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Oxidative Stress and Antioxidant Therapy in Critically Ill Polytrauma Patients with Severe Head Injury

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Abstract

Traumatic Brain Injury (TBI) is one of the leading causes of death among critically ill patients from the Intensive Care Units (ICU). After primary traumatic injuries, secondary complications occur, which are responsible for the progressive degradation of the clinical status in this type of patients. These include severe inflammation, biochemical and physiological imbalances and disruption of the cellular functionality. The redox cellular potential is determined by the oxidant/antioxidant ratio. Redox potential is disturbed in case of TBI leading to oxidative stress (OS). A series of agression factors that accumulate after primary traumatic injuries lead to secondary lesions represented by brain ischemia and hypoxia, inflammatory and metabolic factors, coagulopathy, microvascular damage, neurotransmitter accumulation, blood-brain barrier disruption, excitotoxic damage, blood-spinal cord barrier damage, and mitochondrial dysfunctions. A cascade of pathophysiological events lead to accelerated production of free radicals (FR) that further sustain the OS. To minimize the OS and restore normal oxidant/antioxidant ratio, a series of antioxidant substances is recommended to be administrated (vitamin C, vitamin E, resveratrol, N-acetylcysteine). In this paper we present the biochemical and pathophysiological mechanism of action of FR in patients with TBI and the antioxidant therapy available.

Keywords: antioxidant therapy, oxidative stress, traumatic brain injury, multiple trauma patients

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Introduction

A high percentage of poly-trauma patients present with severe central nervous system (CNS) trauma. Traumatic Brain Injury (TBI) and spinal cord injury (SCI) are responsible for increased mortality and morbidity in most trauma patients. Primary brain injury is characterized by contusions caused by direct impact and include haematomas, intra-parenchymal contusions and bleeding from vascular damage [1]. Primary injuries and pathophysiological imbalances lead to a series of aggressive factors that produce secondary injuries. These include brain ischemia and hypoxia, inflammatory factors, metabolic factors, coagulopathy, microvascular damage, neurotransmitter accumulation, blood-brain barrier disruption, excitotoxic lesions, blood-spinal cord barrier damage, and mitochondrial dysfunction [2,3]. A number of specific aspects of the critically ill patient is associated with TBI, such as mechanical ventilation, suppression of the immune response and infections, and these can lead to a significant increase in the rate of morbidity and mortality. Also, in the case of the critically ill patient, TBI can significantly affect the clinical progress due to the generated changes in systemic conditions such as acute respiratory distress syndrome (ARDS), Takotsubo cardiomyopathy and consumptive coagulopathy. Also, recent studies indicate that Multiple organ dysfunction syndrome (MODS) can occur after severe TBI [1-4].

The consequence of both primary and secondary lesions is represented by increased synthesis of free

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radicals (FR) that induce oxidative stress (OS) [4]. FR aggressive action lead to physiological imbalances of the central nervous system, significantly reducing the survival rate of critical trauma patients.

In this paper we present the biochemical and pathophysiological implications of OS in patients with severe TBI. Moreover, a summary of the existing antioxidant therapy aimed at improving the therapeutical management of critically ill trauma patients, is given.

Biochemical aspects of oxidative stress in case of traumatic brain injury

FR are extremely reactive chemical species. Increased FR biosynthesis capacity, and its reactivity towards macromolecules such as lipids, proteins and nucleic acids, have an aggressive impact for the human body (Figure 1).

