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The use of galantamine in the treatment of post-traumatic oculomotor and trochlear nerve palsy

Zastosowanie galantaminy w leczeniu pourazowego porażenia nerwów okoruchowego i bloczkowego

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Abstract: Purpose: To assess the suitability of galantamine for the symptomatic treatment of post-traumatic oculomotor (III) and trochlear (IV) nerve palsy.

Material and methods: The routine ophthalmic and strabological examination was performed in five patients (4 females and 1 male) at the age of 31 to 57 years (mean 40.7) with the post-traumatic ophthalmic complications. Due to the unilateral oculomotor and trochlear nerve palsy, which had not resolved within 2–6 (mean duration of 4 months) months following traffic accident, galantamine was used. Nivalin and Reminyl were administered in iontophoresis and orally, respectively, for 10–18 months (mean duration of 14 months). The ocular muscle motion exercises and prism correction were also used.

Results: The increased range of ocular motion (100%), reducing of the angle of strabismus horizontally (40%) and vertically (60%), statistically significant extension of palpebral fissure (60%), and regression of diplopia (80% total without correction) were observed. The binocular vision after treatment in the free- and instrument-space environment were also improved (100% simultaneous perception, fusion 80%, stereopsis 60%).

Conclusions: The early galantamine administration in patient with n. III and n. IV post-traumatic palsy accelerates the resolution of post-traumatic ophthalmic symptoms. It is an effective treatment which offers the elimination of strabismus, diplopia and ptosis, at the same time improvings ocular movements and binocular vision.

Key words: galantamine, post-traumatic nerve palsy, oculomotor and trochlear nerves.

Streszczenie: Cel: uzyskanie odpowiedzi na pytanie, w jakim stopniu zastosowanie galantaminy wpływa na leczenie objawów związanych z pourazowym porażeniem nerwów okoruchowego (n. III) i bloczkowego (n. IV).

Materiał i metody: rutynowe badanie okulistyczne i ocenę strabologiczną przeprowadzono u 5 pacjentów (4 kobiet, 1 mężczyzny) w wieku od 31 do 57 lat (średnia 40,7 roku), u których doszło do pourazowych powikłań okulistycznych. Z powodu pourazowego jednostronnego porażenia n. III i n. IV w leczeniu zastosowano galantaminę w okresie od 2 do 6 miesięcy (średnia 4 miesiące) od momentu uszkodzenia nerwów. Nivalin w postaci jonoforezy i Reminyll doustnie były podawane przez 10–18 miesięcy (średnio 14 miesięcy). Dodatkowo wdrożono ćwiczenia ruchomości mięśni okoruchowych oraz korekcję pryzmatyczną.

Wyniki: u wszystkich pacjentów (100%) poprawiła sie ruchomość gałki ocznej, nastąpiła redukcja kąta zeza w poziomie (40%) i pionie (60%), statystycznie znacząco zwiększył się rozmiar szpary powiekowej (60%), ustąpiło dwojenie (80% całkowite bez korekcji), poprawie uległo widzenie obuoczne w wolnej przestrzeni i na synoptoforze (100% jednoczesna percepcja, fuzja 80%, stereopsja 60%).

Wnioski: zastosowanie galantaminy u pacjentów we wczesnym okresie po pourazowym porażeniu nerwów okoruchowego i bloczkowego powoduje szybkie ustąpienie powikłań okulistycznych w porównaniu z czasem ich ustąpienia, kiedy przebieg choroby jest naturalny. Przedstawione leczenie jest skuteczną metodą umożliwiającą likwidację podwójnego widzenia, zeza, opadania powieki, powrót pełnej ruchomości gałki ocznej i widzenie obuoczne.

Słowa kluczowe: galantamina, pourazowe porażenie nerwu, nerwy okoruchowy i bloczkowy.

Introduction

Oculomotor nerve damage is a relatively frequent and very important therapeutic problem. The acquired third nerve palsy can be caused by mechanical trauma (26%), brain tumor (12%), aneurysm (10%) or the increased intracranial pressure. Other causes include ischemia, diabetes (11%), hypertension, giant cell arteritis or stroke (8%). It can be triggered by the infection (5%) or occur secondarily to multiple sclerosis, viral infection and sinusitis (3%). Moreover it is diagnosed after surgery (10%), in the neurological disease such as Guillain-Barre and Fisher syndromes (5%). It can be benign self-limited (2%), miscellaneous (4%) or idiopathic (3%) (1). Fourth nerve palsies are recognized after surgical injury or inflammation. Brain tumors and ischemic (microvascular) neuropathies are rare (2).

