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RESEARCH ARTICLE

STRESS MAY INFLUENCE HOST RESPONSE FOLLOWING SURGERY CAN WE PREDICT POSTOPERATIVE INFECTION WHAT IS BENEFICIALOR HARMFUL?

[1,*]Mózes, T., [2]Gornicsar, K., [3]Grosz, A., [4]Ta. Mózes, Bíró, E., [5]Kovács, L., Ta. [6]Beöthe, Zs. Domján and [7]Buzogány, I.

[1]Military Hospital, Budapest, Hungary
[2]Department of Urology, Péterfy Hospital,
[3]Department of Aerospace Medicine, University of Szeged,
[4]Departement of Psychology, Eötvös Loránd University, Budapest, Hungary
[5]Central Laboratory (Buda), Semmelweis University,Budapest, Hungary
[6]Student in research, Semmelweis University, Budapest, Hungary

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***Corresponding author:* Mózes, T.,**

ABSTRACT

Background: In 1891, William B. Coley injected streptococcal organisms into a patient with inoperable cancer. He thought that the infection he produced would have the side effect of shrinking the malignant tumor. **Hypothesis:** Surgical infection may improve host response. **Methods:** 55 urinary bladder cancer patients, with radical cystectomy and lymphadenectomy were studied. Blood samples were taken on day 0 and day 1, 3, 6, 9 and 14 after operation and at 5-year follow up. TNFα, soluble TNFα receptor I and IL-6 levels in sera were determined by HS ELISA and/or ELISA kits. Plasma cortisol values were measured by RIA kits. **Results:** From 55 patients.27 infected (wound and urine infections) in 30 days after surgery, 5 patients suffered peritonitis 2 died following leakage of small intestine suture.23 uneventfuly healed.All patients were bacterially contaminated, as wound samples taken at the end of operation demonstrated. 21 died due to the metastatic cancer during follow up.On day 0 the circulating values of TNFα were lower in infected patients. TNFα started to increase from day 3 till day 9 never reaching values of uneventful healing group.Soluble TNFα receptor I was elevated in septic group while, IL-6 elevated on day 1 than decreased for 14 days. Cortisol concentrations were elevated on day 0 and a correlation was found between cortisol and TNFα. Number of serum lymphocyte reduced by half one day after operation. Recovery in 5 days resulted in uneventful healing in 10 days septic consequences. If no recovery death occurs. **Conclusions:** Measuring serum TNFα levels before and after operations can predict the outcome. The infection may improve host response. However, the postoperative infection is a double edge sword can result in a severe sepsis and/or can elevate immune response improving the outcome from operation and/or from tumor disease.

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INTRODUCTION

Severe illness and stress strongly activate the hypothalamic-pituitary-adrenal (HPA) axis and stimulate the release of adrenocorticotrophic hormone (ACTH) from the pituitary, which in turn increases the release of cortisol from the adrenal cortex (Jurney, 1987; Reincke, 1993; Arlt, 2003). This activation is an essential component of the general adaptation to illness and stress and contributes to the maintenance of cellular and organ homeostasis. Adrenalectomized animals succumb rapidly to hemorrhagic and septic shock, and steroid replacement is protective against these challenges (Jurney, 1987; Reincke, 1993).

Stressful early life experiences can have short- and long-term effects on neuroendocrine and immune mechanisms of adaptation, which are primarily modulated by glucocorticoids. One study aimed to examine how the stress and immune systems interact to cope with psychosocial stress induced by a single social isolation. This social isolation provoked increased plasma ACTH and cortisol concentrations and reduced TNFαlevels but had no significant effect on IL-6 levels. Single social isolation also induced a dose-dependent cortisol resistance in LPS-stimulated PBMCs compared with controls, which may be an adaptive response in the short term. Moreover, LPS-stimulated cultures from control piglets showed a reduction in cortisol sensitivity with increasing age.

(Tuchscherer, 2010). Radical cystectomy entails simultaneous surgery on the urinary tract, intestines, and lymph nodes; hence, complications frequently occur after this extensive procedure. According tothe literature, the incidence of such secondary conditions varies widely (from 19% to 64%) (Liedberg, 2010). There were 27 (2.5%) perioperative deaths, with a total of 292 (28%) early complications. (8)Tumor necrosis factor (TNFα) plays an important role in host defense and tumor growth control. Therefore, anti-TNFα antibody therapies may increase the risk of serious infections and malignancies (Bongatz, 2006). The hostresponse is an inevitable and unavoidable consequence of any tissue engineering or regenerative medicine strategy for organ restoration. Logically, the manner in which the host responds to the selected intervention will be a critical determinant of the survival and downstream functionality of the engineered organ. Depending on the source of the cells and the type of material chosen, this response may include components of the innate and adaptive arms of the immune system. A number of well-known host responses including transplant rejection, the host response to tissue injury, and the foreign body reaction are described as a basis from which to understand the host response to engineered organs, which may encompass multiple aspects of each of these responses. A focus upon the role of the innate immune system and macrophages in particular is pro vided and new paradigms surrounding the host macrophage response.

