

Non-stopping oral astaxanthin supplement induced massive bleeding may be an etiology of suprachoroidal hemorrhage in any operation including cataract surgery

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Abstract: During many operation (in GU, GS, PS, CS, CVS, NS and even DEN section) including cataract surgery, massive blood of the patients would be easily leaked made it become difficult during approach. To our knowledge, non-stop use of astaxanthin supplement during phacoemulsification developing into SCH was first reported in the world. The abnormal hemodynamics of bleeding tendency from astaxanthin may result in several problems from mild hyphema to severe SCH formation. We must remember that discontinuation of all herbal, OTC and prescription medication at least 2 weeks before surgery if the pharmacologic reaction of them may interfere with hemodynamics. The clinicians should consult the detailed medical history of surgical patients. However, astaxanthin possess the character of bleeding tendency which could influence the processes of operation in any surgery. Therefore, we can't omit the potential adverse reaction and health hazards from some healthy food supplements for patients' safety.

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Introduction

Astaxanthin, a non-known dietary non-provitamin A xanthophyll carotenoid, is present in many well-known sea-foods, such as salmon, trout and red pigment of crustacean shells (e.g., crab and shrimp), lobster, fish eggs and membrane of Asteroidea (e.g. starfish). Recently, astaxanthin is highly values in possessing various pharmacological activities including stronger anti-oxidative activity, anti-tumor effects, anti-inflammatory action, immuno-modulatory activity, and neuro-protective effects. Moreover, it has anti-Helicobacter pylori activity, anti-arteriosclerosis functions, antidiabetic and hepato-protective effects, skin-protective functions, curing renal impairment, improving the semen quality and fertility as well as enhancing the exercise endurance.

As nature's most powerful antioxidant, astaxanthin has been documented to show a wide range of benefits in human clinical studies on several serious health concerns. Due to its molecular structure, astaxanthin is one of the few antioxidants that can move throughout the entire body and provide protection to all of our cells. Furthermore, it has the unique property to protect the entire cell because its polar hydrophilic ends may span across the entire cell membrane. Therefore, astaxanthin, one of the over-the-counter (OTC) medicines has considerable potential in promoting health in healthy peoples.

Besides, the patients with hypertension, diabetes, peptic ulcer and hepatic disorders may search for astaxanthin supplement.

In Taiwan, astaxanthin are common used in many peoples for preventing and curing diseases recently. In fact, the habits of consuming the traditional Chinese herbs, nature or healthy dietary supplements are also popular in the world. In our report, the patient who took astaxanthin supplements and did not stop it before operation suddenly developed into the most serious and rare complication about suprachoroidal hemorrhage (SCH) during cataract surgery. To our best of knowledge, the discontinuation of astaxanthin inducing massive bleeding may be the etiology of SCH in phacoemulsification which is never reported in the world.

Case Report

A 60-year-old female patient suffered from progressively worsening blurred vision and dim sensation in right eye for several months. Hence, she went to our ophthalmic department (Kaohsiung Armed Forces General Hospital, Taiwan) for evaluation. According to her statement, the symptom of decreased visual acuity gradually developed since March 2012. In our clinic, manifest refraction yielded - 4.00 D - 0.50 D X 85 in right eye (OD) and - 3.75 - 0.75 X 90 in left eye (OS) by auto-refraction. Her best-corrected visual acuity

(BCVA) was 6/6 (OS), however, the BCVA only reached to 6/30(OD). The axial length of both eyes were not significantly different (OD: 22.48 mm, OS: 22.78 mm) by A-scan. During detailed ocular check-up, the external eyes, anterior chamber depth, intraocular pressure (IOP), cornea, lens, and retina all revealed normal. Besides, no eyelid lag and retraction, exophthalmos, extra-ocular muscle dysfunction and diplopia were found. Besides, no other ocular diseases such as glaucoma, uveitis and other retinopathy were ever diagnosed. The patient also denied traumatic history and other systemic diseases such as hypertension, diabetes mellitus and connective tissue disorders.

