CASE REPORT OPEN ACCESS

Selenium adjuvant therapy in central nervous system infection

Ladislav Kočan, Janka Vašková, Jozef Firment, Ladislav Vaško

ABSTRACT

Introduction: Bacterial meningitis is associated with permanent after effects resulting from damage to central nervous system structures in affected patients. Massive release of inflammatory mediators and production of reactive oxygen species often complicate the course of the disease and result in the development of sepsis and worsening of the patient's prognosis. Case Report: A 38-year-old male patient of Slovak origin with bacterial meningitis and serious sepsis was admitted to an intensive care unit. During a six-day supplementation of selenite pentahydrate at a dose of 750 µg per day, increased activity of the antioxidant enzyme glutathione peroxidase was recorded, the co-factor of which is selenium and synergistically acting enzyme glutathione reductase, respectively. A concurrent slight decrease in the activity of superoxide dismutase and the reduced levels of inflammatory markers indicated the development of an adequate response of the body to the production of free radicals and their elimination. Conclusion: It has been demonstrated that supplementation of critically ill patients with selenium can improve their antioxidant status and may also decrease oxidation damage to neurons and glial cells. Selenium as an adjuvant showed potential efficacy in reducing complications and improving patients' outcomes in the case of lowered antioxidant status during bacterial meningitis, firstly as a pro-oxidant to aid the elimination of microbial pathogens, and secondly as the antioxidant selenoenzymes. The results obtained allowed us to conclude that this can be a suitable complementary intervention in patients with pneumococcal meningitis and developing sepsis.

Keywords: Meningitis, Sepsis, Selenium, Selenoenzyme

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INTRODUCTION

Even though the range of possible treatments for bacterial meningitis is constantly increasing, the death rate for this disease is still very high (25%) and almost

half of the patients who overcome the disease suffer lifelong neurological consequences. It is a secondary disease which develops after transmission of the pathological agent from another focus of infection (middle ear infections 30%, pulmonary infections 18%, paranasal sinuses infections 2%), and most frequently via the hematogenous route [1]. The groups most at risk are children, immunocompromised patients and elderly people. Meningitis can be associated with subsequent blood borne infective complications such as sepsis, peritonitis and meningitis, which considerably decrease the patient's chances of survival [2].

The respective immune response is significantly affected by the specific anatomic location of the disease. Inflammation is an important component of the pathogenesis of meningitis, particularly in the stage of promotion and evolution of neuron demyelination and degeneration, even in cases where pathogenic micro-organisms have been removed by therapy.

In the case of bacterial meningitis, one has to consider the following cumulative effect of several pathophysiological factors:

1. systemic inflammatory response of the host organism resulting in extravasation of leukocytes to the subarachnoid space, vasculitis, brain oedema and secondary ischemia,
2. stimulation of microglia by bacterial components, and
3. potential direct toxicity of bacterial components on neurons.

The damage to neurons results from the release of reactive oxygen species (ROS), caspases, proteases, cytokines and excitant amino acids after the activation of transcription factors [3]. A significant increase in cerebrospinal fluid (CSF) ROS levels in patients with bacterial meningitis was observed [4]. The central nervous system is particularly vulnerable to the deleterious effects of oxidative stress, due to the high lipid content in the brain, so that an attack on membrane-lipids by ROS initiates a process of lipid peroxidation and subsequent oxidative modification of other cellular components.

Regarding pathogenesis, free radicals also play a key role in development of sepsis, is a serious complication of pneumococcal meningitis [5]. The production of free radicals is in equilibrium with the action of the antioxidant protective system [2, 6]. Superoxide dismutase (SOD) is an enzyme essential for regulating the disproportionation of superoxide radicals to peroxides. Glutathione peroxidase (GPx), of which selenium is a co-factor, acts as non-specific catalyst, facilitating the conversion of peroxides to corresponding alcohols and water, thus preventing the formation of additional ROS produced by the break-down of peroxides by means of glutathione oxidation.

Original studies on selenium supplementation in the critical care environment are from heterogenous groups of patients and include selenium supplemented in various dosing regimes. The available data demonstrate a potential survival benefit from the supplementation of selenium in general Intensive Care Unit (ICU) patients [7], mostly pointed out the narrow therapeutic window for selenium supplementation [6]. Randomised trial [8] showed no effect on new infections or on mortality when parenteral nutrition was supplemented with glutamine and/or selenium (500 μg per day). The supplementation of selenium in patients suffering from pneumococcal meningitis and developing sepsis could be considered a reasonable therapeutic intervention since there is evidence of a decrease in serum selenium levels during infections regardless of the infective agent.

The aim of this study was to point, by means of a case report, to potentially beneficial effects of supplemental adjuvant therapy with suitable micronutrients in critically ill patients.