FR produced in TBI are reactive species of oxygen and nitrogen [5]. Reactive oxygen species (ROS) include superoxide anions (O_2^-), hydroxyl radical (HO^-), peroxyl (RO_2^-), hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl). Reactive nitrogen species (RNS) are represented by peroxynitrite ($ONOO^-$), nitrogen dioxide (NO_2) or various derivatives of nitrogen oxide (NO) [6]. FR biosynthesis involve multiple reactions that produce various species in various conditions. Oxidative chain reaction is activated once the superoxide ion is generated. Superoxide anions are the result of mitochondrial leakage, xanthine oxidase activity and arachidonic acid metabolism. The action of superoxide dismutase (SOD) on superoxide anions form hydrogen peroxide and oxygen. HO^- is one of the most aggressive FRs. It is synthesised following the reaction between hydrogen peroxide and bivalent iron ions (Fenton Reaction) [7]. By combining the reaction of superoxide anion and nitrogen oxide derivatives, peroxynitrite radicals are produced. The reactivity is increased due to the multitude of reactions that take place in the human body. By protonation of the peroxynitrite radical, peroxynitrous acid is obtained which through denaturation produces significant amounts of hydroxyl radicals and nitric oxide radicals. FR`s aggressive reaction on lipids leads to severe physiological imbalances mainly by destroying cellular membrane integrity. Denaturation of lipids occurs by reaction of FR with polyunsaturated fatty acids such as arachidonic acid, linoleic acid, eicosapentaenoic acid,and docosahexaenoic acid. Denaturation reactions follow three important steps, initiation, propagation and termination. In lipid oxidation reactions, initially lipidic radical is being produced (L-). Through its reaction with oxygen, a lipid peroxyl radical is formed (LOO-) which, by attaching to a hydrogen ion (L-H), leads to lipid hydroperoxide (LOOH), a new lipid radical. Following the redox reactions of lipid denaturation, two neurotoxic aldehydes are produced: 4-hydroxynonenal, 2 – propenal. Neurotoxicity is a concequence of their interaction with a number of amino acids: lysine, histidine or cysteine, resulting in inactivation of enzymatic and structural functions of proteins. In redox reactions that involve FR, proteins are also attacked, forming active protein carbonyl species or disulfide bonds.

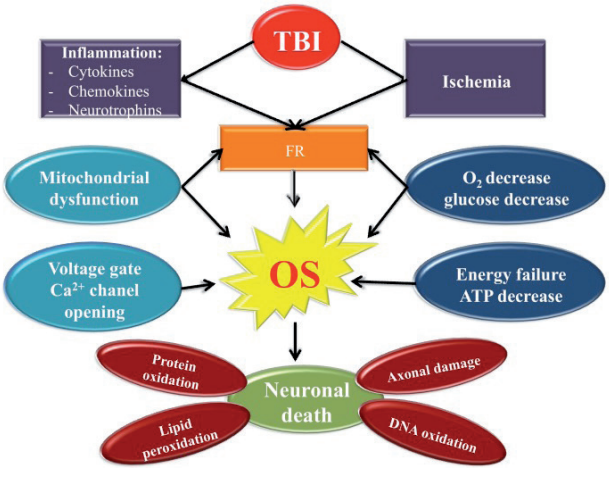

Figure 1. Oxidative stress during brain ischemia and traumatic brain injury. TBI, traumatic brain injury; FR, free radicals; OS, oxidative stress

Radicals formed from this chain of redox reactions attack both the structure of DNA and RNA, seriously affecting the functions of transcription, replication and mRNA translation. Impairment of these functions has direct implications in the decreased ability of the cell survival under stress [8,9].

FRs are responsible for inducing secondary injuries leading to progressive deterioration of the clinical status of patients due to mitochondrial dysfunction, which is responsible for the biosynthesis of peroxynitrite radical, Ca^{2+} buffering impariment, pump Na^+ / K^+ - ATP imbalance and accumulation of intracellular calcium, and microvascular systems damage.

Specific biomarkers for oxidative stress and traumatic brain injury

To highlight the pathophysiological effects induced by activation of OS in patients with TBI, a number of specific biomarkers have been studied (Table 1). One of the most studied biomarker of TBI is S100-calcium binding protein beta (S100B) [10-12].

Falcone et al, studied the correlation of serum and urine levels of S100B and TBI [13], highlighting the correlation between TBI and increased serum S100B.

