OXIDATIVE STRESS PARAMETERS IN POSTTRAUMATIC STRESS DISORDER RISK GROUP PATIENTS


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Increased excitotoxicity in response to stressors leads to oxidative stress (OS) due to accumulation of excess reactive oxygen/nitrogen species. Neuronal membrane phospholipids are especially susceptible to oxidative damage, which alters signal transduction mechanisms. The Contingent of International Operations (CIO) has been subjected to various extreme stressors that could cause Posttraumatic Stress Disorder (PTSD). Former studies suggest that heterogeneity due to gender, race, age, nutritional condition and variable deployment factors and stressors produce challenges in studying these processes. The research aim was to assess OS levels in the PTSD risk group in CIO. In a prospective study, 143 participants who were Latvian CIO, regular personnel, males, Europeans, average age of 27.4, with the same tasks during the mission, were examined two months before and immediately after a six-month Peace Support Mission (PSM) in Afghanistan. PCL-M questionnaire, valid Latvian language “Military” version was used for PTSD evaluation. Glutathione peroxidase (GPx), superoxide dismutase (SOD) and lipid peroxidation intensity and malondialdehyde (MDA) as OS indicators in blood were determined. Data were processed using SPSS 20.0. The MDA baseline was 2.5582 µM, which after PSM increased by 24.36% (3.1815 µM). The GPx baseline was 8061.98 U/L, which after PSM decreased by 9.35% (7308.31 U/L). The SOD baseline was 1449.20 U/gHB, which after PSM increased by 2.89% (1491.03 U/gHB). The PTSD symptom severity (total PCL-M score) baseline was 22.90 points, which after PSM increased by 14.45% (26.21 points). The PTSD Prevalence rate (PR) baseline was 0.0357, which after PSM increased by 147.06% (0.0882). We conclude that there is positive correlation between increase of OS, PTSD symptoms severity level, and PTSD PR in a group of patients with risk of PTSD – CIO. PTSD PR depends on MDA intensity and OS severity. OS and increased free radical level beyond excitotoxicity, is a possible causal factor for clinical manifestation of PTSD.

Key words: Posttraumatic stress disorder, oxidative stress.

INTRODUCTION

The Contingent of the International Operations appears to be subject to various extreme factor actions, which can cause Posttraumatic Stress Disorder (PTSD). PTSD is an anxiety disorder that can develop after exposure to one or more traumatic events, threatening or causing great physical harm; it is a complex of symptoms experienced by survivors of traumatic stress (Satcher, 2000). General PTSD symptoms occur in complex psycho-physiological hypertrophic responses: intrusive experiences of a traumatic event, illusions, hallucinations, persistent avoidance of stimuli associated with trauma, and general emotional numbness, which are present for a period of at least one month. Clinical diagnosis of PTSD, according to the Diagnostic and Statistical Manual of mental disorders (DSM-IV-TR), is per-
formed by means of a clinical PTSD checklist PCL-M (military version). PCL-M includes 17 items. It is recommended for use as an objective diagnostic tool for examination of patients with PTSD and PTSD risk group patients (Anonymous, 2000; Weathers et al., 2001; Watson et al., 2005; Pynoos et al., 2009; McDonald and Calhoun, 2010).

According to available literature data, the PTSD level before Peace Support Missions has been reported as high as 2.4–9.3% in the American Contingent of the International Operations (Hoge et al., 2004; Riddle et al., 2007) and 2.4% in the British Contingent of the International Operations (Iversen et al., 2009). PTSD level after Peace Support Mission is reported as 11.2% in the American Contingent of the International Operations (Hoge et al., 2004) and 4.0–9.5% in the British Contingent of the International Operations (Hotopf et al., 2006; Iversen et al., 2009). Pathophysiology and pathogenesis of PTSD is associated with excitotoxicity. Excitotoxicity is the pathological process by which neurons are damaged due to hyperactivations of the excitatory neurotransmitter glutamate (Li et al., 2001, Jourdain et al., 2007). Excitotoxicity-activated microglia cells appear to become probable sources of chronic oxidative processes leading to oxidative stress (Anwyl, 1991). Neuronal membrane phospholipids are especially vulnerable to damage; the injury leads to the receptor-mediated signal transduction and, furthermore, information processing disorders. Studies on the effects of hyperoxidation, oxidative and carbonyl stresses on cerebral suppression and its relation to brain degeneration with respect of neuronal functions are of great interest and importance. Indeed there are difficulties in rating and interpreting of available literature data, as the studies are inhomogeneous in gender, race, age, nutritional and deployment factors — reservists or regular personnel, and different stressful military experiences in various Peace Support Missions.

