EOSINOPHIL RESPONSE TO TRAUMA AND INFECTION

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DECLARATIONS

CANDIDATE:

This thesis is my original work and has not been presented for a degree in any other University.

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SUPERVISOR:

This thesis has been submitted for examination with my approval as University supervisor.

PROFESSOR A.E.O. WASUNNA
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PREFACE

Rapid metabolic changes occur in a severely injured patient. It is necessary for the physician to be able to monitor the changes accurately so that corrective management can be instituted. It is in view of this that this study has been carried out using a relatively simple parameter as a baseline. It is hoped that this will contribute further towards the management of these patients.
ACKNOWLEDGEMENT

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Finally to all my colleagues and others who contributed towards the success of the thesis I say ASANTE SANA
SUMMARY

A prospective study of an aspect of body response to trauma and infection using eosinophil count as a parameter conducted at the Kenyatta National Hospital over a period of eight months is presented.

A good correlation was found between the eosinophil count and magnitude of trauma and infection. From the results of the eosinophil count it was found that post-operative wound infection could be predicted.

INTRODUCTION

Injury to an individual results in both neuroendocrinological and metabolic responses to the inflicted injury. In the early phase of injury, there is loss of body cell mass, with release of protein split products and enzymes. This is reflected in the increase of urinary nitrogen and amino nitrogen in both plasma and urine and urinary creatinine.

The above changes are accompanied by water, sodium, chloride and bicarbonate ions retention but with increased urinary excretion of potassium and urea. These changes result in metabolic alkalosis in the first 48 hours following injury.

In the injured individual, there is mobilization of the endogeneous energy by gluconeogenesis, glycogenolysis and hydrolysis of the triglycerides to free fatty acids coupled with fall in the serum insulin levels. The rise of glucose level may result in glycosuria. The rise in glucose level
provides readily available source of energy to the tissues especially of the central nervous system, leucocytes and fibroblasts.

The division of phases of response to injury is arbitrary, however the following phases are described depending on the prominent features as the phases usually overlap.

1. Adrenergic-corticoid phase
2. The corticoid withdrawal phase
3. The spontaneous anabolic phase
4. The fat gain phase.

The Adrenergic-Corticoid Phase:

This phase consists of the initial rise of the adrenal medullary hormones; the catecholamines and aldosterone which are respectively responsible for the fall of the eosinophil count and water and salt retention. It is also accompanied by rise in the Adrenocorticotrophic hormones (ACTH) fall in the eosinophil count and rise in the urinary 17-ketosteroids and corticoids. These changes usually occur within the first 48 hours following trauma.

The Corticoid Withdrawal Phase:

This phase usually occurs on the fourth day following trauma and is associated with diuresis with marked potassium conservation and increased loss of sodium in the urine. It is also marked by increased rise in the eosinophil count. The backswing overshoot of the eosinophil count, that is the rise above the pretrauma level, marks the final phase of the response to trauma.
Fig. A
Correlation of Urinary Corticoids and 17-Ketosteroids with total eosinophil count following trauma.
Plasma Corticosterone (ng/ml)

Fig B

- X - Scalded rats
- O - Control
The Spontaneous Anabolic Phase:

This phase occurs on about the sixth day following trauma and requires adequate exogeneous diet. In this phase, there is sustained nitrogen balance, normal eosinophil count and 17-ketosteroid excretion remains low. It is represented by weight gain, fat deposition, water retention and nitrogen accumulation due to increased growth hormone activity.

The fat gain phase is represented by return to normal activity.

Hardy and Randin in 1952 demonstrated the relationship between the urinary corticoids, 17-ketosteroids and the eosinophil count. They demonstrated the inverse correlation between the urinary excretion of the steroids and the total eosinophil count. These relations are shown in Figure A. Following adrenalectomy, there was a marked increase in the eosinophil count. It was also found that the eosinophil count reflected with considerable accuracy the increase in the corticoid excretion following trauma.