Slit-lamp examination disclosed a significant mature cataract which was classified as grade 4 of nuclear sclerosis. Under the impression of cataract formation, we decided to arrange phacoemulsification 2 weeks later. At the beginning, surgery was performed under topical anesthesia by tetracaine 0.5%. After eyelid spectrum was placed, a paracentesis was made with the 11 o'clock limbus. Sodium hyaluronate (Healon GV) was injected into the anterior chamber (A/C). A 2.85 mm temporal clear incision was made with a disposable steel keratome and an anterior capsulorhexis was created by continuous curvilinear capsulorhexis forceps. Phacoemulsification was performed using the Stellaris system (Bausch & Lomb). Very hard nucleus was divided into 4 pieces by Akahoshi Combo pre-chopper at first. After four pieces of nucleus were phaco-emulsified and removed one by one carefully, we began to aspirate residual cortex by irrigation/aspiration tube followed by intra-ocular lens (IOL) insertion. When we prepared to aspirate the retained healon and closed the incisional wound, the A/C space became very shallow suddenly and the eyeball was very hard to palpate without cough and vomiting from the patient. We attempted to reform A/C followed by iris-cornea touch or adhesion by higher pressure from the posterior segment of eye using elevating the bottle of balanced salt solution and utilizing the viscoelastic materials (healon GV) to tamponade the wound, but these procedures all failed. Besides, the red reflex from retina disappeared and vitreous hemorrhage with active oozing was found under surgical microscopy. The impression of SCH was highly suspected, it was very difficult to close the incisional corneal wound by 10-O nylon suture because of the higher pressure from iris prolapse and inner content of eye protruding. We made greater efforts to spend 70 minutes in handling the trouble case completely. When the surgery was completed, we used the mannitol (IV route; 1g/kg body weight), oral diamox (250 mg tid; 750 mg in once day) and brimonide (an alpha-agonist lowering IOP agent) three times per day to control the higher

IOP.

After one day of operation, total hyphema was found because the blood in the A/C space flew from the posterior segment through ruptured posterior capsule possibly (Fig.1). Besides, the IOP was 45 mmHg and her BCVA dropped to only light perception. The B-scan ultrasonography (Accutome, USA) revealed apparent SCH with blood-dense configuration which presented mounts of blood accumulation in the posterior segment of the eye (Fig. 2). The patient was consulted again themselves and she remembered that she had taken oral health food supplements containing astaxanthin every day for 5 years just for healthy promotion. However, she did not discontinue the OCT medication before operation. In addition, we checked the prolonged coagulation profiles of the old women which revealed normal (the prothrombin time = 11.1 seconds (sec) Vs control = 10.3 sec and activated partial thromboplastin time = 28.1 sec Vs control = 27.1 sec). Besides, the platelet count was within normal range and the bleeding time was mild prolonged.



Figure 1. At the next day of operation, we found total hyphema in the anterior chamber of the patient. Besides, the intraocular pressure increased to approximately 45 mmHg for several days in spite of medical control.

Because total hyphema could not absorb and the higher IOP was approximately to 45 mmHg in spite of medical control for 5 days. We made a decision to arrange the secondary intervention at once for the preservation of the corneal function and prevention from the optic nerve and retinal damage. Under general anesthesia, anterior irrigation was performed to remove the hyphema in the A/C space at first. Then, pars plana vitrectomy (PPVT) was used to cut and remove the intraocular hemorrhage including dense blood clots and vitreous hemorrhage. After that, we could find two large, darkly colored dome-shaped elevations arising from the peripheral retina toward the optic disc region. Sclerotomies were performed to

drain black colored fluid from the suprachoroid space and then close the incisional wound on sclera by 6-0 vicryl sutured lines. Finally, the volume of vitreous space was simultaneously replaced with room air through the infusion cannula. When the detachment of choroid was repositioned easily by room air, the photocoagulation around the sclerotomies site on the retinal surface for sealing the wound closely to make sure that the total retina was attached. Finally, we closed the incisional wounds of three ports for PPVT by 6-0 vicryl lines and reformed the anterior chamber by room air followed by deeper periorbital injection of antibiotics and steroids. Two weeks later, no complication was found and the IOP was 18 mmHg without any lowering agent control. Six weeks later, her BCVA had returned to 6/10 and remained stable for 6-month follow-up.