Oxidative stress intensity was assessed considering the malondialdehyde (MDA) plasma level. Unsaturated carbonyl MDA is one of the most frequently used direct indicators of lipid peroxidation. MDA measurement appears to be a suitable quantification method of the end-products of lipid peroxidation. The production of MDA is used as a biomarker to measure the level of OS in an organism and is often used in oxidative stress studies (Moore and Roberts, 1998; Del Rio et al., 2005; Nie et al., 2007). MDA is a naturally occurring metabolic product of polyunsaturated fat degradation (lipid peroxidation), and has been reported to be mutagenic and carcinogenic. Free radical damage to lipids results in MDA reacting with DNA to form adducts to deoxyguanosine and deoxyadenosine and releasing an intermediate product of formaldehyde (Nie et al., 2007). Formaldehyde at low concentrations induces protein misfolding causing a high cytotoxic aggregation. As a metabolic product, MDA might weaken cerebral function during oxidative stress through breaking the homeostasis between excitatory and inhibitory neurons. Being less active than other free radicals, MDA has a rather longer half-life and, thereby, can diffuse from the generation places to other sites, bringing further oxidative stress. Cells are equipped with enzymatic and nonenzymatic antioxidant systems to eliminate ROS/RNS and maintain redox homeostasis. A major class of enzymatic antioxidants, which catalyze the dismutation of superoxide into oxygen and hydrogen peroxide, is known as superoxide dismutase (SOD). Multiple isoforms of SOD exist in different cellular compartments. SOD1 (CuZnSOD) is the major superoxide scavenger found in the cytoplasm, mitochondrial intermembrane space, nucleus, and lysosomes, whereas SOD2 (MnSOD) and SOD3 are found in the mitochondria and extracellular matrix, respectively. Indeed, they impart an important antioxidant defence system and their activity increases upon oxidative stress. Some SOD isoforms resulting from oxidative stress have been linked with human diseases. Thus, mutations in the CuZnSOD can result in familial amyotrophic lateral sclerosis (Milani et al., 2011). Further conversion of hydrogen peroxide occurs through the action of catalase, a heme-based enzyme that is normally localised in the peroxisome. Hydrogen peroxide also can be converted to oxygen through coupled reactions with the conversion of reduced glutathione to oxidized glutathione, catalysed by glutathione peroxidase (GPx). The main biological role of GPx is to protect the organism from oxidative damage. The biochemical function of GPx is to reduce lipid hydroperoxides to alcohols as well as to reduce free hydrogen peroxide to water (Miyamoto et al., 2003). GPx scavenges extremely active hydroxyl radicals without formatting toxic adverse products. GPx is present in a high concentration in the cells and plays a crucial role in ensuring them in a reduced state. The GPx role as antioxidant is particularly important for brain, as it is very sensitive to presence of free radicals. Insufficient GPx amount and/or activity can complicate oxidative stress. Five isoforms of selenium (Se)-dependent GPx are found in humans. Furthermore, enzymes such as glutathione S-transferases are known to have Se-independent peroxidase activity. Nonenzymatic antioxidants (thioredoxin, glutaredoxins, peroxiredoxins), recognised to execute thiol-disulphide exchange reactions, also play a major role in maintaining cellular redox balance (Trachootham et al., 2008). Our research aim was to assess oxidative stress levels PTSD and their correlation in the Contingent of the International Operations.