CASE REPORT

A 38-year-old male patient of Slovak origin with repeating epileptic paroxysms was found unconscious at a railroad station. After arrival of medical emergency rescue team the patient was sedated, intubated, and transferred to the Department of Anesthesiology and Intensive Medicine. A thorough examination resulted in the diagnosis of purulent meningoencephalitis with suspect autogenous origin. For the purpose of ENT specialist intervention, the patient was transferred to the relevant tertiary hospital, the Louis Pasteur University hospital in Košice. The patient required artificial ventilation (AV) and was admitted to the 1st Clinic of anesthesiology and intensive medicine. A sample of CSF was withdrawn for microbiological and biochemical examination (Table 1). The patient was administered intravenously with cefotaxime (3 g every six hours). The cultivation of CSF revealed bacterial infection with *Enterococcus faecalis*, which was confirmed by a blood sample taken from the central venous catheter. On the basis of positive cultures, antimicrobial therapy was initiated. Symptoms of severe sepsis developed during the hours following admission and biochemical inflammatory parameters were elevated. The patient received catecholamine support with norepinephrine (0.1 $\mu g.kg^{-1}$ per minute) to maintain a suitable blood pressure. At the same time, the patient was started on meningitis therapy (cefotaxime 3 g every six hours, meropenem 2 g every 8 hours, vancomycine 2 g per day, antimycotics - fluconasol 20 mg every six hours, antiswelling treatment 100 mL of 20% mannitol every six hours) and hydrocortisone supplementation (50 mg every eight hours) to prevent presupposed vascular collapse due to secondary adrenal insufficiency. Subsequently, tympanomastoidectomy was performed on the left ear.

After the operation, a CT scan of the brain was carried out and an intracranial pressure (ICP) monitoring was introduced invasively to monitor manifestations of intracranial hypertension with a shift in midline brain structures. The patient was in analgosedation and the medication was gradually decreased to acceptable ICP values. During hospitalization, alongside adjuvant therapy, the patient

was administered daily sodium selenite pentahydrate (selenium, hereafter) by continuous infusion at a dose of 750 μg per day for six days corresponding to 250 μg selenium per day. Therapeutic advance was approved by Ethics Committee of Faculty of Medicine, Pavol Jozef Šafárik University in Košice. At the same time, alanyl glutamine solution was administered via a central venous catheter at a daily dose of 100 mL (2 g) for six days. During the supplementation, the plasma dynamics of inflammatory cells were monitored (leukocytes, neutrophil/lymphocyte ratio, thrombocytes) as well as the dynamics (Table 1) of biochemical markers (procalcitonin, fibrinogen, CRP, lactate) and antioxidant enzymes, glutathione peroxidase (E.C. 1.11.1.9), glutathione reductase (GR; E.C. 1.6.4.2) (Figure 1) by kit user manuals (SigmaAldrich, Germany) and superoxide dismutase (E.C. 1.15.1.1) (Fluka, Japan) (Figure 2) and the conscious state by means of Glasgow Coma scale (GCS).

Due of the necessity of long-term AV, we performed percutaneous dilatation tracheostomy and subsequently percutaneous endoscopic gastrostomy (PEG) in order to administer enteral nutrition. The objective neurological findings indicated dominance of quadruparesis predominantly in right limbs, right facial nerve paralysis and expressive aphasia. Control CT scan of the head showed inflammatory changes in the left brain hemisphere. Liquid cultures were sterile. The patient was rehabilitated. Complications during the hospital stay included sepsis and the development of purulent tracheobronchitis. Swabs of the endotracheal cannula confirmed colonisation of Pseudomonas aeruginosa. Due to high levels of laboratory markers of inflammation and sepsis, a CT scan of the brain was carried out which ruled out the presence of a brain abscess. The neurosurgeon did not find evidence to perform decompressive craniectomy. Healing of the incision was protracted, and the wound moist so the attending ENT surgeon recommended only a conservative approach. After a two-week treatment and withdrawal of medication, the patient still showed quantitative consciousness disorder, spontaneous opening of the eyes with goal directed fixation, motoric deficit and expressive aphasia. Breathing was spontaneous with pressure support, gaseous exchange in the blood and the acid-base balance (ABB) were satisfactory. Antiepileptic medication was part of the prophylactic treatment. The patient's circulation was stable and did not require catecholamine support. The patient was nourished via PEG, diuresis appeared sufficient, and the artificial ventilation via T-piece was discontinued.

