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Research Article

How to Avoid Risk of Extraocular Extension from Retinoblastoma Intravitreal Chemotherapy

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Abstract

Intravitreal melphalan chemotherapy started for RB management in many clinics all over the world and had shown its high efficacy. But risk of RB cells extraocular extension after IViI has limited applying of this method.

The method of intraocular retinoblastoma IViI to prevent risk of RB extraocular extension includes intraocular hypotony attainment by preoperative intramuscular diuretic injection; several antireflux manipulations: conjunctiva displacement over the site of IVitI, obliquely-perpendicular injection channel formation, scleral puncture site temporary immediate tamponade by swab following subconjunctival antibiotic solution injection, which also prevents vitreous infection; choosing of different meridians for repeated IViC that prevents scleral thinning.

Since 2010 71 kids at age 2 mo/o - 6 y/o (mean 24,11 ± 6,9 mo) were treated with this method - 102 eyes with RB different stages: T1- 14,6%; T2 - 31,3%; T3 - 54,2% (according TNM- stages WHO- classification). Totally 463 IViI (1 - 18, mean 6, per eye) were performed with simultaneous IVC - chemoreduction (CEV-protocol) 2 - 8 (mean 4) per patient with consolidation treatment (laser-, cryo-, brachytherapy) on indications. No intra- and postoperative complications were registered after IViI. 51 kids (71 eyes) were followed up during 6 - 121 (mean 58,6 ± 25,8) mo. Complete tumor control was achieved in 77,5% eyes with no any signs of extraocular RB spreading after IViI. 16 eyes were enucleated due to tumor relapse or not complete control, haemophthalmos and retinal detachment. Histopathology didn't find tumor cells in injection channels and optic nerve invasion in any case and choroidal invasion on one eye.

All proposed measures allow to improve the RB intravitreal chemotherapy technique, to increase its ablasticity and to reduce the risk of intra- and postoperative complications.

Keywords: *Retinoblastoma (RB); Intravenous Chemoreduction (IVC); Intraarterial (IAC); Intravitreal (IViC)*

Introduction

Recently successful retinoblastoma (RB) management is usually achieved by chemotherapy different types: systemic intravenous chemoreduction (IVC), intraarterial (IAC) and intravitreal (IViC). IViC usually used as a second-line regimen for RB patients with refractory or recurrent vitreous seeds [13,21,22,25] and first-line in primary combined polychemotherapy of big tumors with endophytic growth, multifical RB, retinal and vitreal seeding [3-8]. Ericson and Rosengren were pioneers using intravitreal injections (IViI) of chemotherapeutic agent thiotepa for eye-preservation therapy of RB in 1961 [11]. Their idea was to achieve the highest possible concentration of the chemotherapeutic agent close to the tumor by its intraocular administration while at the same time the systemic concentration kept at the lowest possible level [6,8,13,19,21]. Inomata and Kaneko found that RB was most sensitive to melphalan among 12 tested anticancer

drugs *in vitro* [17] and it was effective and structurally nontoxic to the retina when tested on rabbits [29]. Therefore, now intravitreal melphalan chemotherapy started for RB management in many clinics all over the world and had shown its high efficacy [3,13,21,25].

Nevertheless, unknown risk of RB cells extraocular extension after IViI has limited applying of this method. Fine needle aspiration biopsy [20] and intraocular surgery in eyes with RB [16] resulted in reactivation of tumor necessitating enucleation or leading to orbital and/or systemic metastases. Smith and Smith [26] calculated the proportion of patients with extraocular tumor spread to be 0.007 and 1 metastatic disease after 1304 IViI given in 315 eyes of 304 patients with a mean follow-up of 72.1 months. Suzuki., *et al*. [27] reported results of 1067 melphalan IViI for retinoblastoma (1 - 25 per eye) between 1990 and 2011 into 264 eyes of 250 patients: a postoperative subconjunctival tumor developed in one eye, distant metastasis or intracranial invasion occurred in 11 patients which didn't receive adjuvant chemotherapy.