TNFα is a cytokine that is produced by macrophages, monocytes, endothelial cells, neutrophils, smooth muscle cells, activated lymphocytes, astrocytes, and adipocytes. The brain and the immune system are functionally linked through neural and humoral pathways, and decreased immune competence with higher incidence of infections has been demonstrated in several acute neurological conditions. A strong cytokine mediated anti-inflammatory response was recently observed in stroke patients at higher risk of infection (Chamorro, 2007), although infection due to the decreased pro-inflammatory mediators can be expected as well. . Accumulates the results from literature, (Bongatz, 2006; Mózes, 1991; Bonta, 1991; Mózes, 1992; Mózes, 1991; Siu-Yin, 2008). In 1891, William B. Coley injected streptococcal organisms into a patient with inoperable cancer. He thought that the infection he produced would have the side effect of shrinking the malignant tumor. He was successful, and this was one of the first examples of immunotherapy. Over the next forty years, as head of the Bone Tumor Service at Memorial Hospital in New York, Coley injected more than 1000 cancer patients with bacteria or bacterial products. These products became known as Coley's Toxins. He and other doctors who used them reported excellent results, especially in bone and soft-tissue sarcomas. Despite his reported good results, Coley's Toxins came under a great deal of criticism because many doctors did not believe his results. This criticism, along with the development of radiation therapy and chemotherapy, caused Coley's Toxins to gradually disappear from use. However, the modern science of immunology has shown that Coley's principles were correct and that some cancers are sensitive to an enhanced immune system. Because research is very active in this field, William B. Coley, a bone sarcoma surgeon, deserves the title “Father of immunotherapy” (Edward, 2006). Each year in the United States approximately 5000 people die from bone and soft-tissue sarcomas. To investigate the question of the role of crucial pro-inflammatory mediator, tumor necrosis factor alpha (TNFα) in nosocomial infections the following experiment was performed.

MATERIALS AND METHODS

The study was approved by the ethics committee of hospital. Fifty five muscle invasive urinary bladder carcinoma patiens were involved in this study from January 1, 2009 till December 31, 2018. Exclusion criteria were, inflammation, infection, and taking non-steroid anti-inflammatory drugs and/or antibiotics. After obtaining informed consent, blood samples were taken from donors who had no physical exercise on the morning of blood sampling and had normal temperature. Blood collection happened before operation (day 0) and after operation (day 1,3,6,9,14 and month 6,9, 12 and year 2, 3, 4 and 5). Before closing the wound sample was taken for culture.

Specimen Collection: A Vacutainer system was used for taking blood. Venous blood was collected in EDTA tubes. A separate tube obtaining serum samples, which were stored at -20 ^{o}C until TNFα and cortisol assays

Isolation of periferic blood mononuclear cells (PBMCs): Seven ml whole blood was layered onto 7.0 ml of HISTOPAQUE®-1077 (Sigma, Hungary) in a 50-ml conical tube. Tubes were centrifuged at 400 g for 10 minutes at room temperature. After centrifugation, the opaque interface was transferred into a conical centrifuge tube and mixed with 10 ml isotonic phosphate buffered saline (PBS; pH=7.2). After centrifugation (250 g for 10 minutes), the cell pellet was re-suspended in 12 ml PBS. The procedure was repeated 3 times to remove HISTOPAQUE contamination, then the cells were re-suspended in RPMI 1640 with Hepes (Gibco, UK) and L-glutamine (0.8x10-3 mol/l) supplemented with 5% bovine serum (CM). The cells were counted, distributed into a minimum of two aliqots and cultured as 106 cells/ml CM with or without 1 μg/ml LPS, in round-bottom polypropylene vials (38x 12.5 mm) in 5% CO2/humidified air at 37°C. LPS dose was chosen by dose effect of LPS in this system (0.1 ng/mL-1000 ng/mL). After 24 h, the incubation was terminated by centrifugation at 250 g and aliquots of supernatants were stored at -80°C until TNFα measurements.

Serum TNFα levels were analyzed in duplicate using a commercially available HS ELISA kit (R and D Systems Inc. Minneapolis, USA) according to the manufacturer’s instructions. The test sensitivity was 0.5 pg/ml and intra-assay and interassay coefficients of variation were 8.5 and 10.5%, respectively. Serum TNFαReceptor I. levels were analyzed in duplicate using a commercially available ELISA kit (R and D Systems Inc. Minneapolis, USA) according to the manufacturer’s instructions. The test sensitivity was 0.033 pg/ml and intra-assay and interassay coefficients of variation were 5.2% and 5%, respectively. Serum IL-6 levels were analyzed in duplicate using a commercially available ELISA kit (R and D Systems Inc. Minneapolis, USA) according to the manufacturer’s instructions. The test sensitivity was 0.025 pg/ml and intra-assay and interassay coefficients of variation were 1,6%and 6.3%, respectively. In vitro PGF2 levels were analyzed in duplicate using a commercially available ELISA kit (R and D Systems Inc. Minneapolis, USA) according to the manufacturer’s instructions. The test sensitivity was 0.25 pg/ml and intra-assay and interassay coefficients of variation were 5.2%and 5.0%, respectively. Clinical laboratory values like lymphocyte, counts, and γGT were assessed by routine clinical procedures

Statistical analysis: All data are presented as means± standard deviation (SD) mean). The data were evaluated by a non-parametric two way analysis of variance (Friedman test) followed by the Wilcoxon-Wilcox test to identify differences between measurements performed at different times during observation period. The Mann-Whitney test was performed to evaluate the differences between the groups. A P value of 0.05 or less was considered statistically significant for all tests. Correlation between serum cortisol and serum TNFα levels was calculated by Spearman rank test.