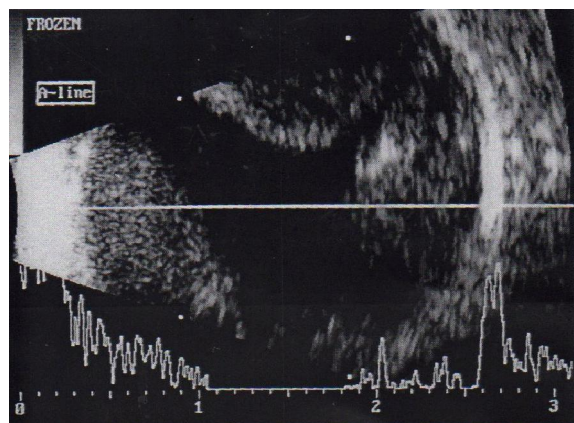


Figure 2. The B-scan ultrasonography revealed apparent SCH with blood-dense configuration which presented mounts of blood accumulation in the posterior segment of the eye.

Discussions

Cataract presents the leading cause of blindness, taking 51% of estimate 39 million blind people throughout the world. Global population growth and increasing longevity will double the number of people with visual loss and blindness from cataract by the year of 2020. In recent years, cataract surgery and the way has been performed has changed considerably with a shift toward non-suture technique, microsurgical IOL implant surgery which required complex and expensive instrumentation. These advances in the technology have resulted in fast recovery periods and better visual outcome. Furthermore, cataract surgery is an increasingly performed surgery in the world. To our surprised, the well-trained doctors performed the cataract surgery with good experience and they sometime may be trapped in trouble. Because of the residency and junior visiting doctor' training programs about

cataract surgery were not adequate; most of the younger ophthalmologists may feel about anxious in cataract operation due to the complexity and un-predictability of every procedure. Indeed, the reaction time of handling the complication during is only 2 to 5 seconds and the poor control of the following technique may result in serious adverse events including irreversible corneal decomposition, severe hyphema, endophthalmitis, lens dropping, vitreous loss associated with complications such as vitreous hemorrhage, malignant glaucoma and retinal detachment, and even permanent visual loss. Thus, the excellent technique is necessary and required in complicated and delicate cataract surgery.

In our patient, SCH is the most devastating, sight-threatening and rare complication associated with intraocular surgery. In a few studies that have qualified the incidence of SCH during and after cataract surgery, the rate having ranged from 0.03 % to 0.13 %. In some studies, about 34% of the patients with SCH who needed secondary intervention and their final visual acuity only achieved 20/100 or 20 /200. Some of the victims had light perception or no light perception and eventually underwent evisceration because of intractable pain. The presenting features on the SCH patients including pain, nausea, vomiting, IOP < 5mmHg (40%), IOP > 30 mmHg (26%), vision loss, retinal detachment, vitreous or retina incarcerated in the wound, flat anterior chamber and vitreous hemorrhage. Nevertheless, rare literature mentioned the sign of hyphema in SCH. In our case, total hyphema occurred after the next day of surgery. We suggested that the sign may be due to the synergistic effects from too much hemorrhage from the iris (no posterior capsule rupture occurred and the blood was relatively impossible from vitreous hemorrhage) and bleeding tendency from the patient's healthy food (astaxanthin).

The pathogenesis of SCH is an explosive accumulation of blood in the suprachoroidal space which is the most disastrous ocular problem. The risk factors of SCH are high myopia, glaucoma, diabetes, hypertension and atherosclerotic vascular diseases, advanced age, longer axial length, elevated IOP, pseudophakia, choroiditis, retrobulbar anesthesia, precipitous drop in IOP, aphakia, inflammation, and various ocular surgeries (cataract extraction, penetrating keratoplasty, glaucoma filtration surgery and vitreo-retinal surgery) and even the Valsalva maneuver^(19,20,21,22,23,24,25). As the effects for various types of surgery, the incidence of SCH following extracapsular cataract extraction (ECCE) is higher than following phacoemulsification. Ling et al. identified that ECCE may more induce the formation of SCH which may further impact retinal detachment,

massive hemorrhage, and apposition of the retina resulting from the hemorrhage. The incidence of SCH sometimes depends on the various surgical procedures during intraocular surgery. For example, the incidence of SCH in intracapsular cataract extraction (ICCE) and ECCE was 0.2%, and 0.13%, respectively. Besides, the modern technique about phacoemulsification, accompanied by the use of topical anesthesia and clear corneal incision techniques showed significantly lower incidence about 0.03-0.06%.