Diagnosis based on thorough clinical neuroophthalmic examination. Additional imaging tests, electrophysiological analysis, and other specialist consultations play an important role in the management of peripheral nerve damage, including oculomotor and trochlear nerves.

Post-traumatic oculomotor nerve palsy leads the paralysis of muscles supplied by that nerve. The most common symptoms include diplopia, ptosis, and pupil dilatation with weak light reflex (3, 4). The acquired trochlear nerve palsy results in diplopia with a characteristic head tilt in opposite direction to the affected nerve, often accompanied by the secondary unilateral hyperactivity of the inferior oblique muscle or, in some cases, by the unilateral superior oblique muscle hypoactivity (5).

Proper treatment including physiotherapeutic procedures plays an important role in the management of peripheral nerve damage (6). The prisms are used in strabismus secondary to the oculomotor and trochlear nerve palsy in order to compensate the eye deviation and to resolve the diplopia. Galvanization or iontophoresis and vit. B1 and B 12 intramuscular injections are not always effective. Surgical intervention is indicated only throughout the period between 6 and 12 months after trauma, due to the possibility of spontaneous regeneration process (7).

In the last decade, acupuncture, botulin toxin injection and newer methods, including the administration of galantamine, were applied in the treatment peripheral nerve damage and neuronaldysfunction. Galantamine (Reminyl, Nivalin) is used for the treatment of various forms of dementia, especially Alzheimer's disease and in patients after facial plastic surgery. Due to its constrictive effect on muscles, it is also used for the treatment of myopathy secondary to myasthenia gravis and poliomyelitis; postoperative urinary bladder and intestinal atonia, as well as curare intoxication (8–10).

Purpose

The purpose of the study was to assess the efficacy of galantamine as a symptomatic treatment of post-traumatic oculomotor (III) and trochlear (IV) nerve palsy (i.e. ptosis, eye movement disorders, and diplopia).

Material and methods

A retrospective analysis of five cases was performed. We included four females (80%) and one male (20%) at the age of 31 to 57 (mean 40.7) years, with ocular complications following trauma, in the analysis. The follow-up ranged from 10 to 18 months (mean 14 months). All patients were diagnosed with the oculomotor and trochlear nerve palsy. The routine ophthalmic and strabologic examinations were performed. The following parameters were determined: visual acuity (Snellen's chart), refraction, near point of convergence (NPC), near point ofaccommodation (NPA) (RAF line), width of palpebral fissure, pupil reactions, type of strabismus, stage of eyeball movements (Wilczek's keratometer) and presence of diplopia in the visual direction (Hess chart), head tilt and binocular vision in the free (subjective test, classic Bagolini test, unilateral Bagolini test, filter test, Titmus fly test) and instrument-space environment (simultaneous perception, fusion, stereopsis).

The therapy included prism correction, which prismsranging from 16 to 30, eye movements exercises (muscle trainer) and galantamine administration over a period of 2 to 6 months (mean 4 months) following the trauma. Nivalin 5.0 mg/ml in iontophoresis was administered once a day for 10 days in two cycles, then treatment was continued with oral Reminyl 8.0 mg administered twice a day for 6 weeks. The therapy was implemented within 2–6 months after nerve damage.

The control group consisted of healthy individuals matched for age and sex.

The statistical analysis using the non-parametric Mann-Whitney-Wilcoxon U-test was performed. The $\alpha=0.05$ was considered statistically significant.

Results

The cerebral concussion as well as oculomotor and trochlear nerve palsy were diagnosed in all our patients. In all it resulted from trauma (traffic accident). One person had the orbital fracture of the inferior and medial wall (20 %). The characteristics of the group were presented in Table I.

