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Oxidative stress/antioxidant balance implication in reducing of intra-ocular pressure in patients with stroke, nicergoline therapy and open-angle glaucoma

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Abstract

Background: The continue efforts for long term reducing of intraocular pressure (IOP) in patients with open angle glaucoma, focused the attention on those patients who received different therapies, other that topical drugs for IOP reduction, that can influence this parameter.. The aim of this study was to evaluate the IOP, total oxidative stress and anti-oxidant capacity of plasma before and after nicergoline therapy in patients with ischemic stroke and associated open angle glaucoma.

Material and method: a group of 35 patients with ischemic stroke and chronic open angle glaucoma (under topical beta-blockers therapy) was studied regarding the values of IOP, total oxidative stress (TOS) and total antioxidant capacity (TAC) before (T1) and after 6 month (T2) of nicergoline therapy.

Results: IOP values for both eyes were significantly reduced when the values of T1 examination were compared with those of T2 assessment. The total oxidative stress parameter was also significantly reduced after nicergoline therapy together with increasing of total antioxidant capacity of plasma.

Conclusions: besides its positive effects on neuronal metabolism for ischemic stroke patients, nicergoline is able to influence the IOP in patients with open angle glaucoma and to improve the plasmatic oxidative stress/antioxidant balance. By this mechanism nicergoiline can contribute to a neuroprotection and better visual function preservation for these patients, improving their chances to neuro-motor rehabilitation and their quality of life.

Key words: *nicergoline, oxidative stress, intraocular pressure, stroke, glaucoma,*

Introduction

One of the most used clinical medications in cerebrovascular disorders, for a large spectrum of actions is represented by nicergoline (NG), and semi synthetic ergot derivate. The importance of using of this drug for stroke patients results from actions as are: enhancement of neurotransmitters function, anti-platelet effect, improvement of metabolic activity due to increasing of oxygen and nutrients delivery to the neurons by vasodilatation effect, and improvement of neuronal cells surviving by reducing apoptosis phenomenon (1). It is also proved to increase the availability of acetylcholine through an increased releasing from cholinergic terminals and a selective inhibition of acetyl cholinesterase (2).NG can also enhance norepinephrine and dopamine turnover in some areas of the brain (3). Due to these properties, NG treatment is widely used for ischemic stroke, and dementia treatment (1,4). Being used for its vasoactive properties, some collateral effects were reported as are beneficial effects in patients with peripheral arteriopathy or reduction of intraocular pressure in patients with concomitant open angle glaucoma, already treated by topical therapy (1,5,6). The anti-oxidant properties of NG were also reported, and could serve also for both reduction of intraocular pressure and neurodegenerative phenomenon associated with chronic open angle glaucoma (COG) (7). Oxidative stress and neurodegenerative process are components of pathogenetic mechanisms in OAG (8). Increased oxidative stress and decreased oxidative status has been reported to be related to trabecular meshwork injury, as a pathogenetic mechanism associated to COG (9,10). Several therapies were already tested for their properties to reduce the oxidative stress in glaucoma, targeting the inhibition of apoptosis signal-regulating kinase, attenuating NMDA receptor activation, or suppressing of inducible nitric oxide synthase (iNOS)

expression (8). Others were addressed to enhance the antioxidant status, as is Valproic acid (used as antiepileptic drug), for its properties to increase the activities of superoxide dismutase (SOD), catalase, and glutathione peroxidase (11).There are medical and surgical therapies aimed to reduce the intraocular pressure (IOP) in glaucoma, but the researches about neuroprotection in glaucoma is widely focused on reduction of oxidative stress, adding a new therapeutic strategy for this disease (12).

Regarding the NG therapy, the adverse effects are mainly related to ergot compounds but are mild and transient being more safe than other ergot derivates as is ergotamine and ergotoxine, none of the clinical studies reported ergotism or fibrosis associated with NG treatment (13). The adverse effect are related to hypotension, dizziness, nausea and bradycardia, orexia and diarrhoea (13). Therefore, nicergoline treatment as a long term therapy for patients with chronic stroke has a good safety profile. Nicergoline therapy, could improve the quality of life in patients with stroke by influencing long term visual function, together with other rehabilitation therapies addressed to these patients (14,15).

The aim of this study was to evaluate the effect of nicergoline therapy on oxidative stress and IOP, in patients with stroke treated with this medication who concomitantly presented chronic opened angle glaucoma under beta-blockers topical medication.