RESULTS

From55 patients.27 infected (surgical site infection SSI) in 30 days after surgery, 5 patients had peritonitis following leakage of small intestine suture 3 survived 2 died.All patients were bacterially contaminated,as wound samples taken at the end of operation demonstrated. Twenty tree patients remained unseptic and 21 died due to the metastatic cancer. On the day 0 the circulating TNFα values were 1 pg(ml in volunteers 2pg/ml I SSI patients and 4 pg/ml in uneventfully healing patients. As can be seen in host respone to tumor patients TNFα alph levels elevated but in different valueslower resulted in infected patients. TNFα started to increase from day 3 till day 9 never reaching values of uneventfully healing group. One year following the immune stimulation by infecton sserun level of circulating TNFα radually decreased in both groups and during 5 years of follow up.Soluble TNFα receptor I was elevated in septic group while, IL-6 ele ngtvated on day 1 than decreased gradually during 14 days. Cortisol concentrations were eievated on day 0 and a correlation was found between cortisol and TNFα. Number of serum lymphocyte reduced by half one day after operation Revovery in 5 daxs resulted in uneventful heajind in 10 days septin consequeces. If no recovery death occur

DISCUSSION

The main findings of present study can be summarized as: (a) patients with uneventful healing and patients with , surgical site infections (SSI) show marked differences in respect of circulating TNFα levels and cortisol levels as well as in the time difference in diagnosis and operations; (b) the TNFα concentration and cortisol values on day 0 outline down-, up-regulated subgroups in the investigated population, on day 0 before surgery in respect of outcome as well (c) patients demonstrated high serum , cortisol levels and low serum TNFα concentrations all suffer of surgical site infection,27 of 55 bladder carcinoma patients demonstrated high cortisol levels with low circulating TNFα levels with wound infections contrary to uneventfully healing group, (d) based on connection between brain and immune system two subgroups of host response to surgery were observed, the uneventfully healing group is beneficial, the downregulated ie harmful resulting in infection:(e)this different host responses can be seen on day 0 before surgery thus can predict the outcome. Nearly 1 in 4 patients who ultimately are diagnosed with bladder cancer has a delay >3 months between their first provider claim for hematuria and diagnosis. Those with more protracted delays have significantly higher rates of mortality from the disease and are more likely to undergo a major intervention, such as radical cystectomy. Patients who had a delay of 9 months were more likely to die from bladder cancer compared with patients who were diagnosed within 3 months.

Present study demonstrated a higher wating time from hematuria till surgery a better outcome. It seems a different immune response may be responsible (Hollenbeck, 2010). Glucocorticoids (GC), the final mediators of hypothalamic pituitary-adrenal (HPA) activation, are important regulators of various physiological systems, including the immune system, and play a major role in the adaptation of organisms to stressful situations. Previous studies in humans and animals have shown that circulating GCs are beneficial during the adaptive process in the short run, but during long-term or repeated exposure to stressors, the effects of GCs on immune function are detrimental (Tuchscherer, 2010; Liedberg, 2010). Furthermore, it is well known that there are crucial interactive loops between GCs and cytokines. Proinflammatory cytokines, produced by activated immune cells, are potent activators of the HPA axis. GCs in turn suppress cytokine production and, by this mechanism, are able to terminate immune processes to protect the organism from an overactive immune system (Stein, 2001; Chamorro, 2007; Bongatz, 2006). A study suggests that GCs may cause alterations in cytokine production, which favor humoral immune responses while suppressing cellular immunity (Marik, 2012). Although this model of immune deviation could be an adaptive mechanism to prevent the immune response from causing tissue damage, maladaptive responses to stress-induced immune alterations may contribute to increased disease susceptibility.

In addition to peripheral cortisol levels, the cortisol sensitivity of different target cells from organisms exposed to stressors should also be considered (Marik, 2002). Several studies have supported the hypothesis that social stressors affect the steroid sensitivity of immune cells in animals and humans. As shown in mice, repeated social disruption stress may cause reduced cortisol sensitivity in splenocytes (Edward, 2006; Rohleder, 2003; Stark, 2001; Avitsur, 2001; Merlot, 2004). In addition, the corticosteroid sensitivity of peripheral blood lymphocytes were decreased in chronically stressed caregivers of patients with dementia (Bauer, 2000). However, acute modulation of GC sensitivity in response to short-term psychosocial stress has only been investigated in a small number of studies. In students, it has been demonstrated that stress associated with academic examinations provokes an activation of the HPA axis with increased levels of cortisol followed by a transient decrease in the cortisol sensitivity of leukocytes ex vivo (Sauer, 1995). Similarly, the social stress induced changes in cortisol sensitivity for pro-inflammatory cytokine production by LPS-stimulated whole blood cultures of healthy humans (Rohleder, 2001). Moreover, there is also evidence for age-related changes in cortisol sensitivity of different target tissues in human and animal models, with greater sensitivity observed in younger individuals (Sauer, 1995). The rapid development of cortisol resistance observed in the present study could be adaptive for the organism to preserve cell function and prepare the immune system for potential unpredictable danger. However, identification of the mechanisms mediating such a rapid modulation of cortisol sensitivity and their possible consequences remains to be investigated. LPS-stimulated PBMCs of younger control piglets were much more sensitive to inhibition of the proliferative response by cortisol than cells of piglets at older age (Hiba! A könyvjelző nem létezik.) This finding confirms an age-dependent effect, because it was documented that neonatal lymphocytes are more sensitive to cortisol inhibition than are those from older pigs (Rohleder, 2001). Production of pro-inflammatory cytokines importantly contributes to host defense against wound infections.

