Neuroprotective Properties of Citicoline in Patients with Unexplained Visual Acuity Loss Related to Silicone Oil Tamponade. Our Experience

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SUMMARY

Aims: To review the findings in the professional literature on unexplained loss of visual acuity (VA) in patients with silicone oil (SO) tamponade and post-removal, and assess the efficacy and safety of citicoline as a neuroprotective agent on anatomical changes and visual function in patients undergoing 25-gauge pars plana vitrectomy (PPV) for rhegmatogenous retinal detachment with large/multiple tears (macula-on/off).
Materials and Methods: We studied 96 eyes, 64 receiving citicoline (5 ml orally 3x daily) after PPV with SO tamponade, performed from 01.01.2023 to 30.06.2023 at the Eye Clinic of SZU and UNB. Best corrected visual acuity (BCVA) was measured using ETDRS charts, and changes in the retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) were assessed using OCT at 1, 3 and 6 months. Complications were monitored and results analyzed statistically.
Results: BCVA improved (citicoline: 19 to 48 letters; non-citicoline: 13 to 42 letters, $p < 0.001$), with better results in the citicoline group ($p < 0.01$). Intraocular pressure remained normal (10–21 mmHg), with a difference at 3 months (19 vs. 17 mmHg, $p < 0.05$). RNFL thickness decreased in T and S quadrants (T quadrant: 55 to 45 µm with citicoline, 52 to 41 µm without, $p < 0.001$), but was higher with citicoline (T quadrant: 50 vs. 44 µm, $p < 0.01$). GCL thickness initially decreased, then increased (T quadrant: 84 to 82 to 88 µm with citicoline, $p < 0.0033$), with higher values in the citicoline group ($p < 0.0125$). Citicoline demonstrated stronger neuroprotection in the GCL (GEE, $p < 0.05$).
Conclusion: Citicoline is a promising neuroprotective agent which potentially reduces loss of VA upon the use of SO tamponade, with positive impacts on the RNFL, GCL and visual function. Further randomized trials are required.
Key words: Citicoline, PPV, SO tamponade, unexplained loss of VA, OCT, RNFL, GCL

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INTRODUCTION

Silicone oil (SO) is a generic term used to describe a group of hydrophobic monomers and polymer compounds formed by silicon-oxygen bonds, termed organosiloxanes. Because of their viscosity and capacity to repel water they are referred to as oils. Standard SOs for ophthalmological use have specific chemical and physical properties, which make them ideal for use as an intraocular tamponade in PPV procedures. SOs are transparent, inert, biostable, biocompatible 100% synthetic silicone polymers, most commonly in the form of polydimethylsiloxanes (PDMS), which are composed of repeating units of dimethylsiloxane [–Si$(CH_3)_2$O–, silicon (Si), oxygen (O), carbon (C) and hydrogen (H)], and thus have different size of chains, i.e. different molecular mass. The different size of the chains influences their viscosity [1]. At present the clinically used range of viscosities of SOs is between 1000 and 5700 mPa.s. (millipascal-second). SOs with a longer molecular length have higher viscosity, which reduces the movement of the SO bubble within the vitreous cavity. SOs are also hydrophobic, with a density of 0.97–0.98 g/cm^3 (gram per cubic centimeter), i.e. they are lighter than water, they have a refractive index of 1.40 and high surface tension on the interface with water of 40 dyne/cm^2, which enables them to integrate optimally with the intraocular aqueous environment. The chemical structure of SOs is illustrated in Figure 1 [2]. SOs

have been used in ocular microsurgery since 1960. Their role is irreplaceable precisely due to their exceptional mechanical properties, thanks to which they can help maintain the retina in the correct position after PPV, which is essential for regeneration and prevention of further complications. They serve as a substitute for the vitreous during PPV, and thereby provide short-term to long-term retinal tamponade until healing is completed and the SO can then be discharged from the eye. This mostly concerns complicated findings of the vitreoretinal interface, when temporary gas tamponade is unsuitable and ineffective [3]. SO tamponade is indicated upon retinal detachment with multiple, large and massive tears, tractional retinal detachment, proliferative retinopathy, persistent macular hole, recurrent vitreous hemorrhage, viral retinitis, endophthalmitis, complications in age-related macular degeneration, tumors, retinopathy of prematurity, venous occlusions, complicated findings in the sole functioning eye, and in seriously ill and immobile patients [4]. Despite the fact that SOs are important and useful surgical tools in vitreoretinal surgery, in the long-term perspective SO tamponades have well-described side effects and complications. These side effects and complications include emulsification of SO, acceleration of the onset of cataract, intraocular inflammation, secondary glaucoma, zonular keratopathy, changes of refraction, migration of SO into the anterior chamber, subretinally, subchoroidally, beneath the conjunctiva and through sclerotomy, as well as secondary epiretinal membrane, peri-SO fibrosis, repeat retinal detachment, abnormal adherence of SO to the retina referred to as "sticky SO", and unexplained loss of VA during SO tamponade and after discharge of SO from the eye, known as SORVL (SO-related visual loss). In the professional literature SORVL is often associated with terms such as retinotoxicity and neurotoxicity of SO. An understanding of the fundamental pathomechanisms of SORVL and their therapeutic influencing is essential for improving the functional results of patients after PPV with SO tamponade, but this requires further studies and randomized trials [5].