Why does the ECCE procedure easily develop into the occurrence of SCH than phacoemulsification? Till now, most authors consider ocular hypotony to be essential in the development of SCH in surgery. For example, in phacoemulsification, this necessitates a change of instruments when the relative stability of the closed system is at risk of being temporarily disrupted⁽²⁸⁾. The newer technique of phacoemulsification can be carried out more rapidly with less manipulation of the globe and maintains the stable condition which effectively decreased IOP. However, in ECCE, nuclear expression causes maximal distortion of the globe, and ocular hypotony is investable. When the larger corneal incisional wound was created and the A/C was open by 7515 Bever Knife, a great deal of aqueous humor may rapid drain out and the hypotony (lower IOP level) happened. Indeed, hypotony was the main cause of SCH which should occur after incision into A/C⁽²⁹⁾. The correct management is to normalize the IOP at once by closing the incisional wound as soon as possible. At the same time, the rapid injection with viscoelastic substance was used to reform the A/C space. However, some literature implicated that coagulopathy and bleeding tendency was the systemic risks for the development of SCH. Recently some authors addressed that pre-operative period of aspirin or warfarin users may experience the bleeding tendency which is also an etiology of SCH. In our case, the patient did not take any medication about interfering with hemodynamic. However, she continued the ingestion of astaxanthin which is clearly proved to increase and enhance the choroidal blood vessels vasodilation, flow velocity and microcirculation. Besides, it also shortens the blood transit time. Oral administration of astaxanthin over at least 4-week period can elevate the choroidal blood flow velocity without any adverse effects.

During many operation (in GU, GS, PS, CS, CVS, NS and even DEN section) including cataract surgery, massive blood of the patients would be easily leaked to extra-cell space and the possibility of SCH may persist. In our case, no special medication use, no systemic diseases, no longer AL, no traumatic history, no past ocular operative history, relatively younger

age, and the method of phacoemulsification was adopted. The above conditions were not the common etiologies about developing SCH. Moreover, we suggested that astaxanthin may own the modulatory effect on nitric oxide (NO) – induced vaso-relaxation and massive blood flew out induce SCH formation⁽³⁵⁾. Some reports even demonstrated that NO was shown to play an important role in choroidal blood flow auto-regulation. The responses of blood vessels of retina and choroid were also regulated and mediated by NO. Therefore, many peoples may take astaxanthin for preventing from stroke and myocardial infarction, and retinal damage.

In ophthalmic fields, astaxanthin protected the retinal cells via reducing stress, especially light induced. It is known to possess the capacity to detoxify O₂ catalytically. Besides, it also might inhibit intracellular DNA degeneration cause by reactive oxygen species (ROS). For example, astaxanthin only may prevent retinal cells from free radicals attack, and it especially could even preserve the peripheral retinal functions (around 28 %) under severe oxidative stress. To our surprised, astaxanthin is a very powerful biologic antioxidant activity: 10 times higher than that of other carotenoids such as lutein, canthaxanthin, and β -carotene and 100 times higher than α -tocopherol. Because of the higher abilities against the oxidative stress which may induce many mechanisms such as ROS, excitatory amino acids, nitric oxide and apoptosis it is highly expected to treat various human diseases including many eye disorders. For example, glaucoma is the common causes of human blindness in the world. The retinal ganglion cell represents the final common pathway of glaucomatous vision loss may be damage. Dong and his coworkers confirmed that astaxanthin may protect the free radicals attack under the cellular and molecular biological level. Thus it is believed to be benefit for glaucoma and other optic neuropathies. Besides, more ophthalmologists suggested that the may astaxanthin may be combined to treat and control the ocular infection, uveitis, cataracts, and various types of the retino-vascular diseases such as diabetic retinopathy, retinal vein occlusion, retinitis pigmentosa, dry type of age-related macular degeneration with choroidal neovascularization. In addition, it may help the preserve of corneal function to solve dry eye and ultraviolet-induced photo-keratitis. Furthermore, astaxanthin may also enhance the accommodation of the eye in middle-aged and older people and improve the asthenopia. In Japan, it is considered as supplying the eye-promoting ability which is benefit for students and computer users⁽⁴⁷⁾.