Descriptive statistics

	group			
	non surgical site ifection		surgical site infection	
	Mean	Standard Deviation	Mean	Standard Deviation
age	60,1	7,4	63,3	5,9
surgery time (min))	356,2	50	371,3	31,6
Blood loss (ml)	923,1	458,5	840	390,6
body weigh (kg)	79,1	11	80,2	16,5

Table 1. demonstrates study population Surgery was performed on the day after admission.

	surgical site infectionN=27	no surgicaI slte infection N= 23	Volunteers N=12	Total N=61
average TNFα (pg/ml) day 0	2.47	3.851	1,12	
SD	3,96	4.92	0,65	
average TNFα pg/ml 1 year	5,03	1,60		
SD TNFα 1 year	11,17	2,56		
time to operation days	835.7	480.4		
SD days	1171.7	581.59		
Metastasis at surgery	12	13		25
N at surgery	9	7		16
L at surgery	3	1		4
death M	10	7		17
death N	2	0		2
death L	1	1		2
death All	13	8		21

Table 2 . TNFα values before and after surgery. Solubilis TNFα in serum of non SSI and SSI patients Abbreviationts M metastasis N lymph node L local in

	Volunteers					
Number of Observati-ons	Se TNFα (pg/ml)	Se TNFα In Vitro A (pg/10^6 cells)	Se TNFα In Vitro B (pg/10^6 cells)	Serum IL-6	PGE2 A (pg/10^6 cells)	PGE2 B (pg/10^6 cells)
1	1,22	0,10	0,26	4.70	1824,00	2029,52
2	1,39	0,09	0,08	0	1577,13	1494,43
3	0,62	0,00	0,28	0,95	1550,65	1620,77
4	1,46	0,06	2,70	0	1648,86	1677,61
5	0,77	0,02	0,24	0	1593,31	1707,06
6	0,60	0,00	0,06	0	1367,28	1445,62
7	0,67	0,13	0,29	0	2107,30	2180,98
8	0,80	0,00	0,28	0	1362,84	1514,56
9	0,97	0,03	0,04	0	1336,60	1550,65
10	0,35	0,00	0,23	0	1367,28	1626,34
11	2,16	0,04	0,45		1573,53	1684,75
12	2,47					
Mean	1,12	0,04	0,45	0,11	1573,53	1684,75
S.D.	0,65	0,05	0,76	0,32	232,35	226,61

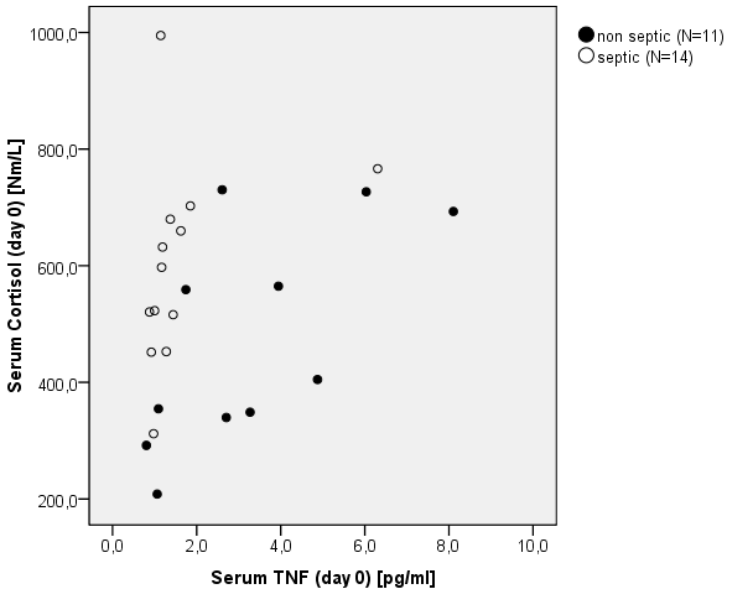


Figure 1. A significant correlation was observed between cortisol and TNFα on day 0