Unexplained VA loss related to SO tamponade

VA is a crucial clinical indicator of the function of the retina and the optic nerve. Loss of VA related to SO tamponade or discharge of SO is considered to mean loss of more than 2 rows on a Snellen chart, without any other manifest ocular pathology, independently of whether the macula was attached or detached upon rhegmatogenous retinal detachment, with an incidence of 5.9–10% in the first 6 months of SO tamponade and 1–33% in the first month after discharge of SO [6]. The conclusions of the studies presented in the professional literature concur on optic nerve neuropathy, macular dysfunction and generalized retinal dysfunction as causes of SORVL. Direct and indirect SO toxicity in SORVL is caused by a complex process, which may be triggered by multiple factors and mechanisms [7]. A number of hypotheses have been proposed as possible explanations for this phenomenon. Several authors state indirect SO toxicity as possible apoptosis of ganglion cells caused by damage to the K+ (potassium cation) pump of the Müller cells, in which long-term SO tamponade impairs transport of K+ to the vitreous, increases its concentration in the subretinal space, and after discharge of SO sudden changes of K+ activate apoptosis. However, a recent study did not determine raised potassium levels in the retro-oil fluid during SO tamponade, thereby controverting this hypothesis [8]. A second hypothesis of indirect SO toxicity is phototoxicity following its discharge, since SO is highly transparent, dissolves the macular pigments (lutein and zeaxanthin), and increases the susceptibility of the ganglion cells of the foveal region to photo-oxidative damage due to increased exposure to direct light. Loss of VA in direct lighting occurred in 4.4% of cases, as against 1.3% upon the use of inbuilt filters to reduce exposure to direct lighting [9]. However, some authors dispute the significance of phototoxicity, because perioperative photostress is limited by the short duration of the procedure, and they did not demonstrate its influence on unexplained loss of VA in phakic and pseudophakic eyes following discharge of SO [10]. A third hypothesis of indirect SO toxicity is long-term mechanical traction (retinal compression) caused by physical and biochemical interactions of SO with the retina which activate the microglia and increase production of growth factors (e.g. vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and nerve growth factor (NGF)). The activated microglia produce inflammatory mediators (e.g. TNF-α (tumor necrotizing factor-alfa), IL-1β (interleukin-1 beta), proteases, ROS (reactive oxygen species) and growth factors), thereby triggering chronic inflammation and oxidative stress, which damage the photoreceptors, synaptic connections, vascular integrity, which impairs perfusion, leads to retinal ischemia and apoptosis of the ganglion cells [11]. Direct SO toxicity is caused by penetration of SO drops into the retinal layers and optic nerve, which leads to damage to the ganglion cells through pressure and activation of the microglia, with subsequent apoptosis [12].

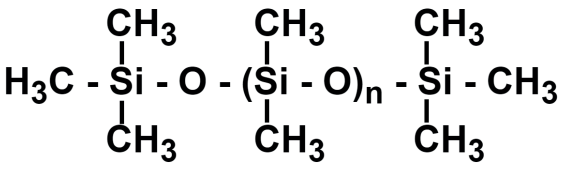


Figure 1. Chemical structure of silicone oil. Dimethylsiloxane: $-Si(CH_3)_2O-$, silicon: Si, oxygen: O, carbon: C and hydrogen: H, n: repeating unit (source: author)

Indication for discharge of SO from eye

Discharge of SO from the eye is a crucial step in ophthalmological treatment, indicated for preventing further damage to the retina and improving visual functions. The decision to discharge SO depends on several factors, including biomarkers, results of imaging modalities, structural changes of the retina and functional indicators [13].

OCT biomarkers and changes in the structure of the retina

OCT has become the clinical standard in monitoring patients with silicone oil tamponade. OCT is a noninvasive imaging modality that enables very detailed monitoring of changes in the structure of the retina, including the in-

dividual layers. From this perspective various imaging indicators are used to evaluate the effects of SO on the retina, which may indicate discharge of SO from the eye [14]:

- Thinning of RNFL: Significant thinning of the RNFL in the peripapillary region indicates damage to the ganglion cells and their axons. The temporal quadrant, which corresponds to the macula, is generally first to be damaged, as demonstrated in several studies. RNFL thinning may thus be a biomarker for early discharge of SO from the eye, even if it is statistically significant only at 6 months after discharge. RNFL thinning does not correlate to loss of VA, because SO has only a mechanical effect on the inner retinal layer and does not cause permanent damage to the photoreceptors. After discharge of SO from the eye, restitution of the RNFL does not occur [15,16].
- Thinning of GCL: Significant thinning of the GCL is in the parafoveal region. After discharge of SO from the eye, restitution of the GCL takes place within 6 months. The value of GCL thickness may serve as a predictive factor for the assessment of resulting VA [17].
- Changes of vessel density in the superficial capillary plexus (SCP) and deep capillary plexus (DCP), and average surface of the foveal avascular zone (FAZ) on angio-OCT (A-OCT): these biomarkers are not reliable for early evacuation of SO from the eye. The conclusions of clinical trials concur in the hypothesis that if SO tamponade influences mechanical blood flow, this is restored after discharge of SO from the eye. Changes of vessel density after discharge of SO from the eye are not statistically significant [15].
- Intraretinal microcysts: Intraretinal microcysts are generally a characteristic biomarker of retinal edema and may develop as a consequence of inflammation, oxidative stress or mechanical pressure. In eyes with SO tamponade they appear after discharge of SO from the eye, as a consequence of RNFL thinning. For this reason they are not a reliable biomarker for early evacuation of SO from the eye [18].

Timing of SO discharge

In eyes in which it is not possible to identify the etiology of loss of VA, studies show that an important role may be played by increased intraocular pressure (IOP) and the length of presence of SO in the eye. Based on clinical observations, it is therefore necessary to maintain IOP within a physiological range and remove SO as soon as the condition of the eye allows. This time frame may vary, but ordinarily SO is discharged from the eye after 3 to 6 months, and in the case of a deteriorating condition discharge should be considered as soon as possible. Longer exposure of the eye to SO increases the risks associated with its mechanical pressure and activation of biochemical reactions on the retina, which lead to a deterioration of visual functions [19].

Diagnosis of structural and functional changes caused by SO tamponade

Mechanical and biochemical irritation of the retina by SO during tamponade of the eye causes complex pathological processes such as increased oxidative stress and inflammation, which lead to activation of apoptosis of the retinal ganglion cells. This apoptosis can be identified with the aid of biomarkers such as proteins associated with apoptosis, and on OCT we can verify thinning of the RNFL and GCL. Progressive thinning of the RNFL and GCL is an important diagnostic marker of apoptosis of the ganglion cells, which signals a worsening of structural changes and visual functions. In such cases intervention is essential in order to avert permanent damage to the optic nerve. An objective indicator of visual functions is VA [20].