Purpose of the Study

To develop a method of intraocular retinoblastoma intravitreal injection in order to prevent risk of tumor cells extraocular extension.

Materials and Methods

The method of intraocular retinoblastoma IViI was developed in the Pediatric Ophthalmology Department of the Filatov Institute of Eye Diseases and Tissue Therapy of NAMS of Ukraine, Odessa, to prevent risk of RB extraocular extension. Since 2010 71 kids at age 2 mo/o - 6 y\o (mean 24,11 ± 6,9 mo) were treated with this method - 102 eyes with RB different stages: T1- 14,6%; T2 - 31,3%; T3 - 54,2% (according TNM- stages WHO- classification). Multifocal tumor growth was found in 24 eyes, tumour capsule break with vitreal seeding - in 49 eyes.

All children underwent preop accurate both eyes diagnostic under general anesthesia, including tonometry, anterior segment biomicroscopy, gonioscopy, if necessary, thorough posterior eye segment examination with maximal mydriasis using several methods of ophthalmoscopy - binocular, ophthalmobiomicroscopy on the slit lamp, as well as using a retinal camera PanoCam with recording fundus images. Ultrasound B-scan of the posterior, and the anterior segments of the eye evaluate the number, location, topography, size and prominence of tumor foci, the presence, type and prevalence of vitreal seeds, detected tumor and vitreal seeds free areas. OCT RB with parapapillar and macular localization to determine papilla opticus involving. MRI of the brain and orbits to exclude pinealoblastoma and tumor orbital growth.

Results

The elaborated IViC technique started with intramuscular diuretic in age-appropriate dosage injection 30 minutes before the IViI to reduce IOP. Next procedures are performed at the operating theatre under general anesthesia with maximal mydriasis using operating microscope as follows:

- Retina and vitreous examination with contact prismatic fundus lens (Figure 1a) to determine IViI site free of tumor and vitreal clones with marking 3,5 - 4 mm from the limbus; in cases of repeated IViC - in different meridians;
- 31 G needle conjunctival puncture at the 1 - 1,5 mm distance from the presumed scleral puncture with its displacement over the site of IViI (Figure 1b);
- Scleral puncture with obliquely-perpendicular injection channel formation (Figure 1c);
- Control of needle position in the vitreal cavity to avoid lens injury and contact with the tumor, slow jet injection of ex tempore prepared 0,1 ml cytostatic in different dilutions depending on the indications;

- Rapid needle removal with simultaneous injection site tamponade by cotton swab (Figure 1c);
- Subconjunctival antibiotic solution introduction at the IViI site to do additional tamponade by roller formation (Figure 1d);
- Eyeball 30 - 60 seconds “shaking” with a forceps in all directions to enable even distribution of the cytostatic in the vitreous;
- Sterile bandage until changing the next day.