The direct way of determining the adrenal activity would be to measure the serum cortisol levels, however the hormone is not stable and has no stable breakdown products, thus urinary corticoids and ketosteroids form a good reflection of the serum levels following trauma. Figure B shows the comparison between traumatised rats and controls, indicating relationship between cortisol levels in traumatised and non traumatised rats. This study was therefore designated to:

- Evaluate the significance of eosinophil count in trauma and infection and to use it in prediction of the likelihood of post-operative wound sepsis.
MATERIAL AND METHODS

A total of 21 patients operated on at Kenyatta National Hospital between July, 1980 and March, 1981 were included in this study. It consisted of 10 laparatomies, 2 prostatectomies, 1 reconstruction of rectal bladder, 2 thoractomies, 1 intramedullary nailing and 5 craniotomies.

Blood was taken in the sequestrene bottles from patients admitted in the various surgical wards in the Kenyatta National Hospital for various types of surgery. The blood samples were taken pre-operatively, immediate post-operatively, on the second, fourth, sixth and tenth post-operative days.

The pre-operative eosinophil count was taken as the baseline. The immediate post-operative sample represented the immediate response to the surgical trauma and was taken as indication of the magnitude of trauma. The second post-operative sample eosinophil count represented the adrenergic-corticoid phase, the fourth post-operative eosinophil count represented the corticoid withdrawal phase, the sixth represented spontaneous anabolic phase and the tenth represented the fat gain phase.

The total counts were carried out in the main Kenyatta National Hospital laboratory, while the differential counts were carried out in the Department of Surgery by Senior Technician in the Department.
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Coarctation of the Aorta

Grafting of abdominal aorta

Gangrene of the foot post-operatively

Ectopic Vasectomy
Partial Bladder

Mitrall valve replacement.

Femur nailing
(10) Acute dilation of the stomach

(11) Encysted Sundural with osrwiro wound infection

(7) Stab wound abdomen perforated gut

(8) Granulation in the pituitary fossa Craniotomy
(12) Perforated D.U.Q.
peritonitis

(9)
Sigmoid volvulus
Resection and
anaestomosis
Peritonitis with adhesion
Laparotomy and appendicectomy

Intussusception
Resection and anastomosis
Sigmoid volvulus
Resection and
Anastomosis

Ruptured Spleen
Splenectomy
BPH
Prostatectomy
RESULTS

From the results of this study, the following interesting observations were made. In all the patients with the exception of the following six cases, 3, 6, 7, 8, 17 and 19 there was a dramatic fall in the eosinophil count comparing the pre-operative and the immediate post-operative values. This represented the response to surgical trauma. In the case 11 (encysted subdural haematoma) in which craniotomy was done the eosinophil count fell from 1050 to 123, in case no. 13 (extradural haematoma) in which craniotomy was done the fall was from 1360 to 823 while in case no. 10 (acute dilatation of the stomach) in which only decompression was done the fall was from 320 to 280, thus the fall in eosinophil count from pre-operative to the immediate post-operative values represented the magnitude of trauma sustained.

The response on the second post-operative day (the adrenergic-corticoid phase) were the same for all the patients except in cases numbers 3, 5, 6, 7, 8, 9, 19 and 20. Apart from the above cases, the second day represented the swing back period, the initiation of the recovery period. In cases numbers 2, 4, 11, 18 and 22 the swing back was more marked and these were operations which did not involve manipulations of the gut.

Considering the cases number 10, 7, 19, 17, 19, and 20 which were cases of laparatomy in which there was some amount of manipulation of the gut, the swing back period was seen to occur between the fourth and sixth days. One noted the similarity of response between cases number 9 and 20 which were cases of sigmoid volvulus with resection and primary anastomosis in which
the swing back period was on the sixth post-operative day. The only possible explanation to this delay in the initiation of recovery as shown by the eosinophil count was that there were substances (toxins) released in obstructed gut by manipulation into the circulation and thus gave response which was a total sum of trauma and infection.