MATERIALS AND METHODS

The prospective study was conducted in the Department of Psychosomatic Medicine and Psychotherapy, Riga Stradiņš University (Riga, Latvia) in close cooperation with the Biochemical Laboratory (Riga, Latvia) and Department of Internal Diseases (Riga, Latvia) of Riga Stradiņš University, and Medical Care Centre of the National Armed Forces (Riga, Latvia). The protocol of study, the protocol of agreement, and the protocol of participation corresponded to the Helsinki declaration on principles of humanity in medicine. The study design was approved by the Ethics Committee of Riga Stradiņš University, protocol No. E-9(2) of 17.12.2009. For our research we used a participant group with the highest possible level of homogeneity to avoid dif-

Difficulty in rating and interpreting of results. In total there were 143 male European participants, average age 27.4, regular military personnel, participants of the Latvian Contingent of the International Operations. Examination was performed before and after the same Peace Support Mission in Afghanistan (six months), with the same tasks during the mission. Clinical examination and laboratory parameters assessment were taken twice: two months before the mission (BL) and immediately after the mission (PL).

Clinical examination was made according to the diagnostic pattern DSM-IV-TR (Anonymous, 2000). The following diagnostic criteria were assessed:

Criterion A: Stressor. The person has been exposed to a traumatic event in which both of the following have been present:
1. The person has experienced, witnessed, or been confronted with an event or events that involve actual or threatened death or serious injury, or a threat to the physical integrity of oneself or others;
2. The person's response involved intense fear, helplessness, or horror.

Criterion B: Intrusive recollection. The traumatic event is persistently re-experienced in at least one of the following ways:
1. Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions;
2. Recurrent distressing dreams of the event;
3. Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur upon awakening or when intoxicated);
4. Intense psychological distress at exposure to internal or external cues that symbolise or resemble an aspect of the traumatic event;
5. Physiological reactivity upon exposure to internal or external cues that symbolise or resemble an aspect of the traumatic event.

Criterion C: Avoidant/numbing. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by at least three of the following:
1. Efforts to avoid thoughts, feelings, or conversations associated with the trauma;
2. Efforts to avoid activities, places, or people that arouse recollections of the trauma;
3. Inability to recall an important aspect of the trauma;
4. Markedly diminished interest or participation in significant activities;
5. Feeling of detachment or estrangement from others;
6. Restricted range of affect (e.g., unable to have loving feelings);
7. Sense of foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span).

Criterion D: Hyper-arousal. Persistent symptoms of increasing arousal (not present before the trauma), indicated by at least two of the following:
1. Difficulty falling or staying asleep;
2. Irritability or outbursts of anger;
3. Difficulty concentrating;
4. Hyper-vigilance;
5. Exaggerated startle response;

Criterion E: Duration. Duration of the disturbance (symptoms in B, C, and D) is more than one month.

Criterion F: Functional significance. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

PCL checklist was worked out at PTSD National Centre, USA in 1993. The PCL has a variety of purposes, including screening individuals for PTSD, diagnosing PTSD, monitoring symptom change during and after treatment. There are three versions of the PCL: PCL-C (civilian), PCL-M (military) and PCL-S (specific). PCL-M asks about symptoms in response to "stressful military experiences" and is used for active service members and veterans (Weathers et al., 2001; Watson et al., 2005; McDonald and Calhoun, 2010). The PTSD Checklist (PCL) is a 17-item self-report measure of the 17 DSM-IV symptoms of PTSD. Respondents are asked about certain troubles during the last month; the answers are evaluated by a 5-point scale. The valid Latvian language PCL-M version was used for objective PTSD evaluation (Voicehovskis et al., 2011). PTSD risk group Incidence rate (IR) was also assessed.

Laboratory assessment of oxidative stress parameters in blood included: intensity of lipid peroxidation assessed by malondialdehyde (MDA) concentration and activity of antioxidant enzymes: glutathione peroxidase (GPx) and superoxide dismutase (SOD). Blood samples were taken from all individuals in morning at 8.00 (before meal). Venous blood was collected into a vacutainer (Venoject II BD) containing lithium/heparin as an anticoagulant.