Subsequently, upon the patient's agreement, he was transferred to the relevant ICU in a regional hospital for follow-up treatment. Following improvement, the patient described in the present case report was transferred from the ICU to the relevant neurological unit. At present, this patient is in office-based care of his

Table 1: Selected laboratory parameters from patient's medical history before and during selenium supplementation

	Day before selenium therapy	**Day after administration of 1st selenium dose**	**Day 7 of therapy**
Leukocytes ($10^9 \times L^{-1}$)	16.9	5.8	9,4
Neutrophils/lymphocytes ($10^9 \times L^{-1}$)	12	8	7
Thrombocytes ($10^9 \times L^{-1}$)	248	165	182
Fibrinogen ($g \times L^{-1}$)	5.46	5.68	1.3
Lactate ($mmol \times L^{-1}$)	3.8	2.5	2
CRP ($mg \times L^{-1}$)	328	124	75
Procalcitonin ($\mu g \times L^{-1}$)	≥10	-	≤ 0.5
GPx ($\mu kat \times L^{-1}$)	0.121	-	0.148
GR ($\mu kat \times L^{-1}$)	0.424	-	0.565
SOD ($U \times mL^{-1}$)	4.500	-	4.063

Abbreviations: CRP C-reactive protein GPx glutathione peroxidase GR glutathione reductase SOD superoxide dismutase

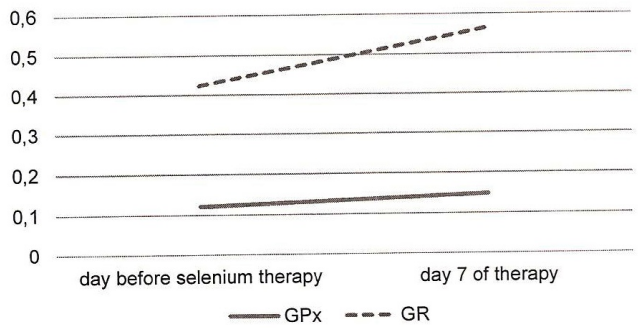

Figure 1: Glutathione peroxidases can have different peroxidase activities depending on the selenium status in an organism. Specifically, the activity of GPx, which contains selenium, was measured in reaction with tert-butyl hydroperoxide. The GPx activity measured did not reach a median value equal to that of healthy individuals (1.1 μkat.l-1); however, plasma glutathione peroxidase is known to be a more easily renewable selenoprotein than other blood components containing GPx. GR activity increased more quickly, mainly indicating high demands on glutathione as well as carbohydrate metabolism remedy.

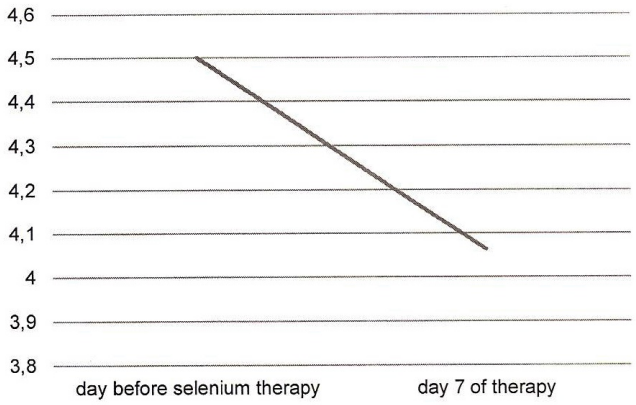

Figure 2: Activity of SOD was established to constitute a relevant parameter in order to evaluate the oxidative stress state of septic patients. An increase in SOD activity indicated an increase in superoxide radical production, leading to lipid peroxidation in addition to the intended goal of microorganism elimination. The initial activity of SOD is higher in comparison to that in healthy people (median 3.1 U.ml-1 measured in 30 individuals), denoting adequate SOD activity but without further selenoenzyme support. The tendency to decrease after six days of selenium adjuvant therapy indicated lowered superoxide production essentially from two points; namely, by successful antimicrobial therapy and as a result of glutathione peroxidase activity restoration.

local general practitioner and his neurological status is normal without neurological deficit.

DISCUSSION

Bacterial meningitis is a serious, life-threatening disease requiring rapid diagnosis and immediate treatment. Diagnostics is based clinical symptoms and predominantly on cytological and biochemical analysis of CSF. Prognosis of acute purulent meningitis depends on the inducing agent, intensity of infection, associated diseases, protective mechanisms and the timeliness of therapeutic intervention. Adjuvant therapy includes antioxidant therapy as protection against free radicals which participate in vasospasms and vasculitis of brain vessels and damage nervous tissue. Free oxygen radicals play an important role in the pathogenesis of the development and progression of this disease [9].