A number of specialized studies report a direct and statistically significant correlation between increased serum levels of S100B and several clinical problems such as the magnitude of injury, degree of survival or post-traumatic neurological sequelae. Serum levels of S100B more than 1.14 ng/mL were correlated with an increase in mortality and morbidity [6,11,14,15].

Another biomarker commonly used for identification and scoring the degree of TBI is glial fibrillary acidic protein (GFAP). This is an insoluble protein and is rapidly induced following brain injuries. Hol et al demonstrated the correlation between serum levels of GFAP and different stages of brain injury [16].

Numerous other studies demonstrate that increased serum levels of GFAP are correlated with an increased intracranial pressure (ICP) and decreased cerebral perfusion pressure (CPP) [17-19]. Values greater than 1.5 ng/mL are correlated directly and significantly with decreased survival rate in critical patients with TBI [15,20,21].

Neuron-specific Enola (NSE) is another specific biomarker for TBI [22,23]. Reports show a correlation between serum levels greater than 12.5 ng/mL of NSE and severe brain injury. NSE is considered one of the most specific biomarkers for TBI, its serum levels being correlated with the intensity of TBI. El-Maraghi et al, reported on the importance of NSE in diagnosing TBI and its specificity for brain damage [24]. Following injury, a specific protein called myelin basic protein is released (MBP), and this is used to predict TBI [25]. Studies report that an increase in serum levels of more than 0.3 ng / mL is significantly correlated with an increase in morbidity or mortality for patients with TBI [20].

Products of metabolism of neurotransmitters are also considered important indicators in TBI. Barco et al highlight increased levels of homovanillic acid

Table 1. Antioxidant therapy in traumatic brain injury

Antioxidant	Mechanism of action	References
Vitamin C	reduced neutrophil oxidative burst; endothelial protective effect; decreases ROS production; prevents vascular leakage; prevents microvascular thrombosis; attenuates sepsis, decreases serum concentration of malondialdehyde;	[34, 45, 51, 66, 70]
Vitamin E	inhibits the multiplication of free radicals in lipid peroxidation reactions; reduces side effects of hyperhomocysteinemia;	[11, 18, 34, 45, 65]
Vitamin B1	inhibits the multiplication of free radicals;	[12, 23, 34, 56, 56, 56]
N-acetylcysteine	inhibits lipid peroxidation; Anti-inflammatory;	[12, 23, 34, 23, 59]
Resveratrol	Anti-inflammatory; antiplatelet; neuroprotective effects;	[5, 8, 9]
Melatonin	modulation of mitochondrial activity; protection of neuronal mitochondrial membrane; maintaining normal parameters and activity of Na + / K +-ATP pump; reduced synthesis of free radicals in the mitochondria;	[3, 4, 12, 11]
Selenium	reduce production of free radicals; inhibit oxidative chain initiation;	[34, 45, 69]
Zinc	reduce production of free radicals;	[12]
U-83836E (second generation lozaroid)	inhibit lipid peroxidation in oxidative chain initiation; minimizes the production of free radicals;	[12, 34, 48, 67]
PEG-SOD (stable PEG-conjugated superoxide dismutase)	improves antioxidant activity of superoxide dismutase enzyme; inhibit the production of free radicals; restores the balance of antioxidant-oxidant;	[12, 34, 56, 65]
methylprednisolone	inhibit lipid peroxidation; mainly used in TBI associated with spinal cord injuries;	[17, 23, 56]

(produced by metabolism of dopamine) in patients with TBI [26]. The product of metabolism of serotonin (5-hydroxy-indoleacetic acid) is another biomarker used in assessing the degree of brain injury [20,27,28].