Activity of glutathione peroxidase 3 (GPx), Enzyme Commission number (EC) 1.11.1.9., was determined in heparinised whole blood by the method of Paglia and Valentine (Paglia and Valentine, 1967) using commercial tests manufactured by Randox Laboratories (UK, Antrim) in a RX Daytona analyser. GPx catalyses the oxidation of glutathione (GSH) by cumene hydroperoxide. In the presence of glutathione reductase and nicotinamide adenine dinucleo-
tide phosphate (NADPH) the oxidised glutathione (GSSG) is immediately converted to the reduced form with a concomitant oxidation of NADPH to the oxidised NADP⁺. The decrease in absorbance at 340 nm is measured. In the presence of hydroperoxide, GPx catalyses oxidation of GSH to GSSG. The latter (GSSG) undergoes NADPH-dependent reduction to GSH catalysed by glutathione reductase. This reaction is accompanied by NADPH oxidation to NADP⁺. Thus, activity of GPx corresponds to the decrease in absorbance at 340 nm induced by NADPH oxidation and one unit of enzyme activity is defined as the enzyme content required for oxidation of 1.0 µmol of NADPH per 1 min at 340 nm and 37 °C.

Malondialdehyde (MDA) level in plasma was measured as suggested by Gavrilov (Гаврилов и др., 1987): at low pH and elevated temperature, MDA readily participates in nucleophilic addition reaction with 2-thiobarbituric acid (TBA), generating a red 1:2 MDA: TBA adduct. The reaction products was extracted with butanol and estimated at 535 nm and 580 nm by spectrophotometry.

The determination of superoxide dismutase (SOD, EC 1.15.1.1) employed xantine and xantine oxidase to generate superoxide radicals that react with 2-(4-iodophenyl)-3-(4-nitrophenol)-5-phenyltetrazolium chloride to form a red formazan dye (Woolliams et al., 1983). The SOD activity was then measured by the degree of inhibition of this reaction.

Data were processed using SPSS 20.0. Statistical significance of mean values was evaluated by means of the Paired-Samples T-Test and one-Sample Kolmogorov-Smirnov test. Interrelationship between parameters was evaluated by the Wilcoxon correlation coefficient; differences were considered as statistically significant at $P < 0.05$.

RESULTS

The main results before PSM (BL) and after (PL) the mission are represented in the Table 1.

![Table 1](https://example.com/table1.png)

![Table 2](https://example.com/table2.png)

DISCUSSION

Prevalence of oxidation processes accompanied by antioxidant defence system failure leads to the development of oxidative stress, which is one of the universal mechanisms of tissue damage. Enzymatic activity of antioxidant systems (catalase, SOD, glutathione peroxidase) in the brain is sig-

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**Table 1**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>N of participants</th>
<th>Normal parameters ¹</th>
<th>Most extreme differences</th>
<th>K-S Z²</th>
<th>AS³</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPx, BL, U/L</td>
<td>106</td>
<td>8061.98</td>
<td>1369.116</td>
<td>.061</td>
<td>.061</td>
</tr>
<tr>
<td>GPx, PL, U/L</td>
<td>29</td>
<td>7308.31</td>
<td>1129.871</td>
<td>.123</td>
<td>.092</td>
</tr>
<tr>
<td>SOD, BL, U/gHB</td>
<td>106</td>
<td>1449.20</td>
<td>137.173</td>
<td>.049</td>
<td>.039</td>
</tr>
<tr>
<td>SOD, PL, U/gHB</td>
<td>29</td>
<td>1491.03</td>
<td>121.739</td>
<td>.219</td>
<td>.219</td>
</tr>
<tr>
<td>MDA, BL, µM</td>
<td>49</td>
<td>2.5582</td>
<td>63475</td>
<td>.067</td>
<td>.067</td>
</tr>
<tr>
<td>MDA, PL, µM</td>
<td>13</td>
<td>3.1815</td>
<td>.68560</td>
<td>.125</td>
<td>.125</td>
</tr>
<tr>
<td>PCL, BL, points</td>
<td>140</td>
<td>22.90</td>
<td>6.734</td>
<td>.190</td>
<td>.149</td>
</tr>
<tr>
<td>PCL, PL, points</td>
<td>34</td>
<td>26.21</td>
<td>9.247</td>
<td>.201</td>
<td>.201</td>
</tr>
<tr>
<td>PTSD, BL, PR+1</td>
<td>140</td>
<td>1.04</td>
<td>.288</td>
<td>.540</td>
<td>.540</td>
</tr>
<tr>
<td>PTSD, PL, PR+1</td>
<td>34</td>
<td>1.09</td>
<td>.288</td>
<td>.532</td>
<td>.532</td>
</tr>
</tbody>
</table>