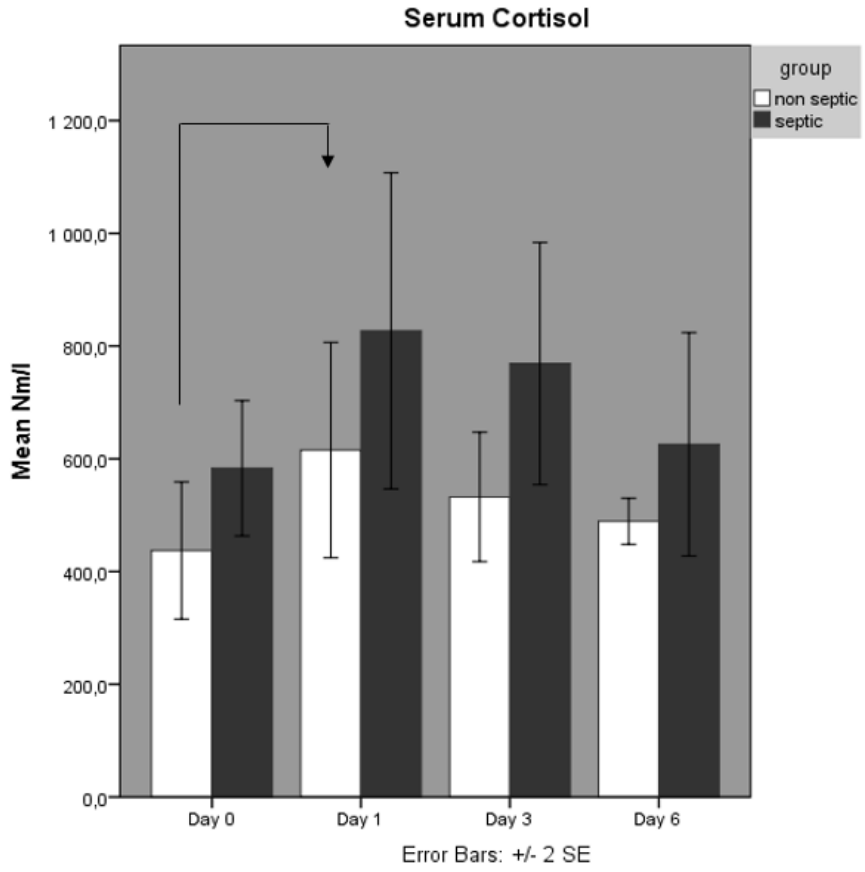


Figure 2. Significantly higher cortisol concentrations were observed in septic group starting on day 0 and day1 with a decline later on. In uneventfully healing group serum cortisol levels on day0 and day1 were lower comparing to septic group and were sustained in the whole investigated period comparing to septic group

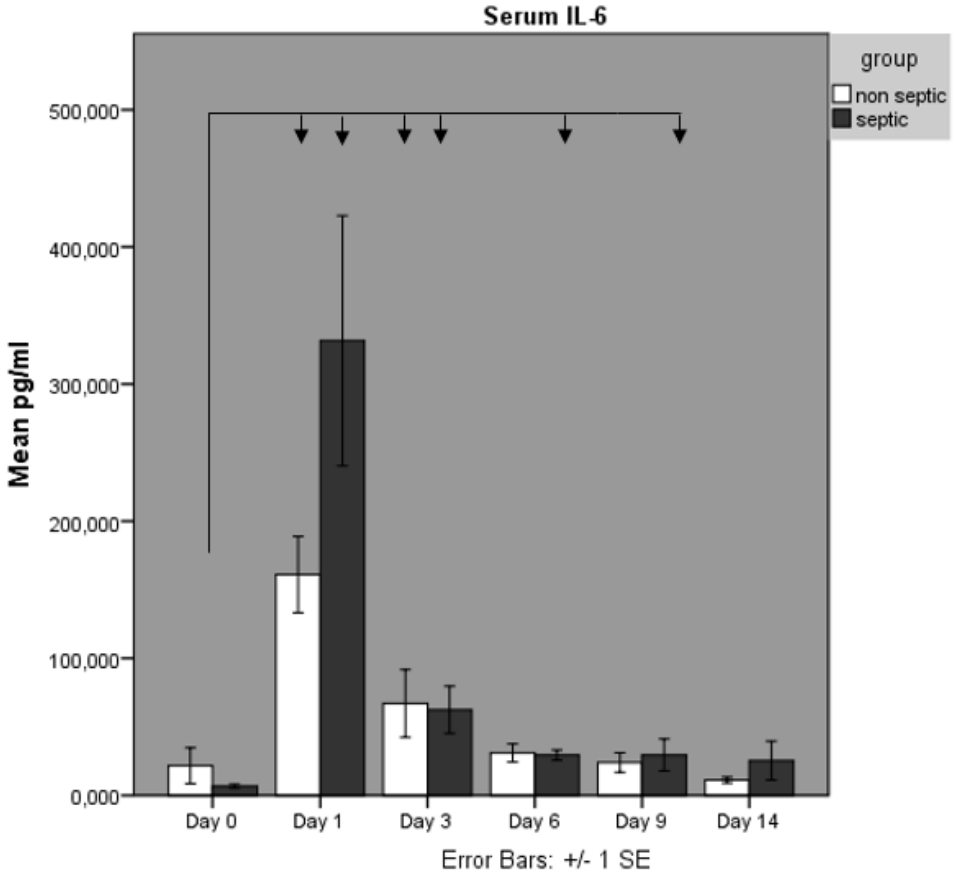


Figure 3. Serum IL-6 was elevated in both and gradually decreased 14 days of observation period Septic (non-septic groups in septic oneit was higher