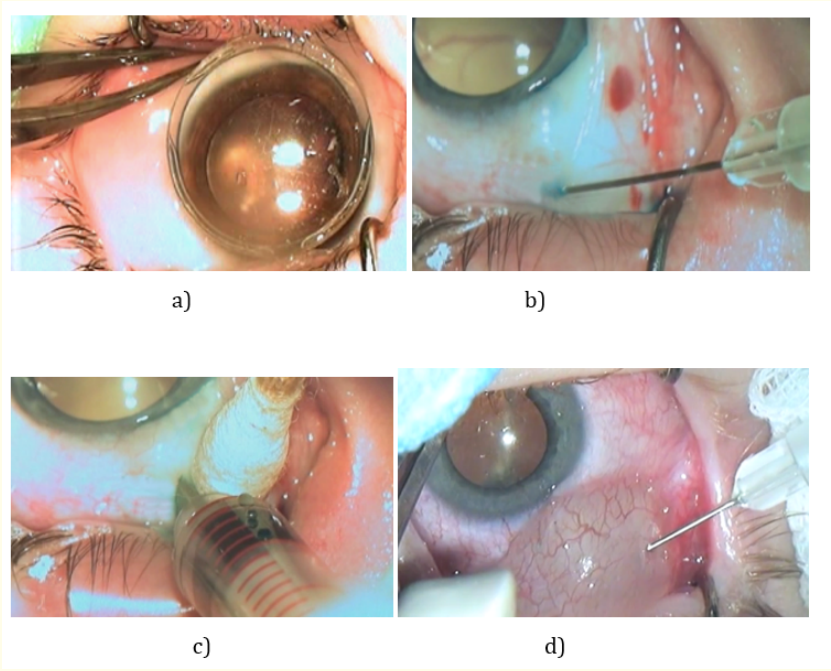

Figure 1: *Steps of IVC by the developed method: a) fundus and vitreous examination under an operating microscope with a contact prismatic fundus-lens; b) puncture of the conjunctiva 3.5 mm from the limbus at 1-1.5 mm distance from the presumed scleral injection; c) 31 G needle puncture of the sclera with formation of an obliquely-perpendicular injection channel and tamponade with a cotton swab upon rapid needle removal; d) subconjunctival antibiotic solution introduction into the injection site.*

Totally 463 IViI (1 - 18, mean 6, per eye) were performed with simultaneous IVC - chemoreduction (CEV-protocol) 2 - 8 (mean 4) per patient with consolidation treatment (laser-, cryo-, brachytherapy) on indications.

No intra- and postoperative complications were registered.

51 kids (71 eyes) were followed up during 6 - 121 (mean 58,6 ± 25,8) mo.

Complete tumor control was achieved in 77,5% eyes with no any signs of extraocular RB spreading after IViI. 16 eyes were enucleated due to tumor relapse or not complete control, haemophthalmos and retinal detachment. Histopathology didn’t find tumor cells in injection channels and optic nerve in any case, only one eye had choroidal invasion.

The following clinical case confirms the efficacy of the elaborated technique.

Child S., 26 m/o, has underwent routine examination of only one eye under general anesthesia at the Filatov Institute Pediatric Ophthalmology Department due to right eye anophthalmos after enucleation 10 mo ago on occasion of monolateral T3 stage RB without invasion, the left eye previously was healthy. RB of the left eye with multifocal growth (6 different size foci): at the upper temporal vascular arcade area at 2 o'clock the gray-white color prominent tumor focus about 4 PD, at 3, 3.30, 4, 10 and 10.30 small gray foci (Figure 2a), were revealed. Left eye visual acuity by Teller Acuity Cards - 0,13, IOP- 18 mm Hg.

The diagnosis was changed to bilateral retinoblastoma, right eye- anophthalmos, left eye - Retinoblastoma T2N0M0 with multifocal growth.

The performed treatment: 3 courses of combined chemotherapy according to the elaborated at the department method [5], which included 10 μg melphalan IViC with simultaneous chemoreduction (CEV-protocol), additional consolidation therapy, included 10 μg melphalan IViC and laser coagulation of all tumor foci. Summary 4 IViI were done, using developed method at different meridians (from 10.30 to 12.30h).

Complete regression of all tumor foci was achieved with the formation of flat atrophic pigmented scars (type IV regress) (Figure 2b). The follow-up is 29 mo with complete tumor control. The LE Visual acuity is 0,7.