Useful markers in the evaluation and optimization of intensive therapy in TBI are represented by inflammatory markers. The following studies show significant serum levels of pro- and anti- inflammatory cytokines and chemokines. Interleukin 1 (IL-1), interleukin 6 (IL-6), tumour necrosis factor alpha (TNF-alpha) are the most representative in case of TBI [20,29,30]. IL-1 has been extensively studied due to its increased specificity. A number of specialized studies correlate the increased serum levels of IL-1 with poor outcomes [20].

Moreover, studies conducted both on animals and in humans reported a direct and statistically significant correlation between increased levels of IL-6 and the extent of brain damage [12,15,20]. Following secondary injuries induced by OS, a number of specific markers are released. Classification of the severity of OS can be done both directly and indirectly by dosing specific markers.

4-hydroxynonenal [31] is a specific biomarker for redox reactions of lipid denaturation while 8-hydroxy-2-deoxyguanosine is used to assess injuries caused by the effect of FR on DNA and RNA and the resultant expression of DNA oxidative damage [20]. Another biomarker extensively used for detection of OS in the brain is 8-epi-PGF2a [32]. Aggression brought by NO derived free radicals are highlighted with biomarker 3NT. After prolonged action of OS, metallopreoteinases (MMPs) are activated, and result in an increased permeability of the blood-brain barrier.

Numerous studies report that increased activity of MMPs leads to destruction of brain microvascular system. Hohl et al, dosed plasma levels of thiobarbituric acid reactive species (TBARS) and carbonyl groups [33]. TBARS is used as an indirect biochemical markers of lipid peroxidation. Oxidative denaturation of proteins was assessed by analytical determination of plasma carbonyl groups. Hohl et al showed a significant difference in plasma TBARS and carbonyl groups in the first 70 hours after severe TBI [33].

Circulating microRNAs as indicator for OS

MicroRNAs are 19-23 nucleotide-containing biomolecules, representing a small fraction of the total mass of ribonucleic acid (RNA) [34], a number of which can be linked to a series of physiological dysfunctions. Thus, microRNAs extracted from biological samples can be used as a biomarker for diagnosis of physiological and biochemical imbalances, including cancer, neurodegenerative disorders, inflammation, infection with different pathogens, metabolism disorders, oxidative stress and poisoning [35,36]. In TBI, some microRNAs were identified and used as biomarkers for both primary and secondary injuries induced by OS.

Guroang et al showed the presence of a considerable number of microRNAs species in the case of FR assault on biological systems, including: microRNA-15a microRNA-15b; microRNA-16 microRNA-20a, micro-RNA20b, microRNA-92, microRNA-106, microRNA-139, microRNA-146b, microRNA-155. They concluded that the microRNA-106b and microRNA-20b family was specific for oxidative stress [37]. Suh et al, reported that microRNA-133 is a biomarker specific for neuronal apoptosis induced by OS [38].

Natural antioxidant systems

The body's natural antioxidant system is represented by a series of enzymes, highly active in inhibiting FR. One of the most effective antioxidant is the superoxide dismutases enzyme systems (SODs) [39]. Depending on the location but also the type of metal ion present at the active site, three types of enzymes have been identified. These are SOD1 (CuZnSOD) identified in the nucleus and cytosol, SOD2 (MnSOD) identified in the mitochondrial matrix and SOD3 (EcSOD) localized extracellulary [40,41]. Antioxidant activity is represented by inhibition of oxidizing activity of superoxide ion and its transformation into molecules of oxygen and hydrogen peroxide [39].

Catalase is another enzyme able to reduce the oxidative effect of hydrogen peroxide by decomposing it to molecules of oxygen and water. Antioxidant activity is due the four porphyrin haem groups present in catalase structure, making it possible to interact with hydrogen peroxide [42,43].