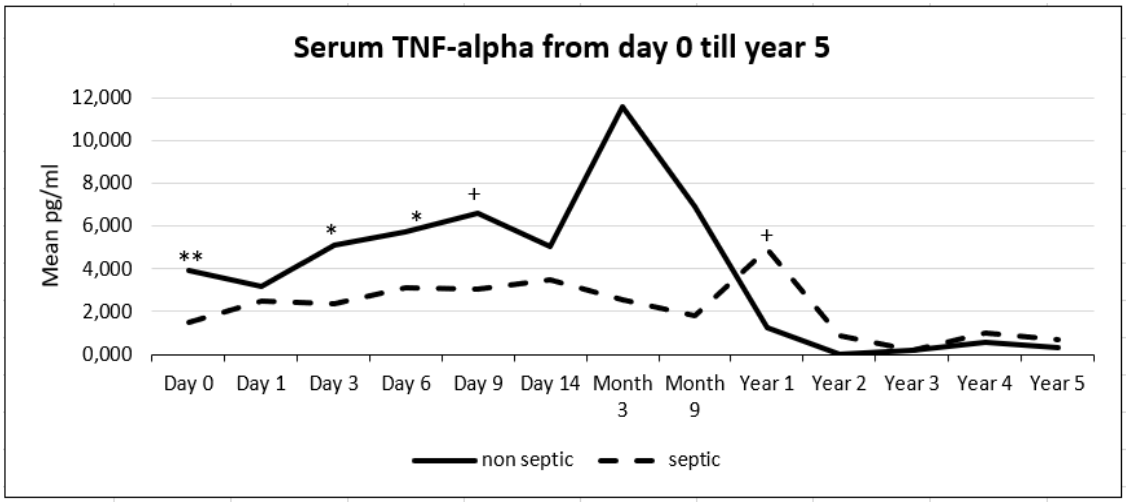
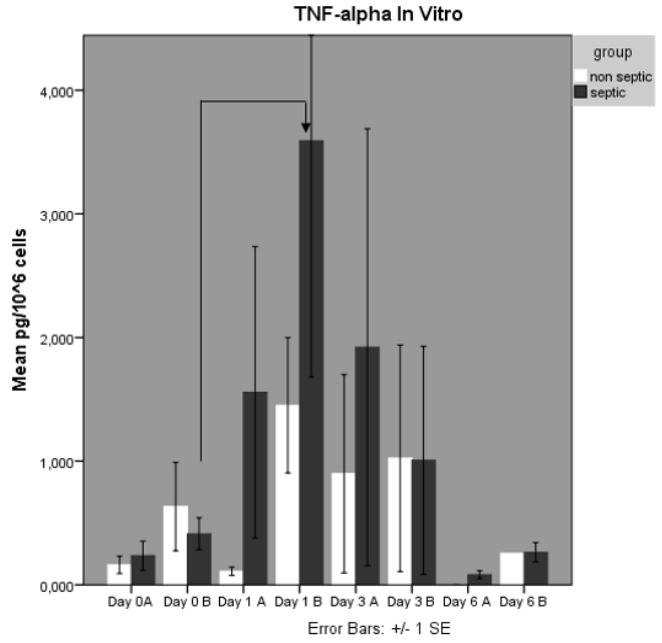


Figure4. On day 0 the circulating TNFα values were lower in infected patients. TNFα started to increase from day 3 till on day 9 never reaching values of uneventful healing group. In uneventful healing group 3 month later was observed the highest TNFα level than gradually decreased2 year after surgery and remained at this level for years during follow up This level is same to volunteers level (Table2.) The highest level of TNFα was observed in septic group 1 year after surgery but less than uneventful from 2 years exactly same values are observed (Table 2.)



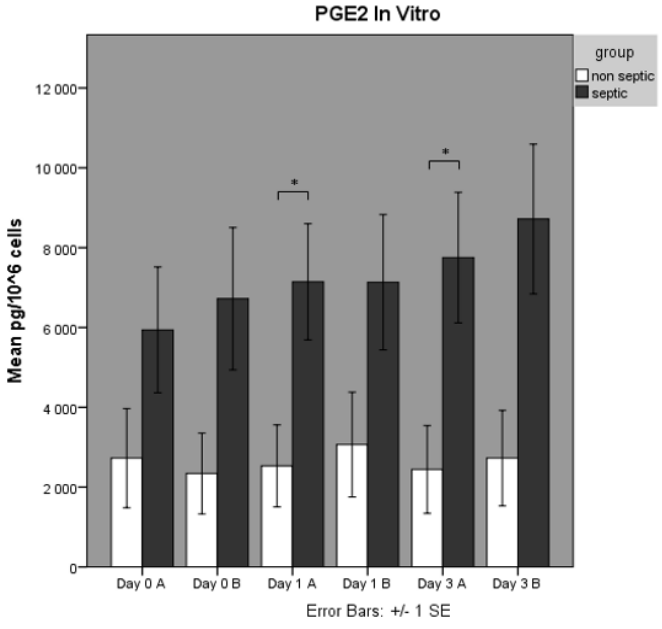


Figure 5. The inducibility of PBMCs was higher in SSI group on day0. Later during the observation period, in SSI group comparing to uneventfully healing group in SSI group remained slightly higher The PGE2 was higher continously

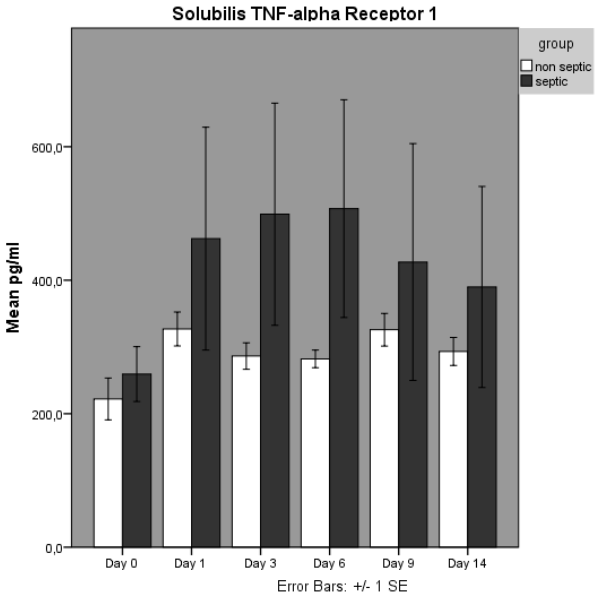


Figure 6. Soluble serum TNFα receptor I was slightly but not significantly elevated in SSI group comparing to uneventfully healing group