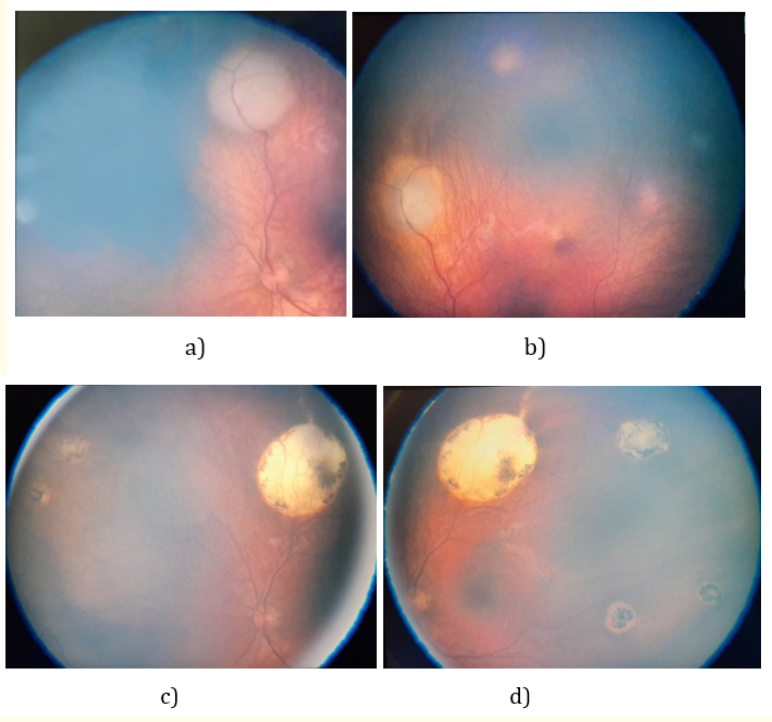

Figure 2: *Photo of the child S. only left eye with retinoblastoma T2N0M0 stage: a, b) before treatment - in the area of the upper temporal vascular arcade 2 h gray tumor focus about 4PD, on the periphery at 3, 3.30, 4, 10 and 10.30 - small gray foci; c, d) complete regression type IV of all tumors after treatment - 3 combined polychemotherapy (IViI + chemoreduction CEV-protocol), IViC and lasercoagulation - with the formation of 6 atrophic foci of RB different sizes at 2, 3, 3.30, 4, 10 and 10.30 hours.*

Discussion

Munier [21] classified mechanisms leading to tumor spread into two categories: passive per-operative and active post-operative. Passive per-operative tumor spread may occur due to the spilling of tumor cells adherent to surgical instruments when removed from the eye, or to the reflux of contaminated humors secondary to variations of intraocular pressure. Active post-operative exteriorization may occur via tumor growth along a contaminated surgical wound, or in consequence to co-localization of the entry site with a parietal tumor. To be effective in preventing extra-ocular tumor spread, the injection procedure should minimize both active and passive mechanisms of exteriorization. The preoperative diagnostic, including ophthalmoscopic and sonographic procedures are carried out to detect tumor and seeds free injection site and prevent contact with them, which can facilitate tumor spreading [5,6,13,22].

Common rules for all IViI were elaborated by American Academy of Ophthalmology to minimize per- and post-injection risks [1,23]: per-operative - the needle should be inserted perpendicularly through the sclera with the tip aimed toward the center of the globe to avoid the posterior lens; injections are generally performed inferotemporally or superotemporally to optimize exposure and to avoid damage to the retina and other eye structures. Possible iatrogenic injuries include lens injury, corneal abrasion, intraocular hemorrhage, and retinal tears [2,14,15]. IOP elevation during IViC can accompanied by vitreous reflux and tumor externalization [22]. One of the most serious injection-related complication is acute-onset endophthalmitis [10,12,18,30]. Data from 14,866 IVsI in 4,382 eyes show 38 cases of endophthalmitis (including those reported as pseudo-endophthalmitis) for a prevalence of 0.3% per injection and 0.9% per eye [18]. A meta-analysis of the literature between January 2005 and May 2012 found that the rate of endophthalmitis was (0.056%) based on 197 of 350,535 intravitreal anti-VEGF injections [12].

The international 10-center cohort study analyzed the current risk of extraocular dissemination of tumor by evaluating 3553 IViC injections to 704 eyes in 655 patients that were performed at high-volume retinoblastoma centers worldwide, with most performed during 10 years (2007 - 2016) [13]. All these centers used at least 2 presumed precautionary injection methods: injecting in a tumor-free location [4,5,25,28], lowering of intraocular pressure by paracentesis or ocular massage [9,22,27,28], cryotherapy to needle tract [9,22,25], subconjunctival chemotherapy [24], ocular surface irrigation [9]. Details of IViC procedure were collected regarding the needle size - ranged from 30 to 33 in gauge and 9 to 12 mm in length; injection site from the limbus ranged from 2.0 to 3.5 mm, and drug volume ranged from 0.04 to 0.20 mL. The number of injections also can associated with extraocular dissemination of tumor at the needle site and it was on the average 4.5 per eye. No extraocular tumor events were related to IViC in this study.