A precondition of the development of purulent meningitis is the colonization of mucous membranes with a pathogenic agent. Bacteremia and subsequent crossing of the hematoencephalic barrier may develop in immunocompromised individuals. The endothelia of cerebral capillaries play a key role in the penetration of bacteria into the CNS [9]. Once bacteria have successfully entered the CSF they start to multiply in the subarachnoid space. Bacteria produce proinflammatory molecules and release active substances by autolysis, which exhibit direct cytotoxic effects. Free oxygen radicals and reactive intermediate nitrogen products are very effective inflammation markers, participating in direct cytotoxic activity and amplification of inflammatory processes. They are produced by granulocytes, microglial cells, endothelium and the bacteria themselves. The cytotoxic effect of radicals is non-selective and, in addition to affecting bacteria, also causes significant damage also to CNS cells. Reactions of free radicals give rise to relatively stable molecules of peroxynitrile. These molecules induce cell death through peroxidation of biomembranes, damage to protein structures, damage to DNS and its excision reparative mechanisms. Selenoproteins such as GPx or thioredoxin reductases as well as methionine sulfoxide reductase are thought to have important antioxidant or redox roles. Selenium is not stored in organisms, so a temporary absence of intake rapidly leads to deficiency. Experimental measurements of selenium levels in critically ill patients with sepsis, SIRS and polytrauma revealed a marked decrease in plasma selenium and significant negative correlation between plasma selenium levels, APACHE II and SAPS II [10]. Intravenous daily intake of 1000 μg sodium selenite pentahydrate was well tolerated by patients in intensive care units [2]. The importance of measuring the selenium dosage became apparent for three reasons: firstly, due to the extreme sensitivity of neural tissue to oxidative injury, leading to intracranial complications and brain damage; secondly, the fact that selenium itself evinces pro-oxidative effect until incorporated into the structure of proteins [11] and finally as global protein synthesis itself is reduced under conditions of stress as a means of serving cellular resources [12].

Increased activity of SOD before selenium administration may result in an increase in the production and accumulation of peroxides and, thus, also to the induction of oxidative stress [13]. With regard to the tendency of decreased SOD activity (9.7%), the levels determined in our study indicated a decrease in the production of superoxide radicals (Table 1, Figure 1).

GPx is an antioxidant enzyme capable of destroying peroxides produced by SOD-mediated dismutation of superoxide anions. Three isoenzymes, cellular GPx, extracellular GPx and phospholipid GPx convert peroxides by supplying electrons from sulfhydryl residues of reduced glutathione. GPx is able to react with both hydrogen peroxide and lipid peroxides. Very low plasma levels of selenium [14] in critically ill patients may therefore be related to low activity of GPx. During the course of selenium therapy we observed that the activity of GPx was increased by 22.3% (Table 1, Figure 1) on day 7 compared to the initial level. Supplementation with selenium, the co-factor of GPx, resulted in increased GPx activity and, thus, also in increased degradation of peroxides, which is indicative of selenium incorporation into proteins and reduced oxidative stress conditions. Assuming the fact that glutathione is required for selenium metabolism, supplementation of glutathione synthesis precursors (alanyl glutamine) could be supportive alone. The key metabolite, hydrogen selenide, is formed from inorganic sodium selenite via selenoglutathione through reduction by thiols and NADPH-dependent reductase [15].

Glutathione reductase continuously recycles the oxidised glutathione back to its reduced form and this regeneration of thiols by means of GR is responsible for uninterrupted degradation of ROS. Decreased activity of GR could be a direct consequence of the overall depletion of antioxidantive substances and their co-factor as well as enzyme inhibition by glucose glycation due to acidosis. With regard to the increased activity of GR (33.3%) observed after the initiation of selenium adjuvant therapy and overall improvement of health, we can presume that the body's adequate response to high oxidative stress was supported as confirmed by the observed inflammatory parameters (Table 1).

CONCLUSION

Combined administration of antibiotics and adjuvant therapy with selenium at a dose of 750 μg per day was carried out for a period of seven days, resulting in an improvement in the patient's condition. The case illustrates the potential usefulness of selenium in clinical usage as an adjuvant and its potential efficacy in reducing complications and improving the outcome for patients in cases of lowered antioxidant status during bacterial meningitis. In this respect, we consider the changes in the activity of SOD against GPx to be interesting parameters for predicting a patient's prognosis. However, further studies are needed to answer the question of the effect of selenium adjuvant therapy against oxidative damage to the CNS and long term outcomes in purulent meningitis.

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Abbreviations

ABB	Acid-base balance
APV	Artificial pulmonary ventilation
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computer tomography
ENT	Ear-nose-throat
ICP	Intracranial pressure
GPx	Glutathione peroxidase
GR	Glutathione reductase
GCS	Glasgow Coma Scale
NADPH	Nicotinamide adenine dinucleotide phosphate, reduced form
PEG	Percutaneous endoscopic gastrostomy
ROS	Reactive oxygen species
SOD	Superoxide dismutase

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Ladislav Kočan – Substancial conctribution to conception and design, Acquisition of data, Drafting the article, Final approval of the version to be published
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Ladislav Vaško – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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