<table>
<tr><th colspan="2">Visual acuity/ Ostrość wzroku</th><th>Refractive error/ Wada refrakcji</th><th>Ptosis/ Opadanie powieki</th><th>Type of strabismus/ Typ zeza</th><th colspan="2">Eye movement/ Ruchomość gałek ocznych</th><th colspan="3">Diplopia/ Dwojenie</th><th>Compensatory head tilt/ Kompensacyjne ustawienie głowy</th><th>Pupils/ Źrenice</th></tr>
<tr><td rowspan="2">0.10 - 0.20</td><td rowspan="2">1.00</td><td rowspan="2">Spherical/ Sferyczna +0.25 → +3.00 Dsph</td><td rowspan="3">5 pers. 100 %</td><td rowspan="2">Divergent Vertical Oblique/ Rozbieżny Pionowy Skośny - 19.5° ↑ 5.5 °</td><td colspan="2">Movement restriction/ Ograniczenie ruchomości</td><td rowspan="2">Horizontal/ W poziomie</td><td colspan="2">Vertical/ W pionie</td><td rowspan="3">4 pers. 80%</td><td rowspan="2">Shape change/ Zmiana kształtu
1 pers. 20%</td></tr>
<tr><td>Light/ Lekkie</td><td>Severe/ Ciężkie</td><td>Image torsion/ Skręcenie obrazu</td><td>No image torsion/ Bez skręcenia obrazu</td></tr>
<tr><td>2 pers. 40%</td><td>3 pers. 60%</td><td>Astigmatism/ Cylindryczna -0.25 → -1.00 Dcyl</td><td>5 pers. 100%</td><td>1 pers. 20%</td><td>4 pers. 80%</td><td>1 pers. 20%</td><td>1 pers. 20%</td><td>3 pers. 60%</td><td>Anisocoria/ Anizokoria 2 pers. 40%</td></tr>
</table>

Tab. I. Characteristic of the study group.
Tab. I. Charakterystyka grupy badanej.

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The best corrected visual acuity (BCVA) in the affected eyes was 0.1–0.2 in two patients (40%) and 1.0 in three subjects (60%). The refractive error ranged from +0.25 to +3.00 spherical diopters, and -0.25 to -1.00 cylindre diopters.

All patients had ptosis (100%). An improvement was observed after treatment which was statistically significant in three patients (Fig. 1).

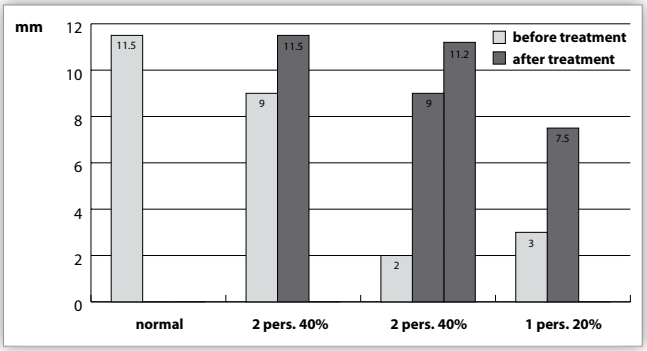

Fig. 1. The palpebral fissure width in a primary position.
Ryc. 1. Szerokość szpary powiekowej w pozycji pierwotnej.

The predominant form of strabismus was exotropia and vertical – oblique strabismus (mean horizontal angle of –19.5° and mean vertical angle of 5.5°). There was a statistically significant improvement in all patients with exotropia and vertical strabismus. In two cases (40%) of exotropia, ortophoria was achieved. In three patients (60%) with vertical deviation, a complete resolution of the angle of deviation was obtained (Fig. 2, 3).

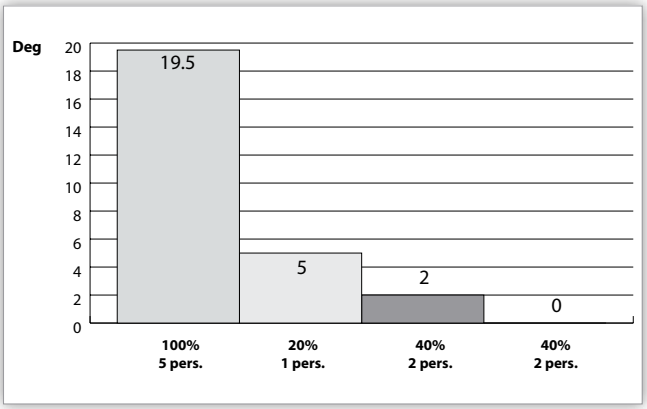

Fig. 2. Angle reduction of horizontal strabismus (mean value).
Ryc. 2. Redukcja kąta zeza w poziomie (wartość średnia).

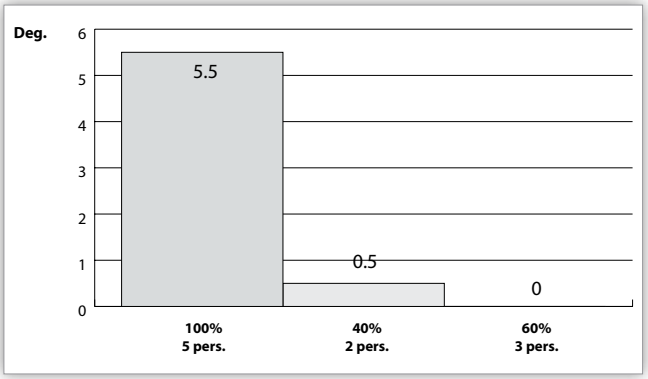

Fig. 3. Angle reduction of vertical strabismus (mean value).
Ryc. 3. Redukcja kąta zeza w pionie (wartość średnia).