The effect of infection on the eosinophil count was demonstrated by cases number 3, 11, 12, 16 and 17. In cases number 3, 12, and 17 there was pre-operative infection. In case number 16, there was both pre-operative infection (peritonitis) and clinically obvious post-operative wound infection. In case number 11, there was only post-operative wound infection.

In case number 3 in which there was ischaemic gangrene the response was that of infection and trauma and was similar to those of sigmoid volvulus with the rise in eosinophil count occurring on the sixth post-operative day. In case number 12 in which there was generalised peritonitis and surgical trauma due to perforated duodenal ulcer, the eosinophil count was depressed beyond the tenth post-operative day. In case number 17 also a case of perforated duodenal ulcer with localised peritonitis, the rise of the eosinophil count occurred on the fourth day thus demonstrating the eosinophil response was directly proportional to the magnitude of infection.

The pattern of eosinophil response to trauma and infection was similar. Compare case number 6 and case number 17. In case number 6 there was pre-operative (pretrauma) trauma. In this
case there was already eosinophil response to the fracture (trauma) of femur to which was added further trauma (intramedullary nailing). This at the time of operation the eosinophil count was still depressed. In case number 17 there was pretrauma (operative) infection and at the time of surgery the eosinophil count was still depressed.

Considering cases number 11 and 16 which had obvious postoperative wound infection, the pattern of eosinophil response had marked similarity, with spikes and fall as occurs in temperature swings in fever. The fall in eosinophil count corresponds to the rise in temperature. Looking retrospectively one can predict from the fluctuations of the eosinophil counts the wounds which were going to be obviously infected from the above data. It should be noted that only two patients out of twenty-two had clinically obvious wound infection with pus discharge and that the number is too small to reach a dogmatic conclusion.
DISCUSSION AND REVIEW OF LITERATURE

Some of the various factors responsible for the hormonal release in trauma are the afferent nerve stimulus from the site of trauma passing through the pain pathways via the hypothalamus to the cortex and is associated with release of ACTH, cortisol, growth hormone and the catecholamines. Other local wound factors which contribute to the release of the above mentioned hormones are:-

a) the collection of oedema fluid,

b) collection of large amounts of sequestrated blood with absorption of potassium which may lead to hyperkalaemia,

c) development of sepsis and especially endotoxin release. Endotoxin directly stimulates the hypothalamus to release ACTH, Anti-Diuretic Hormone (ADH), cortisol, catecholamines, growth hormone and glucagon.

Haemorrhage and hypovolemic shock stimulate the release of renin and subsequently angiotensin, ADH, cortisol, catecholamines, growth hormone and glucagon. Occasionally the body responds to haemorrhage by a rise in blood pressure. This hypertensive response to injury is a good prognostic sign and is thought to be mediated through the sympathetic nervous system. In hypovolemic shock, the administration of 50% glucose intravenously produces an immediate and sustained rise in both systolic and diastolic blood pressure. In trauma the elevated glucose level is accompanied with reduced glucose utilization and hence a shortage of energy substrate. Glucose loading represents the absolute amount of glucose immediately available to the cell as energy substrate. The hypertonic
glucose may actively elicit insulin secretion by facilitating rapid entry of glucose into the cell. This rise in blood pressure to exogenous glucose is a result of the improved cardiac output. When the mechanisms compensating for the hypovoleamia begin to fail after prolonged shock, considerable data now indicate that these changes are due to depletion of energy reserves of the body. If glucose is administered at this time it will prolong the survival time.

Changes In the Endocrine System:

In the endocrine system, the hormones with generally increased secretion in trauma are; ACTH, ADH, renin, glucagon, aldosterone, cortisol and catecholamines. The ACTH and cortisol release is related to the magnitude of trauma, infection, haemorrhage and also use of ether and the response is to some extent diminished by the use of pentothal.