Material and method

35 patients with chronic stroke and nicergoline therapy were included in this study. All the patients were admitted to the Rehabilitation Hospital, Cluj-Napoca, Romania, between 2011-2018 and signed an informed consent. The patients with ischemic stroke, confirmed by neurologic examination and imagistic methods, were undergoing to an ophthalmological examination (including best corrected visual acuity and ophthalmoscopic examination) due to routine checking during hospitalisation period. All the patients had a previous diagnostic of chronic open angle glaucoma and were under the topical treatment with beta-blockers. The intraocular pressure (IOP) was measured at the time of admission (T1), before nicergoline treatment initiation, and after 6 month of NG treatment (T2). The nicergoline dose was 30 mg/day. Exclusion criteria: patients with diabetes mellitus, infectious diseases during admission, anti-inflammatory therapy (nonsteroidal anti-inflammatory drugs or steroidal anti-inflammatory drugs), anticoagulant therapy, anxiolytic therapy, untreated hypertension, hemorrhagic stroke, closed angle glaucoma, intra-ocular lens, optic nerve diseases or corneal diseases.

Oxidative stress and anti-oxidant status evaluation was made by assessing total oxidative stress (TOS), and total antioxidant capacity of plasma (TAC), for each patient, before and after 6 month of nicergoline therapy. The measurement of TOS and TAC was made after a protocol previously described (16,17,18).

Statistical analysis - demographic characteristics were summarized as number of patients or as mean ± standard deviation. Comparison between groups were made with Student test for normal distributed samples and with Mann-Withney test if the numerical data were not normal distributed. $P< 0.01$ was considered with statistical significance.

Results

The demographic data of the patients are presented in Table 1.

Table 1 - Demographic characteristics of the patients at T1 and T2, expressed as number of patients and mean ± SD.

	T1	T2
Age (years) (mean±SD)	61.02 ± 9.29	NA
Gender -men/women (number of patients)	21/14	NA
Smoking (number of patients) - never - former - current	 15 18 2	NA (none of the subjects changed smoking status during investigation period)
Systolic blood pressure (mmHg)	122.28 ± 7.92	123.97 ± 7.15
Diastolic blood pressure (mmHg)	80.48 ± 4.46	81.77 ± 4.7
Dislipidemia (number of patients)	11	10
BMI (Quetelet index)	25.59±2.77	25.65 ± 2.71
Fasting blood sugar (mg/dL)	96.14 ± 12.97	98.05 ± 11.86
CRP (mg/dL)	1.27 ± 0.48	1.22 ± 0.46

NA= non-applicable

None of the data from table 1 had a significant change when T1 values and T2 values were compared.

The values of intraocular pressure (IOP), total oxidative stress (TOS) and total antioxidant capacity of plasma (TAC) are presented in Table 2.

Table 2. Study parameters: IOP left eye (LE) and right eye (RE) - (mmHg) between T1 and T2, TOS (µmol/L), TAC (mEq/L).

	IOP - RE	IOP-LE	TOS	TAC
T1	20.35±1.77	20.06±1.68	29.42±3.34	0.91±0.15
T2	15.47±2.03*	16.17±1.94*	15.77±1.78*	1.84±0.14*

* P < 0.0001 - comparisons between T2 and T1 parameter's values.

The levels of IOP values at T1 were between 20 and 21 mm Hg for both eyes. A significant reduction of IOP is visible at T2 compared with T1 (the mean of the values were reduced under the 20 mmHg for both eyes). TOS and TAC shown significant changes with increasing of TAC and decreasing of TOS. No significant correlations were found between IOP and TOS or TAC changes at T2.

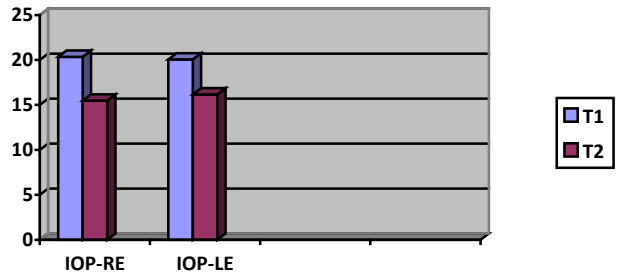

Fig. 1. IOP at T1 and T2 for right eye and left eye (mmHg).

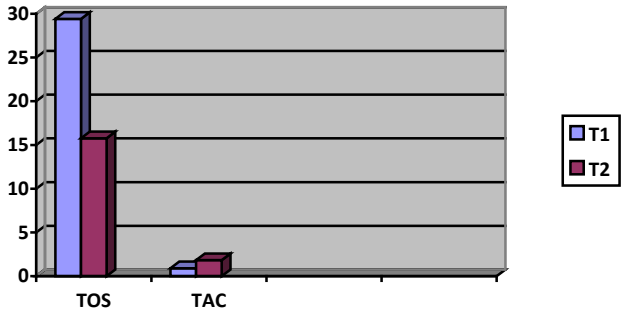

Fig.2 The levels of TOS (µmol/L) and TAC (mEq/L) at T1 and T2.