The significant eye movement limitation was confirmed in four patients (80%). The oculomotor palsy manifested with the restricted upward, adduction, and downward gaze, which corresponded to the abnormalities of the unilateral superior, inferior and medial rectus muscles in the Hess chart (Fig. 4a., b., c., 5).

Fig. 4. Oculomotor nerve palsy (a., b., c.).
Ryc. 4. Porażenie n. III (a., b., c.).

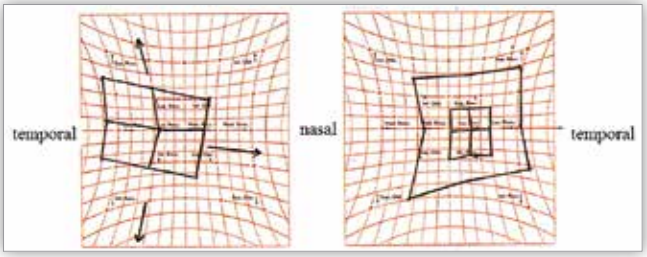

Fig. 5. Hess-card – oculomotor nerve palsy.
Ryc. 5. Karta Hessa – porażenie n. III.

The diagnosis of unilateral trochlear nerve palsy was based on the acute onset of vertical deviation which increased in contralateral side gaze, down gaze and ipsilateral head-tilt together with excyclodeviation which also increased in both down gaze and ipsilateral head-tilt (Fig. 6a., b., 7.).

After treatment, the eye movements towards the innervated muscles in affected eyes improved significantly in all patients (Fig. 8).

The baseline examination showed the extended near point of convergence (NPC) and near point of accommodation (NPA) in all patients, whereas both NPC and NPA were reduced after treatment (Fig. 9).

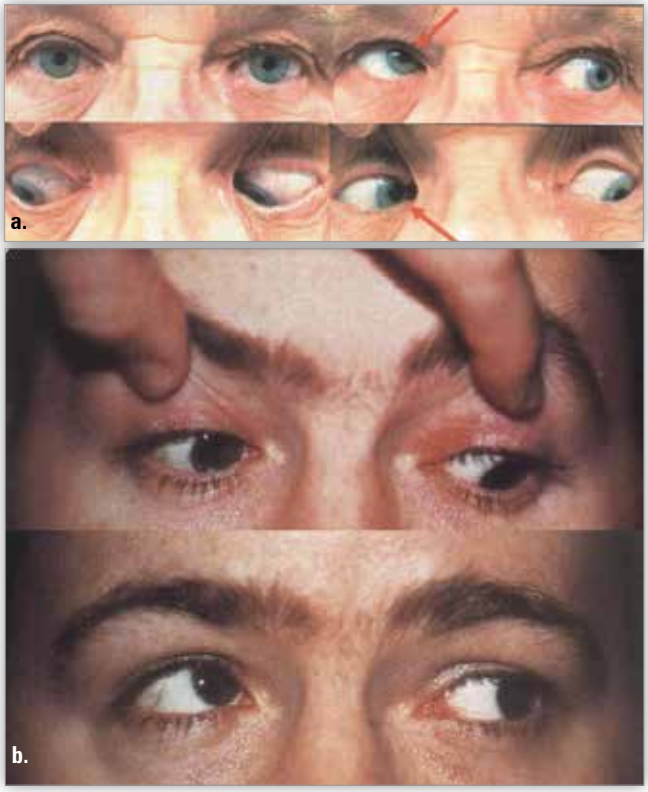

Fig. 6. Trochlear nerve palsy (a., b.).
Ryc. 6. Porażenie n. IV (a., b.).