The catecholamines are released in response to trauma and their effects are shortlived and limited to the day of injury. Usually more nor-epinephrine is released and this results in an increase in cardiac output and rise in blood pressure. They are also released due to the endotoxin direct stimulation on the hypothalamus.

The ADH is released as a result of the stimulation of the supraoptic nucleus by the hypovoleamia aim being to conserve water and salt and to elevate the blood pressure. It may cause dilutional hyponatremia. In head injuries there may be inappropriate secretion of the anti-diuretic hormone.
The stimuli for growth hormone release is due to hypovolemia, direct neural impulse in trauma, and the rise of the amino acids in blood especially arginine although it is noted that arginine levels are reduced in trauma. Its main effect in trauma is to provide energy substrate by its main action which is gluconeogenesis and to potentiate the action of glucagon and catecholamines in mobilization of fatty acids.

The effect of glucagon is to raise the blood pressure and glucose level by glycogenolysis and gluconeogenesis. It also has the effect of raising the levels of cyclic adenosine monophosphate (cAMP) which increases the activity of lipolytic enzymes with lipolysis of triglycerides to free fatty acids and glycerol. It also has anti-insulin effect. Glucagon is an ideal drug for treatment of shock as it increases the cardiac output without further peripheral vasoconstriction and has a selective increase in renal blood flow although it neither prevents nor reverses oliguria in shock.

The hormones with unaltered or decreased secretions in trauma are:- thyroid stimulating hormone and insulin. The goals of the endocrinological changes are directed towards water and salt retention, blood pressure maintenance general mobilization of carbohydrate and provision of ready energy to the muscles, heart, brain and leucocytes and to effect metabolism.

Following severe injury there is marked tissue wasting due to the semi starvation and the extreme catabolism which occurs in the immediate post injury period.

The intensity and duration of the catabolic periods depends
upon the severity of the injury and the presence of sepsis and the success or failure of the body in adapting itself to injury.

The Metabolic Effects of Injury:

The following are the metabolic effects of injury:

a) Hyperglycaemia

b) Mobilization of and elevation of serum levels of free fatty acids (FFA)

c) Catabolism of muscles protein beyond that required as source of energy

d) Increased synthesis of urea and the 'acute' phase reactants (AP-reactants).

e) Increased oxygen consumption in severe trauma and severe sepsis but not ordinarily in the elective surgery.

The carbohydrate energy metabolism depends on: insulin, catecholamines, glucagon, glucocorticoids and growth hormones.

The insulin actions;

Block conversion of Triglycerides to free fatty acids.
Mobilization of amino acids for protein synthesis.

\[
\text{T. G.} \xrightarrow{\text{FFA}} \text{FFA} \\
\text{A. A.} \xrightarrow{\text{Proteins}}
\]

The early elevation of blood glucose is mainly due to the action of catecholamines and to much lesser extent glucagon through hepatic glycogenolysis and suppression of the insulin release. Glucocorticoids and glucagon are responsible for elevation through gluconeogenesis and to a lesser extent growth hormone and catecholamines in the presence of amino acids.
substrate especially alanine. Glucagon is also responsible for the elevation of free fatty acids. How soon after injury in man does hyperglycemia occur? How high does it go? For how long does it persist? Is the level of serum glucose after trauma of any prognostic value? What is the insulin response and in which direction? The rise occurs immediately after trauma and shock and falls to normal usually within 24 hours. There is a definite relationship between the severity of trauma and the level of hyperglycemia. The fall in blood sugar is due to the depletion of liver glycogen stores. The following observations of prognostic value have been made in cases of irreversible shock:

a) Sustained rise in blood sugar level.

b) Rapid rise from about 370 mg% to over 600 mg% within a period of about 2 hours with precipitate fall to about 20% prior to the death are both of poor prognostic signs.