Some of these techniques were re-established by Munier., *et al* [22]. They reported a safety-enhanced injection technique, consisting of an antireflux procedure and sterilization of the needle tract. Transient eye hypotony achieved by an anterior chamber paracentesis, aspirating of 0.1 - 0.15 ml aqueous fluid - the same volume as the one to be injected into the vitreous. The injection is performed using a 32G needle introduced perpendicularly 2.5 - 3.5 mm from the limbus at the desired meridian opposite the seeds through the conjunctiva and sclera under microscope viewing until the needle tip reaches the center of the vitreous cavity, cytostatic introduction lasts no more than 15 seconds and upon removal of the needle is followed by a triple freeze and thaw cryo-applications to sterilize the pars plana entry site. The eye is then carefully shaken with a forceps in all directions to enable even distribution of the drug.

The disadvantages of this technique, in our opinion, are:

- Additional manipulation in the eye with intraocular tumor - anterior chamber paracentesis, which complicates the IViI due to eye hypotony and iris-lens diaphragm forward displacement, changing the intraocular topography;
- Repeated paracentesis in IViC could lead to the anterior chamber shallow with anterior synechias formation, anterior chamber angle closure and possible secondary glaucoma development;

- Perpendicular direction of the injection channel creates a direct path to vitreous reflux;
- Three cryoapplication cycles at the pars plana ciliaris of injection site prolong the operation time, enhance the postoperative inflammation and create conditions for sclera local thinning, ciliary body atrophy with the progressive hypotony development, that is especially important in cases of repeated IViC.

According to our developed IViC technique intraocular hypotony is achieved by preoperative intramuscular diuretic injection, antireflux manipulations include: conjunctiva displacement over the site of IVit introduction with obliquely-perpendicular injection channel formation, scleral puncture site tamponade swab and subconjunctival antibiotic solution injection, which also prevents vitreous infection; choosing of different meridians for repeated IViC that prevents scleral thinning. All these measures allow to improve the technique of RB intravitreal chemotherapy, to increase its ablasticity and to reduce the risk of intra- and postoperative complications (Table 1).

Cause	Consequences
1. Preoperative intramuscular injection of diuretic at the age-related dose	Non-invasive dehydration of the vitreous with temporary eye hypotony
2. Puncture of the conjunctiva at the distance 1 - 1.5 mm with its displacement above the site of IViI.	Creates a valve of conjunctiva that blocks the vitreous reflux
3. The of obliquely-perpendicular scleral injection canal formation.	Reduces the possibility of vitreous reflux due to the topography of the scleral canal.
4. Tamponade of the injection site with a cotton swab.	Simultaneously temporary blocks the vitreous reflux
5. Subconjunctival injection of antibiotic solution until roller formation	Creates long-term blocking of the scleral canal with simultaneous infection of the vitreous prevention.
6. IViI performing in different meridians in repeated IViC.	Prevention of scleral thinning after repeated IViC.

Table 1: *The advantages of the developed IViC method at RB.*

Conclusion

To minimize the risk of extraocular RB extension from IViC, it is necessary to follow special preventive measures: non-invasive preoperative intraocular hypotony achievement; vitreous reflux prevention due to conjunctival valve creation, obliquely-perpendicular scleral injection channel formation, injection site tamponade by the cotton swab and the roller of subconjunctival antibiotic and IViI in different meridians in repeated IViC.

All these procedures are used in developed IViC method, which provides the minimally invasive and safety intervention with high efficacy and without complications and tumor spreading in follow up.

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