolus dose was given if necessary.

In addition to the baseline sample, further blood samples were obtained at 2, 6, 12 and 24 h after the beginning of the surgery and analysed for concentrations of plasma adrenocorticotropic hormone (ACTH) and cortisol, serum osteocalcin and insulin and blood glucose. Plasma and serum were separated immediately from the blood sample. Plasma ACTH and cortisol and serum osteocalcin and insulin levels were measured by routine electrochemiluminescence assay (Immulite-one auto-analyser with DPC kits, DPC, Los Angeles, USA). Blood glucose level was measured by routine enzymatic calorimetric methods (Hitachi 902 auto-analyser with Roche kits, Roche, Manhaime, Germany).

Data were analysed by using SPSS version 10.0 for Windows. The χ^2-test was performed for demographic data. The biochemistry data were evaluated statistically by Mann–Whitney *U*-test to figure out the differences within each group compared with the baseline samples. Differences between groups were analysed by Mann–Whitney *U*-test. Spearman correlation test was applied to analyse the relation between cortisol with ACTH, osteocalcin, insulin and blood glucose concentrations. $p < 0.05$ was considered statistically significant.

RESULTS

Results were obtained from 22 patients (11 etomidate and 11 AA plus etomidate). The two groups were comparable in terms of age, weight and height. There was no significant difference between any variant, including the duration of the surgery (Table 1). The differences in blood pressure values and heart rate of patients within and between the groups were not statistically significant. No significant change in the control values of the levels of plasma cortisol, serum osteocalcin, insulin and blood glucose has been determined, neither within the groups nor between the groups. A statistically significant increase has been determined in both groups at the second and sixth hours after the beginning of the surgery concerning the plasma ACTH levels ($p < 0.01$) (Table 2). There was no particularly significant difference in plasma cortisol concentration, and it was ranging between normal levels at the second and sixth hours in group I and at the second hour in group II, but it was low according to the control levels. Also on the sixth hour in group II, the cortisol concentration was in normal limits, but was higher according to the control level; meanwhile, there was no decrease in osteocalcin concentration level. There was no significant difference in serum osteocalcin level. On the sixth hour, an increase was determined in Group I, whereas no increase was observed in Group II and it was found to be low according to the control level on the twenty-forth hour. There was no correlation between plasma cortisol and osteocalcin concentrations in Group I, whereas the correlation was positive on the twelfth hour in Group II ($r = 0.88$). There was no correlation between the increase in plasma ACTH level and cortisol levels (Figure 1). In both groups, there was no correlation between blood glucose concentration with insulin and cortisol levels.

Table 1 Patients' characteristics and duration of surgery (mean ± SD) in the groups

	Age (years)	*Height (cm)*	*Weight (kg)*	*Duration of surgery (min)*
Group I (etomidate group)	30 ± 12.2	165 ± 5.7	70.8 ± 7.1	93.5 ± 62.1
Group II (etomidate plus ascorbic acid group)	33.1 ± 12.2	164.1 ± 6.5	69.1 ± 11.6	102.9 ± 59.3

Table 2 Cortisol, adrenocorticotropic hormone (ACTH), insulin, osteocalcin and glucose levels (mean ± SD) in the groups

	Duration (h)				
	0	*2*	*6*	*12*	*24*
Cortisol concentration (μg/l)					
Etomidate	16 ± 3.7	13 ± 8.6	13 ± 8.7	14 ± 8.7	18 ± 4.4
Ascorbic acid plus etomidate	15 ± 3.8	10 ± 3.4	19 ± 9.7	14 ± 8.1	5 ± 5.8
ACTH concentration (pg/ml)					
Etomidate	22 ± 3.2	129 ± 22*	99 ± 17*	21 ± 3.5	22 ± 2.9
Ascorbic acid plus etomidate	18 ± 2.5	208 ± 42*	181 ± 38*	20 ± 3.1	20 ± 2.7
Insulin concentration (uIU/ml)					
Etomidate	15 ± 3.6	14 ± 4.6	21 ± 7.3	20 ± 6.4	18 ± 5.2
Ascorbic acid plus etomidate	20 ± 3.7	21 ± 4.8	24 ± 6.5	22 ± 6.4	16 ± 4.3
Osteocalcin concentration (μg/l)					
Etomidate	18 ± 2.7	21 ± 3.6	22 ± 2.6	20 ± 2.8	15 ± 2.6
Ascorbic acid plus etomidate	16 ± 4.8	14 ± 2.3	15 ± 3.8	16 ± 3.1	13 ± 2.1
Glucose concentration (mg/dl)					
Etomidate	85 ± 10	80 ± 15	75 ± 6	123 ± 27	99 ± 17
Ascorbic acid plus etomidate	83 ± 12	108 ± 12	105 ± 13	107 ± 27	125 ± 34

*Significant differences within group, $p < 0.01$.