Discussions

Our result demonstrated that there is a significant reduction of TIO (Table 2 and Fig 1) after NG treatment in both eyes. The reduction of TOS and a significantly increased of TAC was also an observation of our study (Table 2 anf Fig 2). One of the most important pathophysiological theory regarding the optic nerve degeneration associated with chronic glaucoma (including normal tension glaucoma) is related to excitoxic effect of glutamate. (19). Glutamate transporting into the cells is connected with anti-oxidant capacity of cells due to its transformation in glutation, an anti-oxidant enzyme that was reported to contribute to the reduction of optic nerve and retina damage, associated with chronic glaucoma (20,21). Recent reports from experimental and clinical studies demonstrated the pathological implication of oxidative stress in glaucoma, both as a direct effect on trabecular meshwork, on optic nerve and on retina, contributing to their degenerative process (22). An experimental study demonstrated that clearing the excess of glutamate from synaptic cleft can prevent excitotoxic damage of optic nerve and retinal ganglionar cells of retina (19). Oxidative stress increasing, in glaucomatous patients, was reported to be related to mitochondrial dysfunction, that can also play a causative role (22). Therefore these theories postulate the causative and neurotoxic effect of oxidative stress as a pathophysiological loop in chronic glaucoma. The mechanism by which oxidative stress has these effects is not completely understood. In our study the difference between IOP at T1 and T2, together with significantly reduction of TOS and increasing of TAC, demonstrated the beneficial effects of nicergoline in glaucomatous patients (Table 2, Fig 1 and 2). Moreover, borderline intra-ocular levels (those between 20 and 21 mmHg) were reduced below 20 mmHg after initiation of nicergoline treatment. By these effects nicergoline can contribute both to reduction of intraocular pressure and improvement of oxidative stress/antioxidant balance in patients with chronic glaucoma. The anti-oxidant and neuroprotective effect of nicergoline was previously demonstrated (23).

There were other observations that various therapies, that were administrated for different diseases, can have an positive effect in patients with glaucoma. For example α-lipoic acid that can improve the diabetes associated neuropathy (24) reduce the retinal

ganglionar cells death in experimental glaucoma (25). Taking in consideration that diabetes and other metabolic disturbances and disorders are frequent associated with stroke and with increased oxidative stress, the therapy that are able to reduce oxidative stress are beneficial in glaucomatous patients due to their neuroprotective effects (8,26,27). Other experimental study demonstrated that geranylgeranylacetone (GGA), that is administrated for gastric ulcer, is able to inhibit retinal cells apoptosis and to increase the retinal neurons survival, in a experimental model of light induced retinal damage (28). The mechanism related to this neuroprotective effect is by inducing of het shock protein (Hsp) 70 expression that has an cytoprotective effect, by reducing retinal cells apoptosis rate (29).

Besides the neuroprotective effect of nicergoline there is a recent study that reported nicergoline among the drugs that are able to exert corneal protective action, improving corneal endothelial cells survival rate in increased oxidative stress conditions (29). The relationship between chronic glaucoma and corneal endothelial cells damage are still incomplete understood, but one of the theory is related to oxidative stress augmentation (30,31,32).

By targeting the oxidative stress reduction and increasing the anti-oxidant capacity of plasma nicergoline can contribute as a therapy against optic nerve degeneration associated with chronic glaucoma. Despite of anti-glaucomatous topical therapy there are observation that both in glaucoma with increased IOP, and in normal tension glaucoma, there is an associated optic nerve degeneration (33,34,35). According with these result a neuroprotective therapy added to topical therapy contribute to a better visual function preservation for glaucomatous patients. For the patients with stroke, improving of visual function together with specific rehabiltation therapy could contribute to their better quality of life (36,37). More studies are needed to evaluate the long term effect of nicergoline treatment, in patients with chronic glaucoma as are intraocular pressure, morphologic and functional optic nerve parameters, retina and optic pathways. These characteristics can be estimated by electroretinography, visual evoked potentials measurements and optic coherence tomography assessment. In most of the patients that received nicergoline therapy for ischemic stroke, that evaluations are difficult due to their neuro-motor disabilities following cerebral lesions. For those without severe neuro-motor disabilities associated with ischemic stroke and nicergoline therapy these evaluations could be attempted. Data resulting from these studies could better elucidate the long term effect of nigergoline therapy in glaucomatous patients.

Conclusions

Our study demonstrated a significant reduction of intra-ocular pressure for both eyes, reducing of total oxidative stress and improvement of antioxidant capacity of plasma for patients with ischemic stroke, associated glaucoma, and nicergoline treatment. Targeting reduction of oxidative stress in glaucomatos patients could be an hopeful strategy for their long term visual preservation. According with results of this study, nicergoline is able to have a beneficial effect in patients with chronic open angle glaucoma, when is added to topical beta-blockers treatment, due to its ability to reduce intraocular pressure and to contribute to the oxidative stress/antioxidant plasma capacity balance equilibrium.

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