Neuroprotection in the treatment of unexplained VA loss related to SO tamponade

In clinical practice it remains a constant challenge to resolve any applicable neurodegenerative complications associated with SO tamponade, especially upon unexplained loss of VA. A crucial mechanism of toxicity of SO on the retina and optic nerve presented in the professional literature is apoptosis of the ganglion cells triggered by mechanical, oxidative and inflammatory factors. A variety of therapeutic approaches to prevent apoptosis of the ganglion cells are currently being investigated, including the administration of neuroprotective agents which are used because of their capacity to protect the nerve cells against damage by various pathological processes. Neuroprotective agents include: glutamate receptor antagonists (memantine, tacrine, amantadine, cannabinol), calcium channel blockers (nilvadipine), alpha2-adrenergic agonists (brimonidine), gingko biloba, antioxidants (coenzyme Q10, vitamin E, B1), neurotrophic factors (BDNF, CNTF, artemin, BFGF, IL-6, erythropoietin) and citicoline. These molecules act through a variety of mechanisms, from regulation of excitotoxity, through alleviation of inflammation to supporting regeneration of neurons and preventing apoptosis. Within this context citicoline appears especially promising, since its neuroprotective and neuroregenerative effects on the retinal ganglion cells are well documented. In addition to neuroprotective treatment, it is important to time the discharge of SO correctly in order to minimize the risks in association with its long-term presence [21].

Benefit of citicoline in treatment of unexplained VA loss related to SO tamponade

The neuroprotective effect of citicoline consists in protection of the nerve structures and in its capacity to support restoration of the nerve functions. Citicoline (generic name cytidine 5'-disphosphocholine (CDP-Choline)) is a biogenic molecule which plays a key role in a number of physiological processes within the human organism. The chemical structure or citicoline is presented in Figure 2. It is synthesized endogenously and can be consumed also in the form of nutritional supplements and foods for specific medical purposes. In the initial studies citicoline was administered via the means of intramuscular injections, at present it is also available for topical treatment in the form of eye drops and for oral administration in the form of solution and capsules. Its safety as a new type

of food product was confirmed by the European Food Safety Authority (EFSA) in 2014. After consumption it is well absorbed and broken down into two fundamental components, namely choline and cytidine, which are naturally occurring substances within the organism, and which are involved in other metabolic processes, mainly of the nervous system and the brain. Citicoline is a precursor of phosphatidylcholine, the main phospholipid of cell membranes, which supports their integrity and functioning, especially in the nerve cells. In addition, it maintains the level of phospholipids in the nerve tissue, such as sphingomyelin and phosphatidylserine, which are essential for the production of myeline and transmission of signals. As an important source of choline it reduces hydrolysis of phospholipids, protects the neurons against cholinergic decay and supports the synthesis of glutathione, a key antioxidant in the nerve tissue [22]. In the nerve tissue citicoline also plays a significant role in the formation of neurotransmitters, which are the chemical substances responsible for the transmission of signals between the nerve cells. Citicoline plays a significant role in the formation of acetylcholine, a neurotransmitter contributing to cognitive functions. Citicoline also supports the metabolism of the nerve cells by providing components for the production of energy, including synthesis of adenosine triphosphate (ATP), which is of crucial importance for the function and health of neurons in processes such as synaptic transmission and plasticity. On a molecular level it improves dopaminergic and cholinergic transmission, blood perfusion of brain tissues, and inhibits the accumulation of amyloids. Thanks to these properties it is being intensively studied as a promising therapeutic agent in the treatment of neurodegenerative disorders, with positive results [23].

Citicoline has demonstrated neuroprotective efficacy in clinical trials for the treatment of neurodegenerative disorders such as Alzheimer's and Parkinson's disease, cerebral ischemia, traumatic brain injury [21], and in ophthalmology in glaucoma, anterior ischemic optic neuropathy (AION), amblyopia, diabetic retinopathy, age-related macular degeneration (ARMD) or corneal neurodegeneration following LASIK [24], which supports its use for alleviating retinotoxicity and neurotoxicity caused by SO tamponade. Its complex pathomechanism includes restoration of membranes, improvement of mitrochondrial function, modulation of apoptosis, support of neurotransmission, reduction of oxidative stress and neuroinflammation, thereby stabilizing the retinal ganglion cells and visual functions [25]. These properties underline its important neuroprotective role upon damage caused by SO.

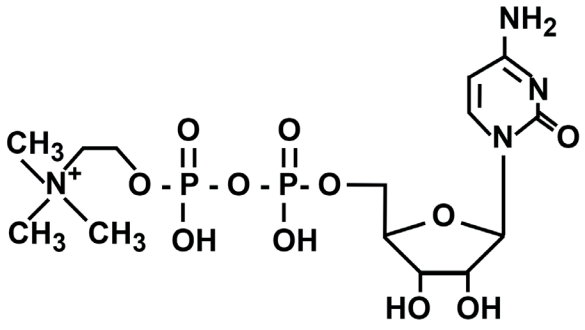


Figure 2. Chemical structure of citicoline

Our observation

The aim was to prospectively evaluate the safety and efficacy of citicoline as a neuroprotective agent administered orally in the form of a solution on anatomical changes of the retina and visual functions in patients with SO tamponade and following discharge of SO, undergoing 25-gauge PPV using the macula-on or macula-off method for rhegmatogenous retinal detachment with large or multiple tears.

MATERIAL AND METHOD

In our prospective observation we analyzed 96 eyes of 95 patients, of whom 61 were men and 34 were women, aged between 27 and 82 years (mean age 52 years). The patients were operated on using PPV with SO tamponade under general anesthesia by a single surgeon for rhegmatogenous retinal detachment with large or multiple tears in the periphery, and with the macula-on or macula-off method, at the Eye Clinic of SZU and UNB in the period from 01.01.2023 to 30.06.2023. If cataract was present, the patient underwent a combined PPV procedure with phacoemulsification and implantation of an intraocular lens (IOL). Before surgery each patient was examined for IOL, BCCVA with the aid of letters on ETDRS optotypes, anterior and posterior segment of the eye on a slit lamp and indirect ophthalmoscopy of the posterior segment. Patients whose medical history included glaucoma, previous vitreoretinal surgery, diabetic retinopathy, epiretinal membrane or high myopia with an axial length of the eyeball greater than 27.0 mm were excluded from the cohort. All patients underwent 25-gauge PPV with SO tamponade under general anesthesia using the instrument Constellation (Alcon). After the insertion of three trocars through the logo typico region by pars plana, the posterior cortex of the vitreous beneath the scleral indentation was removed, the DK line was applied beneath which the retina was reattached, all the identified tears and degenerative changes of the retina were treated by the implementation of laser retinopexy, and laser barrage of the retinal periphery was performed circularly. At the end of the operation, the periphery of the retina was examined beneath the scleral indentation, and SO tamponade of various viscosity was applied to the eye, according to the operating experience of the surgeon. Subsequently, following extraction of the trocars, sclerotomies such as the conjunctiva were sutured using the absorbable suture Vicryl 7-0. After the operation it was recommended that patients were placed in a prone position for a period of 1–2 weeks. Citicoline (Cognizin® Citicoline, Japanese company Kyowa Hakko, Bio, in the form of oral solution 50mg/ml) for oral consumption in the form of solution was administered on the first day after surgery in a total dose of 3x per day in a quantity of 5 ml as a potential treatment for reducing toxicity caused by SO tamponade. The patients were randomized into two groups in a ratio of 2:1, in which the first group contained 64 eyes of patients who were administered citicoline perorally from the first day

