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Can oxidative stress markers help define stroke prognosis?

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ABSTRACT

Objective: To identify which oxidative stress markers can influence early stroke prognosis. Methodology: This is a systematic review carried out in two databases, PubMed and Web of Science, from November to December 2018. Two blinded, independent researchers probed the databases and gleaned descriptors indexed on both sites. “Markers”, “oxidative stress” AND “stroke” were the terms singled out for this study. The inclusion criteria were: the articles needed to have been published in English from 2013 to 2018, as well as include descriptors either in the title or in the abstract, and involve clinical trials with samples composed of stroke survivors. The exclusion criteria were: research involving animal experimentation; duplicate publications; articles without a clear methodology; articles that chiefly addressed any disease other than stroke, and those that were not available in full. Results: This review identified TBARS, catalase, nitric oxide (NO), Thiois, C-reactive protein and SOD as the most recurrent oxidative regulation markers in stroke survivors. These findings may direct new research toward obtaining early prognoses, and therefore enable more accurate decision-making. thus minimizing the costs and time related to the patient rehabilitation process.

Keywords: *Markers, Oxidative Stress, Stroke, Cerebrovascular Accident, Biomarkers.*

1. INTRODUCTION

Cerebrovascular accidents or strokes are the cause of death of more than 6.2 million people in the world annually [1]. In clinical terms, this pathology may present itself as either hemorrhagic or ischemic. Ischemic stroke arises from an arterial-obstructive blood clot in the brain, while hemorrhagic stroke is characterized by ruptured arteries resulting from vascular or hypertensive alterations. However, in the last few years, a number of studies have shown that redox balance is altered after stroke onset [2-4].

Unfortunately, reactive oxygen species (ROS) increase after a stroke, causing damage to vascular brain structures and compromising physical-chemical interactions [5]. The production of free radicals is physiological, being important for biochemical reactions, in the production of energy, as well as a defense mechanism, among other functions[6]. Furthermore, the ROS levels found in the body may be construed as indicators of various comorbidities (including stroke) arising from factors that may be external or internal to the human body[7]. The early identification of varied reactive oxygen species in the ROS levels, activated or otherwise, is hence a necessity. The human organism relies on defense systems against this oxidative aggression consisting of enzymes understood as markers, which in turn act as tools to protect the organism [8].

In this perspective, the patient's oxidative profile could serve as a basis for therapeutic decision. In recent years, the literature has shown that the presence of certain markers in the human body can directly influence stroke survivor prognoses, either positively or negatively. Even though some markers may act predictively, it is not yet known whether an individual marker – or a group of markers, for that matter – acting in isolation have absolute precision in patient prognoses[9]. In addition, these markers, which act as identification tools, are agents whose levels can be observed through experimental measurements that signal the presence of a pathological abnormality or disease in the organism, including a response to a particular pharmacological agent. This review article aims to identify which oxidative stress biomarkers can influence early stroke prognosis.

2. MATERIALS AND METHODS

This is a systematic review and the articles enrolled in the study was retrieved from two online databases:: PubMed (National Library of Medicine and National Institutes of Health) and Web of Science, from November to December 2018. The guiding question was: Which major oxidative stress markers are altered after stroke onset? Two independent investigators carried out the searches,, by combining descriptors indexed in both databases, from which the following were singled out for the purposes of this study: “markers”, “oxidative stress” and “stroke”.

The inclusion criteria were: the articles needed to have been published in English from 2013 to 2018, as well as include the presence of descriptors either in the title or in the abstract, and involve clinical trials with samples composed of stroke survivors. The exclusion criteria were: research involving animal experimentation; duplicate publications; articles without a clear methodology; articles that chiefly addressed any disease other than stroke, and those that were not available in full.

The articles were initially gleaned based on their titles and abstracts, which needed to be in accordance with the aforementioned criteria. The two reviewers then provided due justification for their inclusion or exclusion, and any discrepancies between the results obtained by the initial reviewers were judged by a third reviewer through an additional reading of the articles' titles and the justifications provided for their selection/dismissal. The final selection of articles was carried out by reading the papers in full.