¹ Test distribution is normal; calculated from data; ² Kolmogorov-Smirnov Z; ³ asymptotic significance; SD, standard deviation; GPx, glutathione peroxidase; SOD, superoxide dismutase; MDA, malondialdehyde; PTSD, Posttraumatic Stress Disorder; PCL-M, PTSD Checklist – Military Version
significantly lower than in other tissues. Oxygen radicals (having oxygen with an unpaired electron) are superoxide anion and hydroxyl radical. These are extremely aggressive. Glutamate is a substrate that is able to support maximal \( \text{H}_2\text{O}_2 \) production rates by means of \( [\text{Ca}^{2+}] \) mediated excitotoxicity. Scavengers of free radicals are located in the cytoplasm or on cell membranes; these are mainly substances with low molecular weight: superoxide dismutase, glutathione, glutathione peroxidase, catalase, ceruloplasmin, vitamin A, vitamin E, vitamin C, vitamin K, flavonoids, and coumarins. Lipid peroxidation plays a crucial role in brain injury. The brain contains a large amount of lipids (50% in a dry matter); most of them appear to be unsaturated and become substrates for lipid peroxidation. Phospholipids account for over half of all lipids of nervous tissue. Fatty acid and phospholipids determine structural and functional features of cell membranes, and contribute to its penetration and density. Lipid peroxidation of any intensity results in functional brain disorder (Esterbauer and Cheeseman, 1990; Ginsberg and Bogousslavsky, 1998). Moreover, it could become a
cause of structural and morphological alterations, and degeneration processes.

The PTSD patients note problems in cognition (memory, attention), somatic concerns (headache), and affective deregulation (impulsivity, irritability, anxiety), particularly in the time period shortly after the traumatic event (whether psychological, biomechanical, or both). A biochemical mechanism associated with elevated levels of oxidative stress parameters has been proposed to explain the etiology of PTSD (common etiology of posttraumatic stress disorder, fibromyalgia, chronic fatigue syndrome and multiple chemical sensitivity) (Pall, 2001; Pall and Satterlee, 2001; Pall, 2007; Adibhatla and Hatcher, 2008). Alterations of glutamatergic and NMDA receptor functions play a role in the etiology of PTSD in humans. Some clinical studies have observed a marked increase of cerebral neurotransmitter glutamate in PTSD (Moghaddam et al., 1994; Chambers et al., 1999; Cortese and Phan, 2005). Stress increases glutamate release, which is recognised as an important mediator of excitotoxicity. Since a prominent role of glutamate-related excitotoxicity followed by neuronal damage, glutamatergic pathways may have an important role in stress-related hippocampal degenerative pathology and cognitive deficits seen in patients with PTSD (Moghaddam et al., 1994). Brain imaging studies have revealed a marked reduction in hippocampal volume (Sapolsky, 2000; Reul and Nutt, 2008). Such morphological alterations appear to be positively correlated with the degree of cognitive deficit noted in these patients. PTSD-induced oxidative stress has been proposed to occur in this disorder. Recent clinical studies confirmed the involvement of neurodegenerative pathology in the PTSD pathogenesis (Bremner, 2002). Neurochemically-mediated damage could be conceivably related to neurohumoral dysregulation.