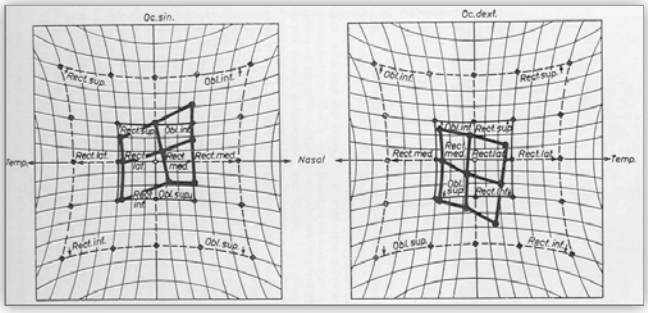

Fig. 7. Hess-card – trochlear nerve palsy.
Ryc. 7. Karta Hessa – porażenie n. IV.

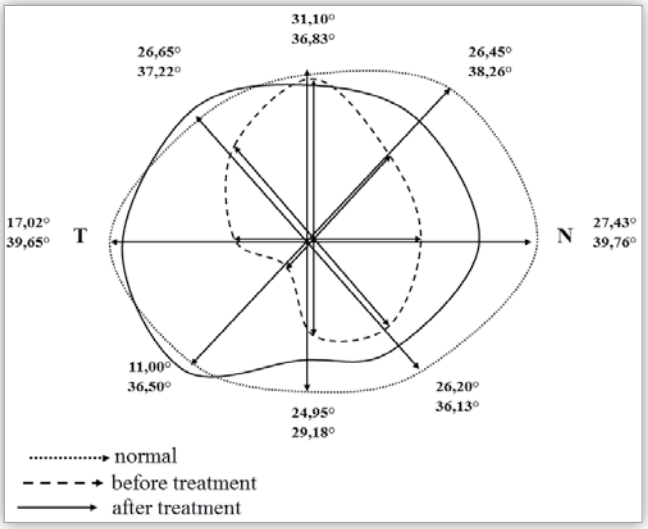

Fig. 8. Ocular range of motion (mean value).
Ryc. 8. Zakres ruchomości gałek ocznych (wartość średnia).

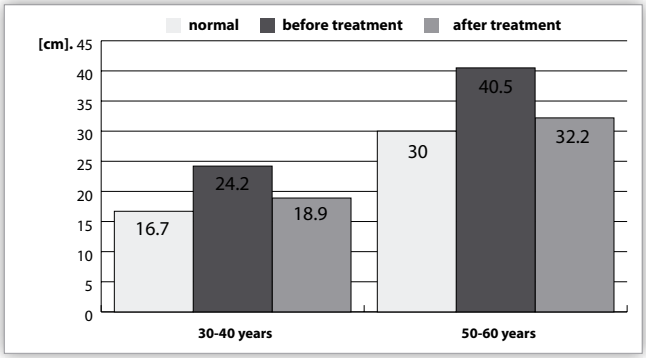

Fig. 9. The near point location (mean value).
Ryc. 9. Położenie punktu bliży (wartość średnia).

Vertical diplopia was observed more frequently. It was associated with head tilt in three patients (60%) whereas plain vertical diplopia, without head tilt, was shown in 1 patient (20%). Horizontal diplopia was observed in one case (20%). Additionally, in four patients (80%) head tilt was observed, which resolved after prism correction used for diplopia equalization (Fig. 10).

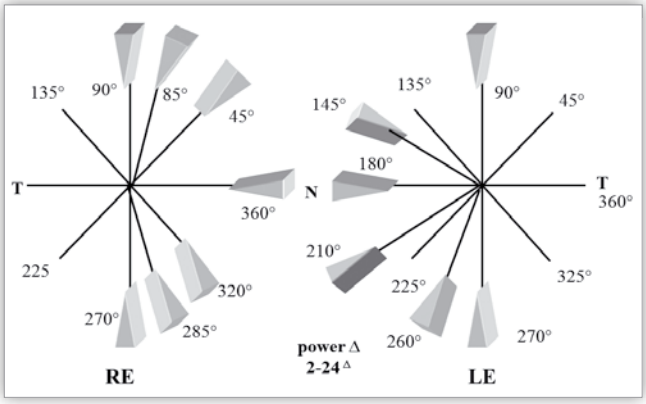

Fig. 10. Prism positioning in the patient with vertical-oblique diplopia in abduction.
Ryc. 10. Ustawienie pryzmatów u osób z dwojeniem pionowo-skośnym w odwiedzeniu.

Diplopia resolved in four subjects (80%). In one case (20%) it persisted whenwithout prisms only, and was not reported when the patient was using the prescribed correction.

The change of the pupil shape due to sphincter muscle injury was observed in one patient (20%), and anisocoria was initially found in two patients (40%). Both resolved during the follow-up.