after surgery, and the second group consisted of 32 eyes of patients who were not administered citicoline perorally after surgery. The age, sex and duration of the disease was comparable between both groups. The patients were assessed at 1, 3 and 6 months after PPV with SO tamponade, and at 1, 3 and 6 months after discharge of SO. All patients underwent discharge of SO under general anesthesia by the method of 25-gauge PPV with tamponade by Ringer's solution on a Constellation instrument (Alcon). After the insertion of three trocars through the logo typico region by pars plana, SO was removed from the vitreous cavity. Subsequently, following extraction of the trocars, sclerotomies such as the conjunctiva were sutured using the absorbable suture Vicryl 7-0. During the follow-up observation period after the operations we assessed the change in BCCVA in all the patients with the aid of letters on ETDRS optotypes, and assessed changes of RNFL and GCL thickness with the aid of OCT (Spectralis®, Heidelberg Engineering, Germany), IOP, duration of SO tamponade with point in time of discharge of SO and occurrence of complications after surgery and during use of peroral citicoline solution. The obtained results of both groups were statistically processed, numerically expressed with the aid of arithmetical averages and presented in synoptic graphs.

STATISTICAL ANALYSIS

The statistical software IBM SPSS Statistics, version 23 (Armonk, NY: IBM Corp.) was used for the data analysis. The normal distribution of data for the parameters was verified by means of a Shapiro-Wilk test. A Friedman test for non-parametric data or repeated ANOVA measurements for normally distributed data were used for analyzing changes of quantitative variables within the framework of each group during the observation period. In the case of significant results, post-hoc comparisons were conducted with the aid of a Wilcoxon signed rank test (non-parametric data) or a paired t-test (parametric data) with Bonferroni correction ($\alpha = 0.05/21 = 0.0024$). For a comparison of the parameters between the groups at individual points in time we used a Mann-Whitney U test for non-parametric data or an independent t-test (or Welch t-test in the case of unequal variances, verified by a Levene test) for normally distributed data. For the analysis of the course of the parameters during the observation period between the groups we used a mixed ANOVA for normally distributed data or generalized estimating equations (GEE) for non-parametric data. In order to reduce the risk of type I errors in the analysis of four parameters we used a Bonferroni correction ($\alpha = 0.05/4 = 0.0125$). All the analyses were conducted on a level of statistical significance of $\alpha = 0.05$.

RESULTS

The average observation period was 5.7 months (1–9). In the first group the mean point in time of discharge of SO was SO 161 days, in the second group 126 days. Throughout the entire observed cohort the mean value of BCCVA was expressed with the aid of letters of ETDRS optotypes of 5 letters.

Analysis of functional results (BCCVA)

The BCCVA data had a non-parametric distribution (Shapiro-Wilk test, $p < 0.05$). The Friedman test demonstrated a significant improvement of BCCVA during the follow-up observation period after surgery ($p < 0.001$). The post-hoc analysis (Wilcoxon test, $\alpha = 0.0033$) detected an improvement of BCCVA in the group with citicoline from 19 to 30 letters (with SO at 1M to with SO at 3M, $p < 0.001$) and in the group without citicoline from 13 to 22 letters (with SO at 1M to with SO at 3M, $p < 0.001$), with a further improvement at the end of the observation period to 48 letters in the group with citicoline (without SO at 6M, $p < 0.001$) and 42 letters in the group without citicoline (without SO at 6M, $p < 0.001$). The Mann-Whitney U test ($\alpha = 0.05$) demonstrated higher BCCVA in the group with citicoline at all four points in time after surgery ($p < 0.01$) in comparison with the group without citicoline. GEE confirmed a faster and more consistent improvement of BCCVA in the group with citicoline ($p < 0.01$).

Both groups demonstrated a significant improvement of BCCVA after PPV (from 19 to 48 letters in the group with citicoline, from 13 to 42 letters in the group without citicoline (Graph 1), which corresponds to an improvement of visual acuity from approximately 20/200 to 20/40 (Snellen scale), typical of successful PPV upon retinal detachment as a consequence of anatomical reattachment of the retina. However, the group with citicoline achieved higher BCCVA at all four points in time, which indicates that citicoline probably supported the survival of the ganglion cells and nerve fibers, as also confirmed by the results of the analysis of the RNFL and GCL.

Analysis of IOP

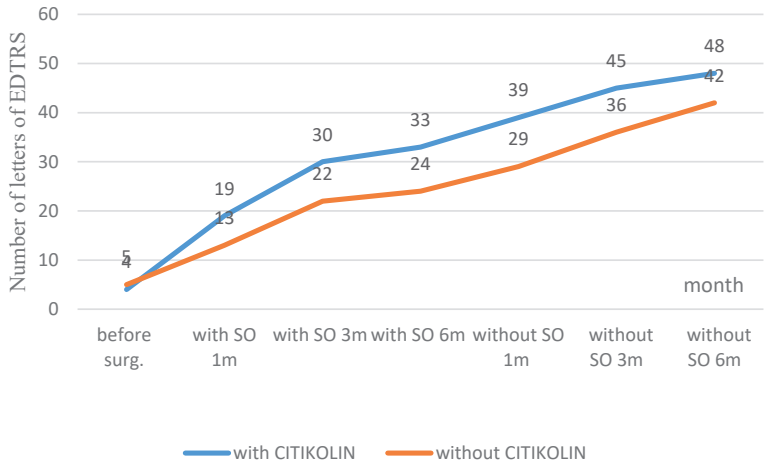
The IOP data had non-parametric distribution (Shapiro-Wilk test, $p < 0.05$). The Friedman test demonstrated significant changes of IOP in both groups within the observation period ($p < 0.001$). The post-hoc analysis (Wilcoxon test, $\alpha = 0.0024$) detected an increase of IOP after surgery in the group with citicoline from 10 to 19 mmHg (from before surgery to with SO at 1M, $p < 0.001$) and in the group without citicoline from 9 to 18 mmHg (from before surgery to with SO at 1M, $p < 0.001$), a decrease after discharge of SO in the group with citicoline from 19 to 13 mmHg (with SO at 1M to without SO at 1M, $p < 0.001$) and in the group without citicoline from 18 to 13 mmHg (with SO at 1M to without SO at 1M, $p < 0.001$), and at the end of the follow-up observation period a slight increase in the group with citicoline from 13 to 15 mmHg (without SO at 1M to without SO at 6M, $p < 0.0024$) and in the group without citicoline from 13 to 15 mmHg (without SO at 1M to without SO at 6M, $p < 0.0024$). The Mann-Whitney U test ($\alpha = 0.05$) demonstrated higher IOP in the group with citicoline only at 3 months after PPV with SO tamponade (19 vs. 17 mmHg, $p < 0.05$); at the other points in time the differences were not significant ($p > 0.05$). GEE did not confirm any significant interaction of time × group ($p > 0.05$).