3. RESULTS

A total of 128 articles were extracted from both databases. Out of these, 112 articles were excluded after being reviewed by the blinded researchers. After the full reading of the remaining publications, 2 of them were selected from the Pubmed basis, whereas 14 articles were yielded from the survey of the Web of Science database. 16 papers thus made up the final selection of articles for this study. Figure 1 illustrates the sequence of events in the article selection process:

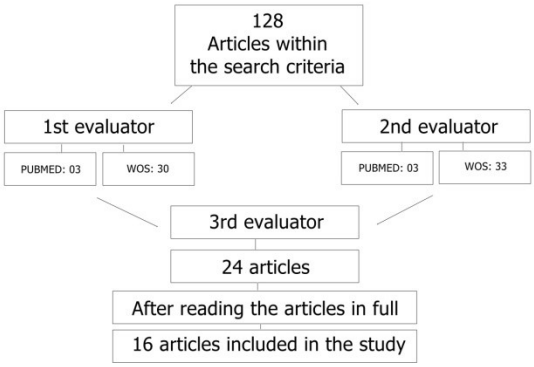

Figure 1. Flow chart of the article selection process

This study identified TBARS, catalase, nitrite, NO, Thiois, C-reactive protein and SOD as the most present (recurrent) oxidative regulation markers following stroke onset. These findings may direct new research to define early prognoses and thereby enable more precise decision-making processes. TBARS is a byproduct generated by lipid peroxidation (6). The increase in thiobarbituric acid levels has been related to a decrease in antioxidant defenses, especially free thiol (2).

According table 1, some authors have considered this relationship between variables as a predictive factor for worsening stroke prognoses. These authors[10] were emphatic in stating that significantly higher levels of TBARS on the seventh day following stroke onset define (or could define) a poor prognosis. These results corroborate the findings of Paspalj et al [3] in the same interval of seven days after stroke onset, although this author did not ascertain any statistical significance. Moreover, they suggest that TBARS may not be sensitive enough to indicate prognosis and clinical monitoring. However, the effects of dynamic regulation of cerebrovascular blood circulation by NO, as well as antioxidant, anticoagulant and anti-inflammatory agents have led some authors [3] to infer the possibility of a better prognosis based on NO levels in comparison with TBARS-based prognoses.

Furthermore, the study verified a relation between lethality and upward trends in the levels of this biomarker between the third and seventh days after stroke onset, albeit without statistical significance. However, the pathophysiological mechanism involved has not yet been elucidated. Conversely, SOD can aid in the protection of antioxidant system components in the post-ischemic phase[11]. This biomarker presented a slight elevation in the blood levels of cadavers, but no statistical relevance was noted[3].

However, Žitnanova [5] produced a sample with a statistically significant elevation of SOD in larger quantities on the seventh day after stroke onset. It could be construed as an adaptive response of the organism to pre-ischemic conditioning. Additionally, catalase and SOD both work by protecting the antioxidant system in post-ischemic conditions[11]. The available evidence indicates that there is a decrease in protein performance in cases where there are hemolytic alterations.

Paspalj et al [3] point out that the levels of catalase demonstrated a slight increase in patients who did not survive, but no statistical relevance was verified. But for Žitnanova[5], there was a statistically significant increase in catalase levels, especially on the seventh day. In another aspect, Chen et al. [12] comprehend thiol as a relevant biomarker for the measurement of increased oxidative damage. Işık et al [13] reported on the difficulty of directly identifying the presence of free radicals in the human brain and that an alternative to this problem would consist of indirect identification. These authors proposed that thiol levels could be understood as indirect parameters of oxidative stress for ischemic stroke in humans. The study further stated that the redox status of thiol groups is an important oxidative stress marker for stroke survivors. In this study, thiol levels were noted to be lower in ischemic stroke survivors when compared to the control group of healthy individuals.

Thiol levels were lower in post-stroke when compared to the control group as showed by Işık et al [13] and Tsai et al [10]. In the acute phase of stroke thiol levels are even lower when the disease occurs in larger vessels; the same on the first and seventh days following stroke onset, and gradually increased until the thirtieth day when it was similar to the levels found in the control group (tabele 1).

In summary, the authors agree that if the control and intervention groups are compared, thiol levels will be lower for the intervention group. In addition, for Lorenzano et al [4], C-reactive protein was considered a biomarker present in the acute phase of stroke, emphasized in the first nine hours after the onset. However, as a biomarker, it has no relevance to the prediction of the disease. This biomarker could prove useful for understanding the progression of stroke symptoms in humans.

Table 1. Results of the literature review of studies on ROS and stroke performed in the Pubmed and Web of Science databases.

Author	Aim of Study	Biomarkers	Results
[15]	To analize oxidative stress, breakdown in the acute phase of stroke	albumin, total antioxidant status, total oxidant status (TOS) and oxidative stress index (OSI)	serum IMA levels were significantly higher in patients with CAH compared to healthy adults.
[16]	To determine if there is association	osteoprotegerin (OP), kappa-B and	Osteopontin increased on 7th day. levels of