There is no insulin level rise in response to the traumatic hyperglycemia and this is thought to be due to the overwhelming suppression effect of the catecholamines, but there is a rise in response to the exogenous administered glucose as noted above. The infusion of 50% glucose and insulin has only the effect of reduction in catabolism with preservation of the nitrogen and reduction in the rise of urea. This effect of preventing the rise of urea and potassium is a great help in the acute renal failure following traumatic shock.
Fat metabolism in trauma is modified by the rise in various hormones and enzymes.

In protein metabolism following trauma or sepsis there is increased urinary nitrogen excretion within the first one week and may persist for 3-7 weeks, there is muscle protein catabolism in excess of energy requirement from protein sources which constitutes about 15% of energy requirements. There is increased urea synthesis from products of gluconeogenesis, increased albumin synthesis and globulins which is thought to be due to antibody production against micro-organisms. Haptoglobulins and fibrinogen levels rise within 4-6 hours after injury and the seromucoids and ceruloplasmins levels rise several days after injury. The benefit to the body is that the rise in fibrinogen improves clotting, haptoglobulins prevent kidney damage by binding haemoglobin released as a consequence of the injury. Other reactions like AP-reactants and the C-reactive proteins which are released soon after injury may help in binding toxic products or inactivate lysosomal enzymes whose release triggers production of toxins.
Persistent renal failure has little specific effect on plasma amino acids and the amino acids conjugates\(^{27}\). The marked loss of body nitrogen, sulphur and phosphorus in urine following injury cannot be minimised by exogeneous protein intake. It has been noted that catabolism which follows severe injury caused by trauma persists in face of what is probably the maximum protein and caloric intake, it may be modified by diet but not altered by it. In peritonitis in which there is protein loss through exudation and transudation, protein metabolism data indicate a predominantly anabolic process with rise in serum protein levels except albumin\(^{26}\) the aim is to preserve protein for repair of the damaged tissue.

Infection and trauma may produce either hypercoagulation or hypocoagulation of blood. Factors responsible for hypercoagulation are acidosis, increased levels of ACTH and cortisol which are responsible for increased platelet count and reduced capillary fragility. Epinephrine is also initially responsible for hypercoagulation. Factors responsible for hypocoagulation are the multiple transfusion syndrome, extracorporeal circulation and disseminated intravascular coagulopathy due to depletion of circulating fibrinogen due to diffuse intravascular thrombosis or increased fibrinolysis. The effect of endotoxin shock is the lowering of platelet count and prolonging of prothrombin time\(^{14}\), prolonging of clotting time\(^{16}\) and activation of endogeneous heparin and fibrinolysin. Preheparinisation showed a protective effect against fibrinogen fall which is thought to be due to the failure of the liver to manufacture more fibrinogen and also due to consumption in the intravascular clotting process.
The initial hypercoagulability is due to the elevated levels of catecholamines, plasma dilution of anti-coagulation inhibitors, rise in thromboplastin material due to platelet lysis and activation of fibrinolytic enzymes\textsuperscript{2}.

In haemorrhagic shock if clotting time is taken to represent the overall change in coagulability and degree of severity of shock, it is found that the initial hypercoagulability depends on the severity of shock. Within about 17 hours\textsuperscript{13} the clotting time reverts to normal. This is followed in about 27 hours later by hypocoagulability. It was found that the larger the oscillations between the hypercoagulability and hypocoagulability and the more frequently the oscillations occured the worse was the prognosis and in all patients that it occured all died. In correlation between clotting time and other physiological parameters in combat trauma, and sepsis, it was found that non survivors had a more marked prolonged clotting time\textsuperscript{19} and the presence of fibrin split products made prognosis even worse especially if associated with hypotension and acidosis. The low platelet counts are significantly related to the volume of blood required for resuscitation\textsuperscript{36}. In resuscitation usually massive transfusions are used but this has little effect on the fall in platelet count and fibrinogen levels but it prolongs prothrombin time, partial thromboplastin time but these are temporary as they very rapidly return to normal.