In both groups IOP changed similarly and stabilized within a normal range (10–21 mmHg). Citicoline did not

have a significant influence on the course of IOP, which was expected, since it does not affect the regulation of intraocular pressure. The only statistically significant difference in the group with citicoline at 3 months after PPV (19 vs. 17 mmHg) is clinically insignificant, because both values are within the normal range and the difference is small. The mean values of IOP of both groups within the follow-up observation period are documented in Graph 2.

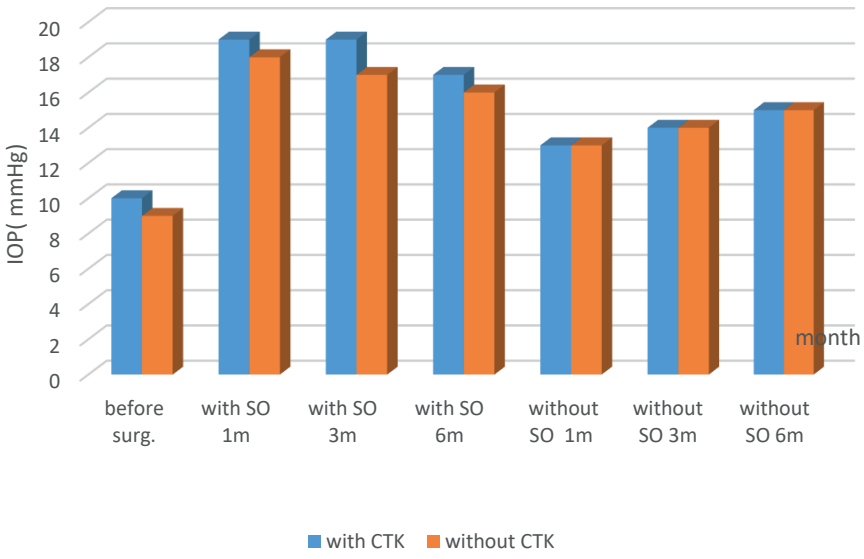
Statistical analysis of RNFL

RNFL in the quadrants (T, N, S, I) had non-parametric distribution (Shapiro-Wilk test, $p < 0.05$). The Friedman test demonstrated significant changes of the RNFL over time ($p < 0.01$). The post-hoc analysis (Wilcoxon test, $\alpha = 0.0033$) detected a decrease of RNFL in the T quadrant in the group with citicoline from 55 to 45 µm (with SO at 1M to with SO at 6M, $p < 0.001$) and in the group without citicoline from 52 to 41 µm (with SO at 1M to with SO at 6M, $p < 0.001$), and in the S quadrant in the group with citicoline from 120 to 114 µm (with SO at 1M to with SO at 6M, $p < 0.0033$), and in the group without citicoline from 116 to 109 µm (with SO at 1M to with SO at 6M, $p < 0.001$). RNFL thickness decreased in both groups in the first 6 months after vitrectomy with silicone oil (with SO at 1M to with SO at 6M), especially in the T and S quadrants, and after discharge of SO



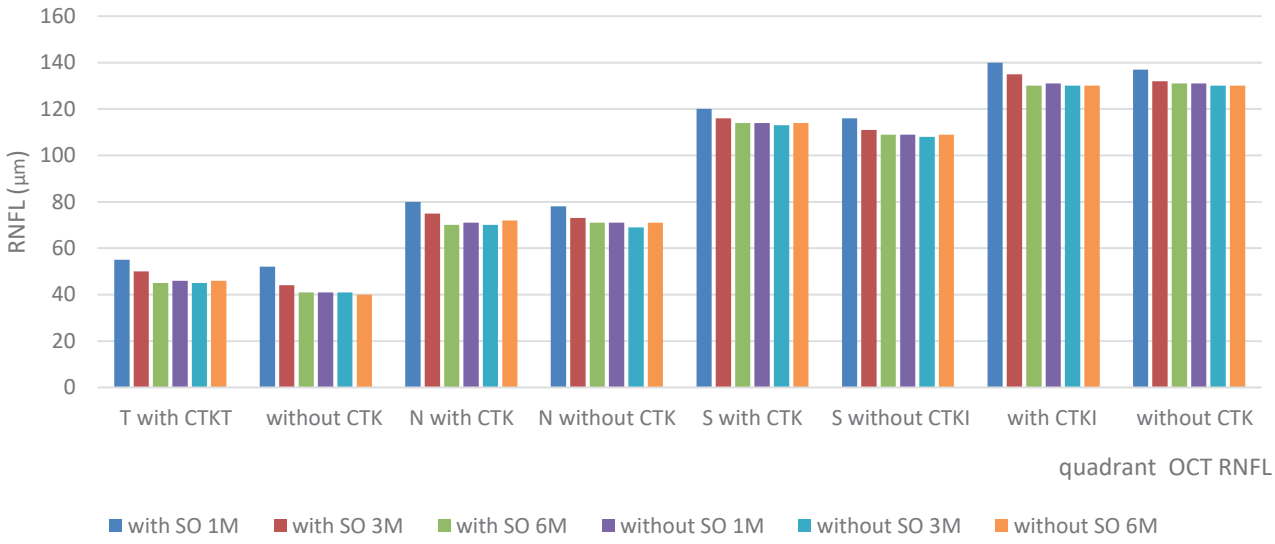
Graph 1. The line graph illustrates the average values of BCVA in letters EDTRS before surgery and its gradually increasing improvement at 1, 3, and 6 months after PPV surgery with SO tamponade and at 1, 3, and 6 months after SO removal (without SO). The data compares eyes treated with citicoline to those that were not