However, the character of astaxanthin owns NO which has a key role in the maintenance of vascular tone. The increasing concentration of NO may

enhance the dilation of blood vessels and the volume of blood. It is no wonder that the peoples taking astaxanthin reveals that the bleeding tendency induced the sign of easily bleeding in clinics. Indeed, we also found that the most famous health food supplements and OTC medications are ginkgo, deep-sea fish oil, natto, astaxanthin, ginseng, monascus, and more extracts for various medical medicinal plants such as *Rhodiola rosea*, *Polygonatum alte-lobatum* Hayata, *Arctium Lappa* L. (Burdock), *Astragalus membranaceus*, *Cassia tora* L, *Elutherococcus senticosus*, *Anredera cordifolia* and *Cymbopogon cittatus*. In our original study, some of them may result in different level of bleeding tendency and are easy to neglect risk about bleeding tendency from health food supplements in cataract surgery⁽⁴⁸⁾. In USA, about 51% of patients took alternative medicines such as herb and dietary supplement. In addition, the female ones like to take the complementary medicine more than the male ones. Many patients with cardiovascular diseases all need aspirin and warfarin to control their general condition. Aspirin, clopidogrel and warfarin are the most common and widely used anticoagulant and is considered an effective drug in the primary prevention of myocardial infarction and the secondary prevention of ischemic stroke and cardiovascular events in the world. Hence, the use of aspirin and/or warfarin may increase the prothrombin time (PPT) and show bleeding and oozing in eye surgery. Now combined use of OTC medications and prescription drug is becoming increasingly popular. For example, omega-3 from low dose aspirin demonstrates reduction of gingival inflammation and modulation of cytokines in the crevicular fluid. An increasing trends exist in co-prescription of aspirin and ginkgo for Taiwan' elderly population in the past few years. Even ginkgo and astaxanthin may be combined to treat the human season rhinitis and asthma, as well as enhance the immune abilities of childrens.

Some older patients undergoing cataract are all victims with cardio-vascular diseases take regular systemic medications, including anti-platelet and anticoagulant treatments. According to several reports, more than 28% of these patients take aspirin, 2 % take clopidogrel and more than 5 % take anticoagulants. Several studies suggested that the need for stopping oral anticoagulation prior to ocular surgery because aspirin and warfarin could increase PTT and bleeding tendency. Therefore, the associated problem including bleeding from discontinuing these drugs may impact the operative procedure and even prognosis and outcome especially in subtle surgery. However, the similar sign was also found in some health food supplement which is the cause of bleeding tendency. Many patients and even doctors may neglect the

physiological and pharmacological effects of the OTC medications including astaxanthin induced oozing⁽⁴⁸⁾. Recently the issues are well valued. In USA, about 51% of patients took alternative medicines such as herb and dietary supplement during the 2 weeks before operation or interventional approach. Thus, we also suggested that the patients who will have operative schedule should discontinue taking astaxanthin supplement before surgery at least 3 weeks because of its stronger bleeding tendency. Besides, the doctors must keep in mind during pre-operative consultation for patients' safety.

Conclusion

To our knowledge, non-stop use of astaxanthin supplement during phacoemulsification developing into SCH was first reported in the world. The abnormal hemodynamics of bleeding tendency from astaxanthin may result in several problems from mild hyphema to severe SCH formation. We must remember that discontinuation of all herbal, OTC and prescription medication at least 2 weeks before surgery if the pharmacologic reaction of them may interfere with hemodynamics. The clinicians should consult the detailed medical history of surgical patients. In our report, astaxanthin possess the character of bleeding tendency which could influence the processes of operation, especially the tiny eye surgery. Therefore, we can't omit the potential adverse reaction and health hazards from some healthy food supplements for patients' safety.

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