The acid-base changes in trauma and sepsis are to a large extent related to the changes in respiratory system\textsuperscript{11}. Alkalosis may be due to hyperventilation occuring in mild and moderate
trauma and may be associated with hypocalceamia and hypo-
kaleamia.

The acidosis is usually due to the rise in the lactate and pyruvate levels, the lactate level being determined by the circulatory status of the patient\textsuperscript{19} and is little affected by blood transfusion. The effects of acidosis are:-

a) Reduction in myocardial contractility.
b) Reduction in myocardial and peripheral vasculature response to catecholamines with predisposition to cardiac arrhythmias and acute renal failure.

There may be pulmonary insufficiency following trauma (Post-traumatic pulmonary insufficiency syndrome) the other causes of the syndrome being: oxygen therapy, alveolar collapse, loss of pulmonary surfactant, viable immunologically competent leucocytes in fresh transfused blood, sepsis and endotoxin damage to the capillary wall. In haemorrhagic shock\textsuperscript{12} there is increased pulmonary artery resistance, rise in arterial blood lactate levels, increased pulmonary shunting and fall in surfactant levels. This makes pulmonary insufficiency the second most common cause of death in patients whose renal survival time is prolonged.

In severe trauma and shock there is increase in serum bilirubin, serum glutamic-oxalate transaminase (SGOT), prolongation of prothrombin time, fall in urea production, fall in fibrinogen level and lowered capacity of aerobic metabolism. Is the irreversible shock due to the reduced capacity of the liver to detoxify injuries products released in shock?
The Gastro-intestinal tract responds to trauma with reduction in peristalsis with ileus, reduced mucin production leading to mucosal necrosis thought to be due to absorption of toxins and a stress ulcer may form. There is renal function suppression with the fall in glomerular filtration rate.

The formed blood elements response to trauma are:

a) Fall in the lymphocyte count.
b) Fall in the eosinophil count.
c) Rise in the polymorphonuclear cells and
d) Rise in the platelet count.

These changes are in response to the 17-hydroxycorticosteroids. This may be associated with defect in the neutrophil antibacterial function which may be demonstrated by stimulated Nitrobluetetrazolium (SNBT)\textsuperscript{12} and has been used for prediction of sepsis in burn patients. Total RBC volume following trauma is partitioned into the rapidly circulating, slowly circulating and the non circulating components and usually there is about 70\% extracellular volume deficit which can be corrected by the administration of sufficient electrolyte and colloid solutions\textsuperscript{22}.

In endotoxic shock there is increased lactic acid metabolism with fall in FFA, amino acids leading to fall in acidosis with improved citric acid cycling and energy production. There is stabilization of the lysosomal membrane, inhibition of anaphylatoxin production from complement and inhibition of complement fixation in the endotoxin system by inhibiting endotoxin-antibody reaction.
CONCLUSION

Eosinophil count is a good parameter of response to trauma and infection, and has a good correlation with endocrinological response. It is much easier to measure and can be used in surgical trauma for prediction of wound infection.

RECOMMENDATIONS

It is recommended from the above study that eosinophil count should be used more often in the severely injured patient as a parameter of response to trauma. This could easily be done by taking blood at the first contact with the patient and then in the follow up periods so that comparisons can be made between patients with various types and severity of injuries. The relationships between the resuscitation measures could also be worked out and this may be used to rectify management of the severely injured patient.
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APPENDIX

METABOLIC RESPONSE TO TRAUMA.
The Eosinophilic Response.

<table>
<thead>
<tr>
<th>Name</th>
<th>IP.NO.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Sex</td>
</tr>
</tbody>
</table>

Blood sample before induction of Anaesthesia.
Blood sample at the end of the Anaesthesia.
Type of operation.

Examination of blood sample:

- **HB**
- **WBC. Total**
  - Differential