BCVA –Best corrected visual acuity, SO – silicone oil, PPV – pars plana vitrectomy, M – month, before sur. – before surgery, ETDRS – The Early Treatment Diabetic Retinopathy Study



Graph 2. Bar chart of the average values of IOP (mmHg) during the follow-up period before surgery, at 1, 3 and 6 months after PPV with SO tamponade, as well as and 1, 3 and 6 months after SO removal (without SO). The data compares eyes treated with citicoline to those that were not

IOP – intraocular pressure, mmHg – millimeter of mercury, surg. – surgery, PPV – pars plana vitrectomy, SO – silicone oil, m – month, CTK – citicoline



Graph 3. Bar chart of the average values RNFL thickness (µm) in quadrants OCT RNFL during the follow-up period at 1, 3, and 6 months after PPV with SO tamponade, as well as at 1, 3, and 6 months after SO removal (without SO). The data compares eyes treated with citicoline to those that were not

RNFL – retinal nerve fiber layer, µm – micrometer, PPV – pars plana vitrectomy, SO – silicone oil, M – month, CTK – citicoline, T – temporal quadrant OCT RNFL, N – nasal quadrant OCT RNFL, S – superior (upper) quadrant OCT RNFL I – inferior (lower) quadrant OCT RNFLm – mesiac, CTK – citikolín, T – temporálny kvadrant OCT RNFL, N – nasálny kvadrant OCT RNFL, S – superiórny (horný) kvadrant OCT RNFL, I – inferiórny (dolný) kvadrant OCT RNFL

(without SO at 1M to without SO at 6M) it stabilized with insignificant changes in thickness ($p > 0.05$).

The Mann-Whitney U test ($\alpha = 0.0125$) demonstrated greater RNFL thickness in the T quadrant in the group with citicoline (with SO at 3M: 50 vs. 44 µm; without SO at 6M: 46 vs. 40 µm, $p < 0.01$) and in the S quadrant (with SO at 3M: 116 vs. 111 µm; without SO at 6M: 114 vs. 109 µm, $p < 0.01$); in the N and I quadrants the differences were not significant ($p > 0.0125$). GEE confirmed a slower decrease in RNFL thickness in the T ($p < 0.01$) and S quadrants ($p < 0.05$) in the group with citicoline, while in the N and I quadrants the interaction time × group was not significant ($p > 0.05$). Citicoline thus demonstrated a protective effect on the RNFL in the temporal and superior quadrants, in which the group with citicoline manifested a slower decrease of RNFL thickness in comparison with the group without citicoline.

Change of thickness of the RNFL in the temporal, superior, inferior and nasal quadrants over time in eyes with SO tamponade and after discharge of SO in both groups is presented in Graph 3.

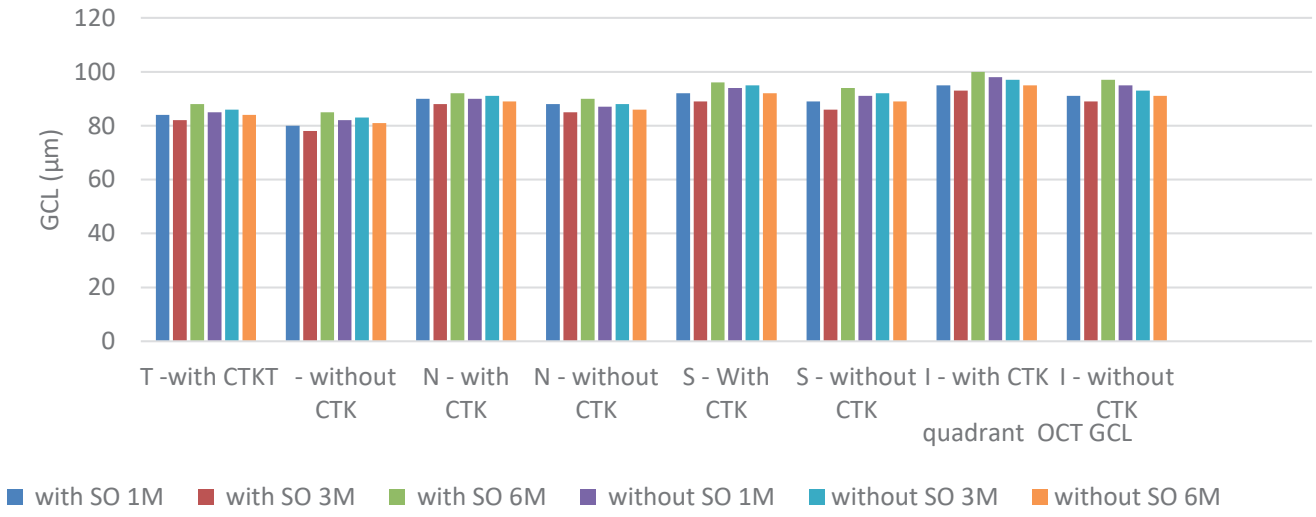
Statistical analysis of GCL

GCL in the quadrants (T, N, S, I) had non-parametric distribution (Shapiro-Wilk test, $p < 0.05$). The Friedman test demonstrated significant changes of the GCL during the observation period ($p < 0.01$). The post-hoc analysis (Wilcoxon test, $\alpha = 0.0033$) detected a decrease of the GCL in the T quadrant in the group with citicoline from 84 to 82 µm (with SO at 1M to with SO at 3M, $p < 0.0033$) and in the group without citicoline from 80 to 78 µm (with SO at 1M to with SO at 3M, $p < 0.0033$), with a subsequent increase at 6 months after PPV with SO tamponade to 88 µm in the group with citicoline (with SO at 6M, $p < 0.001$) and to 85 µm in the group without citicoline (with SO at 6M, $p < 0.001$). In the S quadrant there was a decrease in the group with citicoline from 92 to 89 µm (with SO at 1M to with SO at 3M, $p < 0.0033$) and in the group without citicoline from 89 to 86 µm (with SO at 1M to with SO at 3M, $p < 0.0033$), with an increase at 6 months after PPV with SO tamponade to 96 µm in the group with citicoline (with SO at 6M, $p < 0.001$) and to 94 µm in the group without citicoline (with SO at 6M, $p < 0.001$). GCL thickness in both groups changed over time – initially decreasing, then increasing.