Bio-production of glutathione (GSH) results from the interaction of glutamate and cysteine. The antioxidant activity of GSH is dependent on reduced NADPH as the electron donor glucose-6-phosphate dehydrogenase. GSH antioxidant action maintains redox balance within the normal range [44]. Glutathione peroxidase (GPX), a protein that contains selenium, is responsible for reducing peroxidases. Numerous studies have

shown a intense decrease in the level of GPX with a concomitant increase in lipid peroxidation in TBI [45]. Glutaredoxins (Grxs) are present in the human organism in two forms. Grx1 is present in the cytosol and intermembranous space and Grx2 is present in the mitochondrial matrix. Both enzymes are responsible for protein deglutathionylation [45]. Another endogenous antioxidant system responsible for breakdown of hydrogen peroxide is the peroxiredoxins (Prxs) [46]. They are ubiquitous thiol peroxidases, identified in six structural forms. Prx1, Prx2 and Prx6 are found in the cytoplasm, Prx4 in the endoplasmic reticulum and Prx3 and Prx5 in mitochondria [47]. An intensely studied antioxidant is heme-oxygenase (HO) [48]. HO is a microsomal enzyme with an important role in ensuring cell cycle of Fe^{2+} ions [49]. In addition to changes at the biochemical level, many optical microscopy studies using routine immunohistochemistry stains show a close correlation between the OS and structural changes of the brain and cerebellum.

During haemorrhage, tissue accumulates haem which activates heme oxygenase (HO-1) involved in the metabolism of heme and its conversion to carbon monoxide, iron ions and biliverdin [50]. Biliverdin is a powerful antioxidant and therefore HO-1 expression is considered to be protective against oxidative stress. In subarachnoid haemorrhage, ischemic, traumatic brain injury and neurodegenerative diseases, the presence of HO-1 was demonstrated in microglia, astrocyte and neurons [50,51].

In humans, the presence of microglia, positive for HO-1 was demonstrated six hours after traumatic brain injury [52]. Histopathological changes in the brain and cerebellum depend on the aetiological agent of the primary injury.

Bhalla et al showed differences between the cerebellum and brain histology in rats with brain injuries induced by administration of aluminium compared to control group [53], with disruption of the layers, presence of vacuolar spaces and loss of Purkinje neuron layer. It was noted that lithium treatment partially restored the organ architecture and led to improvement of enzyme activity in the cerebellum in proportion to the administered dose. The authors concluded that lithium played a neuroprotective role [53].

Antioxidant therapy strategy

Major imbalances between oxidants and antioxidants are associated with prolonged hospital stay, with significant contributions to increased mortality and morbidity in critically ill patients. Antioxidant therapy in patients with TBI should address the inhibition of the synthesis of ROS and RNS, blocking of the initiation of lipid peroxidation and inhibition of the propagation of the chemical biochemical [1].

A study by Blass et al showed a significant decrease of plasma micro-nutrients and significantly decreased levels of ascorbic acid, retinol, 25-hydroxycholecalciferos, beta-carotene, zinc and selenium in patients with multiple trauma. It further revealed significant differences between antioxidant capacity between the control group and the group with trauma [54].

One of the most studied compounds having an antioxidative effect for neuronal cells is N-acetyl-5-methoxytryptamine (melatonin) [55]. Under normal physiological conditions endogenous production of melatonin is stimulated by a number of precursors including serotonin, arylalkylamine N – acetyltransferase and hydroxyl tryptophan [3]. Together with specific energy and metabolic imbalances, melatonin production is affected, resulting in significant decreases in its serum levels. The antioxidant activity of melatonin is modulated by specific receptors (MT1 and MT2) present on the surface of the neuron [3,56].

It is well documented that by interacting with the mitochondrial membrane and by optimizing oxidative phosphorylation and maintaining normal levels of ATP, melatonin is responsible for protecting brain membranes and mitocondrial activity. Several studies show that melatonin administration considerably decreases blood-brain barrier permeability (BBB), resulting in decreased cerebral oedema. It was also shown that high doses of melatonin increase the activity of endogenous antioxidant enzymes [3,57].