Author	Aim of Study	Biomarkers	Results
	between serum levels of some molecules and deterioration in ischemic stroke.	Osteopontin (OPN),	Serum OPN were correlated with ischemic lesion on 7th and 90th days.
[17]	The effects of periodic limb movements during sleep on hypertension, inflammation and oxidative stress and urinary excretion of hydroxy-2-deoxyguanosine in recent ischemic stroke survivors.	C-reactive, interleukin 6, Total antioxidant capacity (TAC) and 8-hydroxy-2-urinary deoxyguanosine	periodic limb movement was independently associated with decreased antioxidant capacity in women who survived ischemic stroke.
[10]	Identify immunoproteasome proteins as predictors of hypertension after stroke.	Immunoproteasome proteins	Protein concentrations increased with augmented severity of bleeding.
[18]	To investigate whether there is an association between metabolic biomarkers of endothelial dysfunction in patients with acute ischemic stroke	markers of vessels	Endothelial biomarkers are associated with the severity of acute ischemic stroke
[13]	To stabilish the oxidative profile of the protein, antioxidant defenses and thiol levels	Protein Carbonyl; Thiol; acetylcholinesterase (AChE); glutathione S-transferases (GST)	An increase in the carbonyl content of proteins and the expression of AChE was observed in the control groups. The total amount of thiols, acetylcholinesterase activity, and GST activity were lower than in groups of ischemic patients (control).
[20]	To explore the relationship between oxidative and nitrosative stress, as assessed by urinary biomarkers, and the risk of incident stroke.	Urine analysis 8-iso-PGF2 / urinary creatinine	The results showed a tenuous association between the plasma levels of PGF2-isoprostane and the occurrence of coronary disease, with an insignificant odds ratio of 1.08 (95% CI, 0.91-1.29)
[4]	To determine if plasma concentrations of inflammation, oxidative stress and tissue damage biomarkers predict infarct growthin hyperacute phase	Oxidative stress, plasma, and inflammatory biomarkers , C-reactive protein; matrix metalloproteinase	A potential role of oxidative stress in promoting brain tissue injury and cell death was identified.
[21]	tyrosie and phenylalanin as diagnostic markers in ischemic stroke (AIS) in clinical acute phase.	Phenylalanine (PHE) and Tyrosine (TYR)	PHE / TYR was highly elevated in the acute phase of AIS, and that this elevation is coupled to the inflammatory response.
[3]	To measure oxidative stress biomarkers in patients who survived acute ischemic stroke during different phases of the acute phase of stroke	Nitric oxide (NO) in the form of nitrite (NO2), superoxide anion (O2), hydrogen peroxide (H2O2), superoxide dismutase (SOD) and catalase (CAT) and TBARS	Findings indicated that O2 and NO may serve as the most relevant adjuvant biomarkers to monitor disease progression and evaluate therapies
[22]	To evaluate the kinetics of peroxiredoxin during the acute phase of ischemia and its ability to determine onset in a population of patients with known onset of less than 24 hours	Peroxiredoxin 1 (PRDX1)	PRDX1 levels were elevated during the first hours after stroke onset, suggesting that it could play a role in identifying patients with cerebral infarction who fall within the therapeutic window for reperfusion therapies
[23]	To investigate the association between uric acid and stroke.	Uric acid (UA) , magnesium ,Ca+ and Vitamin D levels.	Patients with low magnesium levels had low UA levels in ischemic stroke
[24]	To determine thiol level (?) and acid reactive thiobarbituric acid levels in different types of stroke, and assess its association with clinical outcomes.	thiobarbituric acid (TBRAS) and free thiol	Serum TBARS was significantly higher and free thiol was lower in patients with stroke than in controls on days 1 and 7 after acute ischemic stroke.
[25]	To determine the association between low- oxidized lipoprotein and the National Institute of Scale Stroke scores among patients with acute ischemic stroke.	Cholesterol, Total cholesterol.Low-density oxidized lipoprotein. Triglycerides; low- density lipoprotein. High density lipoprotein	The Low-density oxidized lipoprotein concentration resulted in an increase of 0.027 in the National Institute of Scale Stroke score.
[25]	To describe a metabolic signature of acute ischemic stroke (AIS)	Amino acid aspartic transferase; alanine aminotransferase; uric acid; lactate; tyrosine; tryptophan;	A marked disturbance of the AIS metabolism in serum was found, mainly associated with amino acid related metabolism. Tyrosine, lactate and tryptophan can be considered as potential AIS markers
[5]	To determine the range of oxidative stress markers and antioxidants in stroke patients over a 3-month period following acute ischemic stroke.	Plasma lipid peroxides and 8-isoprostanes in urine. Protein carbonyls, paraoxonase, glutathione peroxide, Superoxide dismutase (SOD) and catalase.	deleterious effects by free radicals is high after 24 hours of stroke and 3 months after stroke (?). This oxidative damage is reduced due to the activated antioxidant system.

4. CONCLUSIONS

The identification of SOD, Thiol, NO, TBARs, and catalase was especially evident on the seventh day after stroke onset. The early detection of these elements could be used as a clinical routine for generating stroke prognosis and thus become a part of the clinical decision-making process based on the evidence found in this systematic review.

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