The Mann-Whitney U test ($\alpha = 0.0125$) demonstrated a consistently greater GCL thickness in all quadrants in the group with citicoline during the period with SO and after discharge of SO ($p < 0.0125$) in comparison with the group without citicoline, which indicates the positive influence of citicoline on preservation of a greater number of ganglion cells. GEE confirmed a slower decrease of GCL thickness in all quadrants in the group with citicoline ($p < 0.05$). Discharge of SO from the eye was followed by restitution of the GCL in both groups, which was more pronounced in the patients using citicoline, as presented in Graph 4 and Figure 3.

Comparison of course of RNFL and GCL over time

The RNFL manifested a consistent decrease in the T and S quadrants in both groups during the observation period (with SO at 1M to with SO at 6M), which may indicate greater damage to the nerve fibers as a consequence of vitrectomy or silicone oil. By contrast, GCL thickness in the T and S quadrants initially decreased (with SO at 1M to with SO at 3M),



Graph 4. Bar graph of average GCL thickness values (µm) in quadrants OCT GCL in the observation period 1, 3, 6 months after PPV with SO tamponade and 1, 3, 6 months after SO drainage (without SO), in eyes with citicoline and without citicoline

GCL – Ganglion Cell Layer, µm – Micrometer, PPV – Pars Plana Vitrectomy, SO – Silicone Oil, M – Month, CTK – Citicoline, s CTK – with CTK, Bez CTK – without medical treatments, T – Temporal Quadrant OCT GCL N – Nasal Quadrant OCT GCL S – Superior Quadrant OCT GCL I – Inferior Quadrant OCT GCL

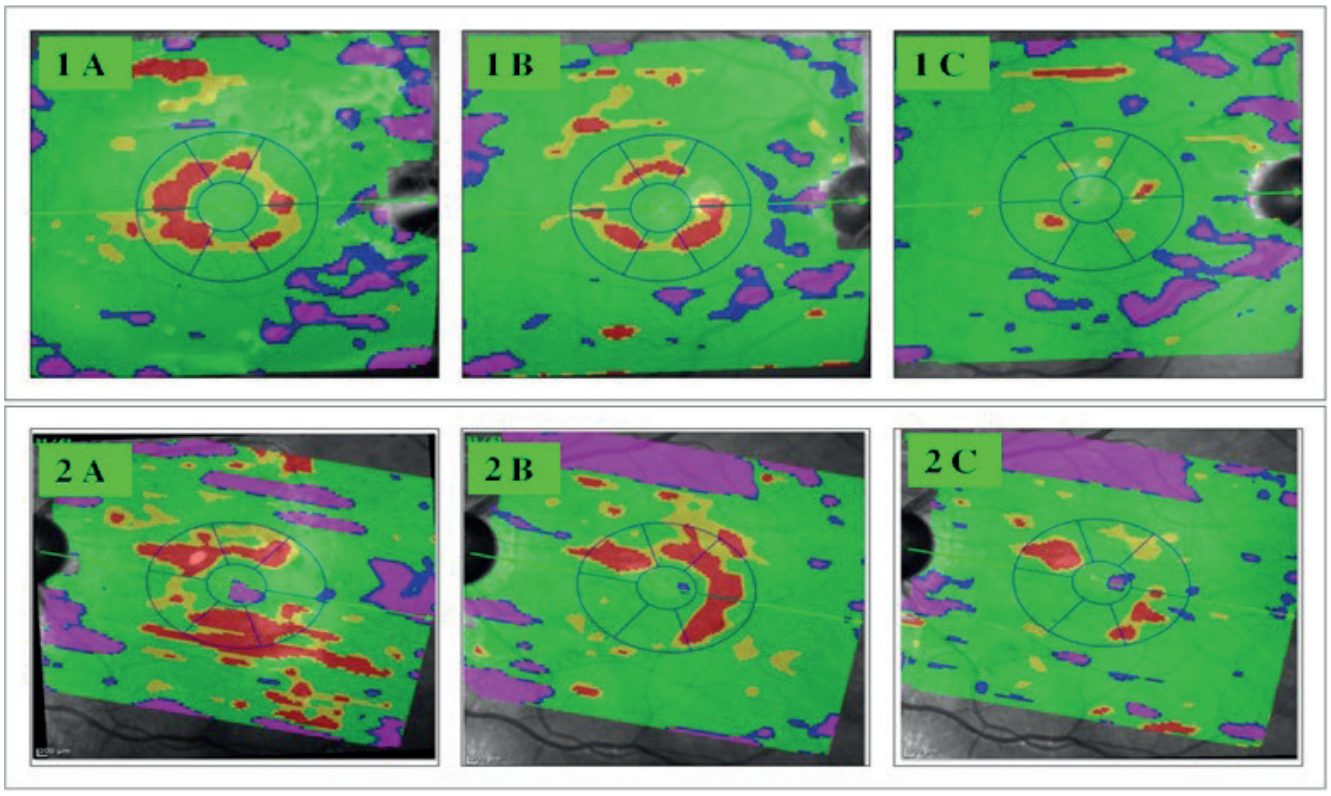


Figure 3. It shows the macular ganglion cell layers' thicknesses in the foveal and parafoveal areas of the eyes before SO removal and after SO tamponade (one month and three months after SO removal), comparing eyes treated with citicoline (**1A, 1B, 1C**) to those that were not (**2A, 2B, 2C**): 1A and 2A – before SO removal, 1B and 2 B – 1M after SO removal,
1C) and 2 C) – 3M after SO removal. Three months after SO removal, ganglion cell layers in the macula were gradually thickened (**1B, 2B, 1C, 2C**). Ganglion cell layers showed a greater increase in thickness in the eyes treated with citicoline (**1B, 1C**) than in the eyes that were not. (**2B, 2C**)

SO – silicone oil, M – month

but then increased (with SO at 3M to with SO at 6M) in both groups, which may indicate a certain regeneration or adaptation of the ganglion cells, probably influenced by citicoline.