Another antioxidant used mainly in head trauma associated with spinal cord injuries is methylprednisolone. This glucocorticoid steroid is recommended in TBI associated with spinal cord injuries due to inhibition of lipid peroxidation. Studies suggest the administration of 30 mg / kg as a bolus (intravenously) followed by infusion during 23 hours of 5.4 mg/kg [58].

U-83836 is a pharmaceutical compound described as second generation lazaroid and its effects have been reported in many studies. Antioxidant effects of this preparation are due to inhibition of lipid peroxyl radical (LOO-) which blocks the redox chain reaction [59].

Superoxide ion is one of the most aggressive FR. Its neurotoxicity is given by a number of factors, including

biosynthesis accelerated by neutrophils, increased production during the inflammation response, increased reactivity of nitric oxide and peroxynitrite production. SOD is the only enzyme with antioxidant capacity able to inhibit oxidative activity of superoxide ion by converting it into oxygen and hydrogen peroxide molecules [39].

Numerous studies on the incorporation of SOD enzyme in various matrices able of controlling the release of active substances, reported significant decreases in biochemical markers specific to OS. Porfire et al, demonstrated the antioxidant of SOD entrapped in liposomal formulation with polyethylene glycol matrix [60].

A substance with high antioxidant capacity extensively studied lately is resveratrol (3,4,5 - trihydroxy-trans-stilbene) [61]. This is a polyphenol compound found mainly in black grapes. The antioxidant activity of resveratrol is mainly associated with the modulation of mitochondrial activity [62].

Song et al studied the antioxidant effects of resveratrol, highlighting that its main feature is to regulate the expression of sirtuin 1 (NAD - dependent histone deacetylase class III), responsible for the modulation of metabolism of mitochondria, and PGC - 1alpha (proliferation activated receptor coactivator - 1alpha), responsible for mithocondrial biogenesis [63]. In several studies, due to its neuroprotective properties, resveratrol is recommended for use to combat the side effects induced by the OS.

The beneficial effects of antioxidant therapy with vitamin C were observed in a number of studies on ischemia reperfusion syndromes. High doses of vitamin C have beneficial effects, especially on the lung, liver and brain [64]. Intravenous administration of high doses lead to reduced injuries caused by the OS with reduced neutrophil oxidative burst [65] and endothelial protective effects [66]. There is a decreased biosynthesis of free radicals, protective mitochondrial activity, minimization of energy failure, attenuation of sepsis, reduction of microvascular thrombosis rate, normalization of coagulation and prevention of vascular leakage [67].

Nathens et al studying the antioxidant therapy in the critically ill, reported a number of benefits following the association of vitamin C with Vitamin E [68]. The intravenous administration of 1000 mg/day of vitamin C and 1000 IU Vitamin E given orally produced significant decrease in the duration of mechanical ventilation, ICU length of stay, multiple organ failure and mortality [68]. Also, the combination of vitamin E with selenium resulted in reducing OS due to synergic antioxidative activity. Several studies indicate that the administration of selenium with vitamin E inhibits lipid peroxidation.

Administration of folate, vitamin B12, B6 and B1 have antioxidant effects due to normalizing the plasma level of homocysteine, thus lowering the incidence of cerebral venous thrombosis [69].

Şenol et al, demonstrated that administration of N-acetylcysteine together with selenium lead to normal serum values of OS biomarkers [70]. Furthermore, N-acetylcysteine is responsible for regulation of erythrocyte glutathione peroidase, minimizing the excitotoxic agents activity and inhibition of redox chain of lipid peroxidation [70].

Conclusions

Following TBI, secondary injuries due to generated changes, contribute significantly tothe survival rate of critical ill patients.

OS and neurodenaturation of specific factors often lead to death.

Research on FRs and their role in secondary injuries aims to maximize, optimise and diversify antioxidant strategies. In conclusion, the implementation of targeted antioxidant therapy in critically ill trauma patients with severe head injury is recommended due to a reduction in the number of post-traumatic complications. However, further studies are required to arrive at a definitive and appropriate antioxidant therapy.

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