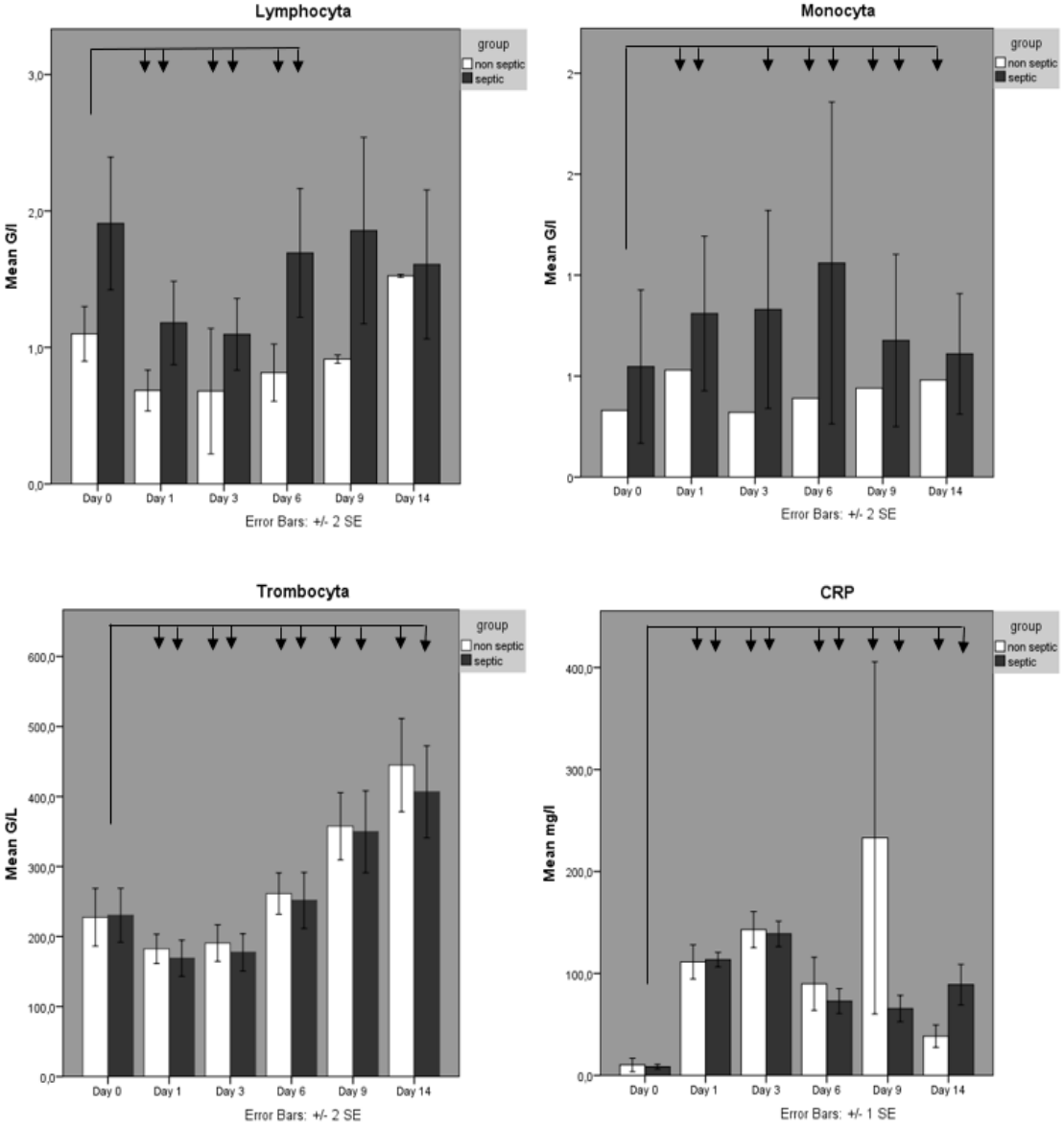


Figure 7. Lymphocyte count was reduced almost by half on days 1and 3 Recovery started on day 6 in both groups Monogyte count changed parallel in both groups.Platelet count was reduced seriously on days 1 and 3 recovery started and an overproduction was observed from day 9,14 CRP levels highly and transiently increased in both groups indicating an inflammatory process

(Masuda , 2007). Enhanced production of IL-6 TNFα IL-‘ occurs very early in infection. TNFα and IL-1 are reported to be potent inducers of IL-6 suggesting that these cytokines may regulate each other so effecting the early immune response to infection.Synergistic effects of TNFα and IL-1 in eliminating tumors from mice in aggregation to stimulate in neutrophil infiltration Aggregate stimulating the synthesis of thromboxane have all been repported that combined administration of TNFα and IL-1 resuted in a significant enhasment resistance to Listeria beyond obtained either with monokine In vitro IL-6 synthetizes with IL-1 to control first steps of TT cell actvation Thymocyte proliferation is mediated by IL-6 Indeed it has been suggested that activaton of IL-1 on thymocyte proliferation is mediated (Murapa, 2011). Soluble forms of the two molecular species of the cell surface receptors for tumor necrosis factor (TNFα) have been detected in normal urine. Using enzyme-linked immunosorbent assays for these soluble receptors. It has been determined their levels in the sera of 40 healthy subjects and 59 patients with solid tumors.