The main conclusions are:

1. MDA intensity increased during PSM; MDA intensity reflects the rate of lipid peroxidation and OS severity.
2. GPX activity is decreased in the PTSD risk group and is not efficient to overwork and/or control OS.

3. SOD activity is increased in the PTSD risk group but is not efficient to overwork and/or control OS.

4. There is positive correlation between increase of oxidative stress – MDA level, PTSD symptom severity level, and PTSD Prevalence rate (PR) in the studied group of patients with risk of PTSD (Contingent of the International Operations). PTSD PR depends on MDA intensity and OS severity.

Our results suggest that the production of free radicals resulting in lipid peroxidation seemed to be related to PTSD. The present results showed that patients with PTSD differed from healthy controls in both antioxidant system activity (GPx, SOD) and lipid peroxidation (MDA) level. Therefore, we conclude that OS, increased free radical level beyond excitotoxicity, is a possible causal factor for clinical manifes-

Fig. 7. PCL-M scores distribution, points, before the mission.

PCL-M, Posttraumatic Stress Disorder Checklist – Military Version

Fig. 8. PCL-M score before (BL) vs after the mission (PL).

PCL-M, Posttraumatic Stress Disorder Checklist – Military Version

Fig. 9. Negative correlation between MDA and GPx.

MDA, malondialdehyde; GPx, glutathione peroxidase
tation of PTSD. Our results need to be confirmed by more comprehensive and detailed further studies to support the findings we found in PTSD.

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REFERENCES


OKSIDATĪVĀ STRESA PARAMETRI POSTTRAUMATISKĀ STRESA SINDROMA RISKA GRUPAS PACIENTIEM

Paaugstināts eksaitotoksisitātes līmenis kā atbildes reakcija uz stresoriem lieka reaktivā skābekļa/slāpekļa uzkrāšanās rezultātā izraisā oksidatīvo stresu (OS). Neironālo membrānu fosfolipīdi ir ļoti jutīgi pret oksidatīvo bojājumu, rezultātā mainot signālu pārneses mehāнизmu. Starptautisko operāciju kontingents (SOK) tiek pakļauts dažādiem ekstremāliem stresoriem, kas varētu izraisīt posttraumatiskā stresa sindromu (PTSS). Pieejama pētījuma dati nav viendabīgi pēc dzimuma, rases, vecuma, uztura un dažādiem dienesta faktoriem un stresoriem, kas apgrūtina to salīdzināšanu. Pētījuma mērķis: novērtēt OS līmeni PTSS riska grupā. Pētījumā piedalījās 143 dalībnieki — Latvijas SOK, regulārais militārais personāls, viņi, eiropieši, kurus vidējais vecums ir 27,4 gadi, ar vienādiem uzdevumiem misijas laikā — tika izmeklēti divus mēnešus pirms un uzreiz pēc sešu mēnešu ilgas Miera uzturānas misijas (MUM) Afganistānā. PTSS novērtēšanai izmantota PCL-M anketa, apstiprināta latviesu valodas "militārā" versija. Asinīs noteiktī OS rādītāji: glutationa peroksidāze (GPx), superoksīda dismutāze (SOD) un lipidu peroksidāciju intensitātes rādītājs — malondialdehīds (MDA). Dati tika analizēti, izmantojot SPSS 20.0. MDA līmenis (2,5582 µM) pēc MUM pieauga par 24,36% (3,1815 µM) pēc MUM samazinājās par 9,35% (7308,31 U/L) pēc MUM samazinājās par 24,36% (3,1815 µM). GPx līmenis bija 22,90 punkti, pēc MUM tas pieauga par 147,06% (0,0882). Autori secina, ka pastāv pozitīva korelācija starp OS pieaugumu, PTSS simptomu smaguma pakāpes līmeni un PTSS IK pacientiem PTSS riska grupā (SOK). PTSS IK ir atkarīgs no MDA līmena un OS smaguma. Iespējams, ka OS un eksaitotoksisitātes rezultātā palielināta brīvo radikālu līmenis ir veicinošs faktors PTSS kliniskās izpausmes attīstībai.

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