Comparison of differences between groups (Mann-Whitney U test)

The group with citicoline had a greater RNFL thickness only in the T and S quadrants, while in the N and I quadrants the differences were not significant, which indicates a limited effect of citicoline in these areas. By contrast, the group with citicoline had a greater GCL thickness in all quadrants (T, N, S, I), which points to the stronger protective effect of citicoline on the ganglion cells in comparison with the nerve fibers.

Comparison of course over time (GEE)

GEE confirmed a slower decrease of the RNFL in the T ($p < 0.01$) and S quadrants ($p < 0.05$) in the group with citicoline, while in the N and I quadrants the interaction time × group was not significant ($p > 0.05$). In the GCL GEE demonstrated a slower decrease and more stable course of thickness in all the quadrants (T, N, S, I) in the group with citicoline ($p < 0.05$). Citicoline therefore demonstrated a more pronounced neuroprotective effect on the GCL, which is of crucial significant for preserving visual function, as are also confirmed by the results of BCCVA.

The incidence of postoperative complications was relatively low. We did not record repeat retinal detachment in any of the eyes. An increase of intraocular pressure during the observation period was recorded in 13 patients (13.5%) throughout the entire cohort, and was managed by means of administration of local anti-glaucomatous therapy. In 4 patients (4.2%) from the entire cohort we recorded development of dispersion of erythrocytes into the vitreous cavity shortly after surgery, with spontaneous regression within a maximum of 1 week after surgery. None of the above postoperative complications that occurred in our cohort were serious, and all were well managed by pharmacotherapy. We did not record any complications upon the use of citicoline in our cohort.

DISCUSSION

A relatively small number of studies on citicoline in ophthalmology are available in the PubMed database, and most of them focus on its potential in the treatment of neurodegenerative disorders such as glaucoma, AION, amblyopia, diabetic retinopathy, ARMD and neurodegeneration of the cornea following refractive procedures such as LASIK.

An early study focused on intramuscular administration of citicoline. In 1995 Campos et al. recorded a significant improvement of visual acuity in as high as 92% of patients (46 out of 50) without side effects in a placebo-controlled trial on 50 patients with amblyopia [26]. In 1999 and 2005 Parisi et al. confirmed a positive influence of intramuscular administration of citicoline on retinal function, the visual pathway and bioelectrical response of the cortex in two placebo-controlled trials on patients with open-angle glaucoma [27, 28].

Oral administration of citicoline has been the subject of several studies. In 2008 Parisi demonstrated an improvement of pattern-electroretinogram, visual potentials and visual acuity in a group with citicoline in comparison with a placebo on 26 patients with non-arteritic AION [29]. In 2013 Ottobelli et al. recorded a retardation of the progression of chronic glaucoma [30], in 2019 Lanza et al. in a two-year prospective study demonstrated an improvement of RNFL thickness and the visual field [31], and in 2023 Arrico et al. demonstrated stabilization of the visual field upon long-term use of citicoline [32]. An important multicentric, double-blind, placebo-controlled crossover study conducted by Rossetti et al. in 2023 on 155 from five European eye clinics demonstrated a statistically significant improvement of quality of life in association with sight in patients with glaucoma, especially in more severely visually affected patients [33].

Citicoline in the form of eye drops has also confirmed its regenerative and protective properties. In 2019 Cinar et al. recorded an improvement of restoration of corneal sensitivity following a LASIK procedure [34]. In 2020 Parravano et al. demonstrated a retardation of neuroretinal degeneration and microvascular changes in patients with diabetic retinopathy after three-year application of eye drops with citicoline and vitamin B12 [35]. In the same year Rossetti et al. confirmed a positive influence on the progression of glaucoma in concurrent anti-glaucomatous therapy [36], and Fogagnolo et al. recorded regeneration of corneal nerves in patients with diabetic retinopathy [37]. V roku 2021 Parisi et al. demonstrated an improvement of macular bioelectrical responses (mfERG) in patients with mild non-proliferative diabetic retinopathy after three-year application of eye drops with citicoline and vitamin B12 [38].

These studies with citicoline, administered either perorally or topically, demonstrated its protective and regenerative effect on the ganglion cells of the retina, in alleviating oxidative stress and supporting the regeneration of neurons, which are crucial mechanisms in the treatment of chronic neurodegenerative processes in various ophthalmological diagnoses. None of the above-presented works examined its effect within the context of retinotoxicity and neurotoxicity induced by silicone oil, which highlights the originality of our study. Our results demonstrated that citicoline in the group of eyes with citicoline retarded the decrease in RNFL thickness in the T and S quadrants ($p < 0.05$), reduced loss of GCL thickness in all quadrants ($p < 0.05$) and contributed to a more rapid and consistent improvement of BCCVA (from 19 to 48 letters, $p < 0.01$) in comparison with the group of eyes without citicoline (from 13 to 42 letters). Our findings support the hypothesis concerning the neuroprotective effect of citicoline also within the context of retinal damage caused by silicone oil.

CONCLUSION

The current aim of PPV with SO tamponade is not only to achieve anatomical success, but also to allevia-

te retinotoxicity and neurotoxicity, which contribute to SORVL. Treatment with citicoline, which has neuroprotective, anti-inflammatory and regenerative effects, may improve VA and protect the structure of the retina against damage caused by SO. Our results demonstrated that citicoline retards the decrease of RNFL thickness, protects the ganglion cells and improves VA, although it does not have a significant influence on IOP. Even if citicoline is unable to entirely eliminate the toxic effects of SO, it reduces the severity of structural and functional changes of the retina and optic nerve. As a promising nootropic pharmaceutical it alleviates retinotoxicity and neurotoxicity caused by SO tamponade, improves functional results and protects the ganglion cell layer following PPV, especially during and after the discharge of SO. Further randomized clinical trials with larger cohorts of patients are required in order to confirm the efficacy of citicoline and to determine the optimal doses. These studies should also examine molecular mechanisms such as apoptosis of the ganglion cells and oxidative stress caused by SO, by which they would expand our knowledge about its therapeutic potential.

According to the available data in the PubMed database there are no publications to date which have focused on this issue. Our study therefore lays the foundations for opening up a new field of clinical research focusing on the use of citicoline in alleviating the toxic effects of SO, and thereby contributes to expanding knowledge in ophthalmology. Our study is the first to contribute to knowledge about the therapeutic potential of citicoline in retinotoxicity and neurotoxicity induced by silicone oil.

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