The mean ± SD concentrations of both the soluble type I (p55) and type II (p75) receptors were significantly higher in the cancer patients than in the concentrations of about 1 - 2 ng/mL are found inthe serum and urine of healthy controls: 1.96 ± 1.19 versus 0.79 ± 0.9 ng/ml ($P < 0.001$) and 6.43 ± 4.8 versus 3.2 ± 0.6 ng/ml ($P < 0.001$), respectively. The incidence and the extent of the increase correlated with the staging of disease. Sera of the cancer patients had a marked inhibitory effect on the in vitro cytocidal activity of TNFα. This inhibition was proportional to the content of soluble TNFα receptors and could be fully abolished by the addition to the sera of specific antibodies against the receptors. Among the cancer patients, the incidence of increase in the concentrations of soluble TNFα receptors (about 70%) greatly exceeded that of the serum carcinoembryonic antigen (about 26%), a commonly used cancer marker. The origin of the serum soluble TNFα receptors in cancer patients and the physiological implications of their effect on TNFα function remain to be elucidated (Aderka, 1991). It has been reported previously that macrophages obtained from renal patients on continuous ambulatory peritoneal dialysis (CAPD) during an episode of infectious peritonitis display a decrease in intracellular cAMP levels and in spontaneous in vitro release of PGE2 and PGI2. Such macrophages also release large quantities of IL-1 beta and TNFα when stimulated in vitro by LPS. In view of the interregulatory effects between PGE2 and macrophage cytokines (IL-1 beta and TNFα) in their production.

It has been examined to what extent the LPS-induced release of either IL-1 beta or TNFα in vitro from CAPD-originated peritoneal macrophages is affected by graded doses of exogenous PGE2 (range 0-1000 ng/ml) and by the cyclooxygenase inhibitor indomethacin (INDO) (10(-6) M). IL-1 beta and TNFα were determined using an enzyme-linked immunoabsorbent assay and an immunoradiometric assay, respectively. It has been found that PGE2 invariably induced a dose-dependent decrease in TNFα release. In peritoneal macrophages collected during an infection-free period, TNFα release decreased from 3225 pg/ml (controls) to 353 pg/ml at 1000 ng/ml of PGE2, and in peritoneal macrophages collected during an episode of infectious peritonitis, it decreased from 4100 pg/ml (controls) to 545 pg/ml at 100 ng/ml of PGE2. However, PGE2 failed to influence the secretion of IL-1 beta. INDO induced an approx. two-fold increase in TNFα release, but had no effect on IL-1 beta release.

These findings indicate that exogenous and endogenous PGE2 controls the release of TNFαrather than IL-1 beta from LPS-stimulated peritoneal macrophages (van den Bemd, 1992). There have been suggestions that the production of pro-inflammatory mediators by human monocytes in response to interferon-gamma (IFN-gamma) may be controlled by changes in prostaglandins. Therefore it has been investigated tumor necrosis factor alpha (TNFα) and interleukin-1 (IL-1) activities and prostaglandin E2 (PGE2) levels in the supernatants of highly purified human monocytes cultured for 18 hr with recombinant human IFN-gamma. IFN-gamma (100 U/ml) did not stimulate monocytes isolated by counter-current centrifugal elutriation for detectable TNFαor IL-1 activities, or PGE2 production. However, IFN-gamma synergistically enhanced lipopolysaccharide (LPS)-induced TNFα and IL-1 activities. In contrast, there was no consistent change in PGE2 levels upon addition of IFN-gamma to LPS-treated monocyte cultures. The TNFα and IL-1 activities induced by LPS and by LPS with IFN-gamma were reduced by PGE2, and stimulated by indomethacin. As reported previously for IL-1 activities, the regulation by cyclo-oxygenase products of TNFα activities reflected predominantly a control of the production of immunoreactive TNFα, rather than the measurement of TNFα bio-activity.

However, the addition of indomethacin or PGE2 to monocyte cultures did not change the extent of IFN-gamma synergy with LPS for increased TNFα and IL-1 activities. The results of this study suggest that, despite control by cyclo-oxygenase products of TNFαand IL-1 production in human monocytes, IFN-gamma may enhance TNFα and IL-1 activities independently of this regulatory mechanism. These findings are contrary to those suggested for the regulation by prostanoids of IL-1 production by murine macrophages. (Hart, 1989). In summary, this study shows that a exposure to psychosocial stress causes activation of the HPA axis and suppression of circulating TNFα. Furthermore, isolation induces a state of cortisol resistance in blood immune cells as increasing inducibility of PBMCs to LPS. Taken together, host response following surgery is modified by brain and stress. Determination of serum A, cortisol and TNFα as well as inducibility and count of PBMCs can show the subgroups of host responses what may predict outcome of surgery. Our results indicate the double face behavior of TNFα e.g. high thus finally will die. The normoregulated host response is the most beneficial.

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