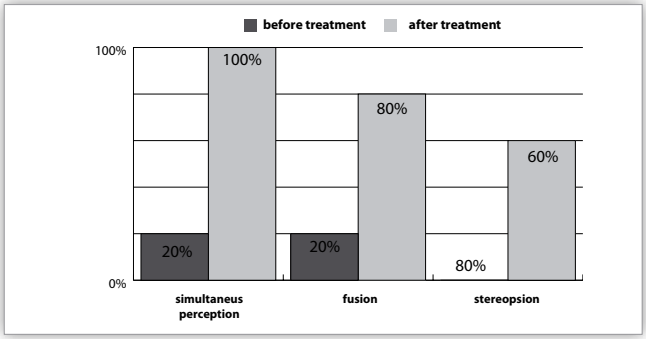

Fig. 11. Binocular vision status in an open space and synoptophor before and after treatment.
Ryc. 11. Stan widzenia obuocznego w wolnej przestrzeni i na synoptoforze – przed leczeniem i po leczeniu.

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Binocular vision disorders in the free- and instrument-space environment were identified in all patients. Follow-up data regarding binocular vision indicated statistically significant improvement in the perception (100%), fusion (80%), and stereopsis (60%), as compared to baseline (Fig. 11).

The complete cure was achieved in 60% of patients, in the remaining 40% diplopia resolved, but they still required prism correction.

Discussion

Our study is the first to present beneficial therapeutic effect of galantamine combined with standard treatment in patients with post-traumatic oculomotor and trochlear nerve palsy.

There is little information about the effect of galantamine on oculomotor nerve and muscle function. Similarly, there are no studies showing the effect of galantamine administration on oculomotor nerve function, so we cannot compare the results of our study with opinions and outcomes of other researchers.

Our data provides the evidence that the complex treatment including both galantamine and standard conservative therapy quickly restores the function of the damaged nerves. Additionally, it improves the activity of the associated muscles and reduces ocular complications.

These results indicate that new method of galantamine administration as physiotherapy (iontophoresis) as well as its oral administration contributed to the therapeutic success in our patients. Galantamine is a naturally occurring isochinolin alkaloid extracted from snowdrop flowers. It belongs to the indirect acting parasympathomimetics. Galantamine is a reversible and competitive acetylocholinesterase inhibitor, which also acts as a positive allosteric modulator of nicotinic acetylcholine receptors. The effect ofgalantamine on muscarinic receptors is significantly lesser as compared to the one of neostigmine. It facilitates the impulse conduction across the synapses at the neuromuscular junction (motor end-plate) and resolves the neuromuscular conduction block caused by other substances. Galantamine is transported by the blood-brain barrier; it facilitates the neurotransmission within the central nervous system and enhances the excitation processes. Furthermore, it causes contraction of smooth and skeletal muscles, and miosis, decreasing the intraocular pressure and vasodilatation at the same time (8, 9). These observations have led to the use of galantamine in our patients with the oculomotor and trochlear nerve dysfunction. Galantamine was administered 2 to 6 months following the nerve damage, while surgical treatment is recommended after 6–12 months of follow up.

According to numerous experimental studies the therapeutic effect of galantamine in patients with nerve palsy is based on the repair-regenerative processes in the nervous tissue (6, 8, 11). Some preclinical and clinical studies support potential efficacy of cholinesterase inhibitors, although the effect of galantamine on the oculomotor nerve has not been examined. Interestingly, we observed a positive correlation between galantamine administration and decreased palsy duration, faster restoration of muscle function, and resolution of accompanying symptoms in our patients compared to the natural course of the regenerative process after traumatic damage. It can be probably due to the faster nerve regeneration. The oculomotor nerve has the ability to regenerate. The repair process should take place within 3 to 5 months, that is without pathological synkinesis. If this process prolongs, this may lead to unpleasant consequences, such as the "misdirection phenomenon" (4).

No significant side effects of galantamine, such as nausea, vomiting, and diarrhea were observed.

The improved efficacy of medical treatment of nerve damage following trauma by using galantamine results in faster nerve regeneration. It increases muscle strength, restoring the full range of motion, and resolves symptoms associated with the eye deviation. Therefore it improves the efficacy of complex therapy, during the waiting period for the possible surgical intervention. Galantamine is the most-promising drug candidate.

Conclusion

Administration of Nivalin and Reminyl in the early post-traumatic period positively affected the accelerated resolution of post-traumatic oculomotor (III) and trochlear (IV) nerve palsy. It is an effective treatment which offers the elimination of strabismus, diplopia and ptosis, at the same time improvings ocular movements and binocular vision.

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