DISCUSSION

We have shown that, in conditions that AA is either given or not in the anaesthesia that is provided with etomidate induction and isoflurane, no significant change was observed in cortisol, osteocalcin, insulin and glucose levels. But in patients who were given AA, although it may not be statistically significant, no decrease in osteocalcin levels in respect of the increase in cortisol level was observed, and the correlation was positive. Despite not determining the diagnosis that etomidate and isoflurane are boosting surgical stress in our study, it was determined that AA is blocking the decrease in osteocalcin level during increase in cortisol response.

The studies concerning the effects of AA and etomidate on stress response were varying in terms of chosen method and parameters; moreover, they were contradictory (4–8). Besides, it has been declared that the stress response is directly proportional to the severity of surgical trauma and that the body may give higher endocrinal and metabolic response to intra-abdominal operations than superficial body operations (9). We have not been up against the same method and parameters as we practiced, concerning the effects of AA on surgical, endocrinal and metabolic response.

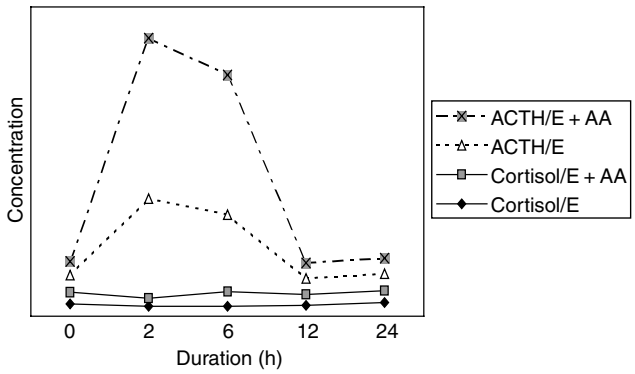

Figure 1 Changes in plasma cortisol (μg/l) and adrenocorticotropic hormone (ACTH) (pg/l) levels in patients. AA, ascorbic acid; E, etomidate

In a study in which anaesthesia is provided by etomidate induction and isoflurane maintenance, the levels of glucose and cortisol were reported to be higher than the control levels (10).

Schaag et al. (7) reported that, during the anaesthesia provided by etomidate plus alfentanil infusion, no significant change in cortisol levels has been observed in the patients who were given or not given 0.5 g/h AA, but it has been implied that AA given before anaesthesia brings cortisol to normal levels (8).

Despite being statistically insignificant, we observed that cortisol levels were low in Group I at second and sixth hours and in Group II at second hour. In the studies which were similar to ours (11,12), the cortisol level in the etomidate Group at the first and second hours was observed to be low. In another study, whether AA is given or not, no significant change in the cortisol levels was observed (7). The conclusion of these studies has similarities with the conclusion of our study.

It has been reported that there is a reactive increase in plasma ACTH level due to the blocking of adrenal steroidogenesis by etomidate. Duthie et al. (12) have determined that in the general anaesthesia induced by using etomidate, there has been significant but clinically inconsiderable decrease in cortisol and corticosterone levels at fifteenth minute and first hour and a surplus significant increase in ACTH level at 15 min, 1 and 4 h.

Moore et al. (13) also have studied the efficacy of etomidate in endocrine response related to surgery and anaesthesia and

reported that ACTH plasma levels are not influenced and that etomidate affects only adrenocortical functions.

In our study, it has been determined that ACTH level has reached the highest level on the second and sixth hours in both groups, and there is no correlation between cortisol level and the increase in ACTH level.

The major metabolic response to stress is hyperglycaemia, and it increases in parallel with the severity of trauma (13,14).

We have not observed any change in insulin plasma concentration and blood glucose concentration as to the control values in either of the groups during our study. We also have observed that the negative correlation that should occur between insulin and glucose has vanished. The reason why blood glucose level does not increase can be explained by blocking of the cortisol by etomidate and the vanishing of correlation between cortisol and glucose.

Stressful physiological states, such as myocardial infarction and major abdominal surgery, are associated with significantly decreased circulating osteocalcin concentrations that occur 1–2 days later. The mechanism(s) for this widespread biological phenomenon are unknown, but glucocorticoids, which would have been increased in these states, have been shown to inhibit osteoblastic activity (15,16). Lind et al. (17) stated that serum osteocalcin levels decreased during torsion test in rat humerus, and this decrease in osteocalcin can be inhibited by supplying with AA.

It has been reported that, etomidate prevents the decrease in plasma osteocalcin concentration in the post-operative period by inhibiting cortisol response to the surgery, with only a non-significant decrease that is observed at the twenty-forth hour (11,18). In our study, we observed statistically non-significant decreases in serum osteocalcin levels in both groups at the twenty-forth hour. Also, in the AA group, we determined a positive correlation between osteocalcin and cortisol at the twelfth hour. This positive correlation can be explained with the inhibitory effect of AA on the decrease of osteocalcin as stated by Lind et al. (17).

In conclusion, AA given before anaesthesia achieved by etomidate is not sufficient for the prevention of surgical stress response and AA induction before anaesthesia should be preferred, particularly for the prevention of decrease in osteocalcin levels.

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