

Improving the ablative capacity of intravitreal chemotherapy for retinoblastoma

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Background: Intravitreally (IV) administered cytostatics are believed to be a promising local chemotherapy for retinoblastoma (RB) because this approach enables the highest level of chemotherapeutic agent after its direct injection into the ocular cavity. Intravitreal administration is, however, invasive. Among the factors that prevent the wide use of intravitreal chemotherapy (IVitC) for RB is the risk of intraocular complications. In addition, exteriorization of the intraocular tumor may occur through the injection channel or extrabulbar tumor spread may occur.

Purpose: To develop a technique of IVitC for intraocular RB to improve its ablative capacity through the prevention of extrabulbar tumor spread.

Material and Methods: An ablative technique of IVitC was developed at the Department of Pediatric Eye Disorders, the Filatov institute, and used to perform 253 IV injections in 30 children (37 eyes) with T1 to T3 retinoblastoma.

Results: The advantages of the newly developed IVitC technique are as follows: achieving ocular hypotony without additional paracentesis; preventing reflux from the vitreous cavity by displacing the conjunctiva above the intravitreal entry point and forming an obliquely perpendicular injection channel; treating the site of scleral puncture with cotton swab tamponade and applying antibiotic solution subconjunctivally; preventing an infection of the vitreous and scleral thinning in repeat IVitC. There were no perioperative or postoperative complications. In addition, there were no signs of extrabulbar tumor spread during follow-up after IVitC. The number of IV injections per eye ranged from 1 to 13.

Conclusion: An improved ablative capacity of the developed IVitC technique was achieved by reducing (a) reflux from the vitreous through a number of above manipulations and (b) traumatic effect of intervention, as well as preventing complications, which enabled the minimal invasiveness and safety of the technique.

Introduction

Some researchers believe that intravitreally (IV) administered cytostatics are a promising local chemotherapy for retinoblastoma (RB) because this approach enables the highest level of chemotherapeutic agent after its direct injection into the ocular cavity, with the concentration in the body kept low [1-9]. Intravitreal administration is, however, invasive. It has been reported that the adverse events associated with intravitreal chemotherapeutic injection for RB include ocular hypertension, cataract, intraocular hemorrhage, endophthalmitis, etc. [10, 11]. In addition, exteriorization of the intraocular tumor may occur through the injection channel [12, 13] or extrabulbar tumor spread may occur, leading to (a) increased risk of orbit tumor spread and metastasis and (b) decreased survival. Consequently, to make intravitreal chemotherapeutic injection as safe as possible, measures should be designed to prevent tumor spread after local chemotherapy for intraocular RB.

The purpose of this study was to develop a technique of intravitreal chemotherapy (IVitC) for intraocular retinoblastoma to improve its ablative capacity through the prevention of extrabulbar tumor spread.

Material and Methods

An ablative technique of IVitC was developed at the Department of Pediatric Eye Disorders, the Filatov institute, and used to perform 253 IV injections in 30 children (37 eyes) with T1 to T3 retinoblastoma. A preoperative bilateral eye examination was performed under general anesthesia and included tonometry and anterior segment biomicroscopy using a 30 SL-M slit lamp microscope (Opton, Berlin, Germany). In addition, slit-lamp gonioscopy with a Goldmann lens or microscopic gonioscopy with a 10-mm Volk mini four-mirror gonioslens

was performed, if required. A dilated posterior segment examination included binocular ophthalmoscopy (using a Keeler Spectra IRIS Spectacle Indirect Ophthalmoscope with a 20 D Volk lens), slit-lamp biomicroscopy (using a Volk Digital Wide Field Lens or Volk three-mirror gonio fundus lens) and wide-field fundus imaging using PanoCam camera system (Visunex Medical Systems, Inc., Fremont, CA). The Aviso Ultrasound Unit (Quantel Medical, Clermont-Ferrand, France) with 10-MHz and 20-MHz probes was used to perform ultrasound scanning of the posterior segment and, if required, the anterior segment. Number of tumor foci; location, topography and size of the tumor focus; thickness of the tumor; presence, type and dissemination of vitreous seeding; and presence of sites with no tumor foci or seeding were assessed. Magnetic resonance imaging (MRI) of the brain and orbit was performed to exclude pineoblastoma and orbital tumor involvement. Follow up duration ranged from 6 months to 2 years.

Results

We have developed the ablative IVitC procedure which is performed in the operative room and under the operative microscope, requires general anesthesia and maximum midriasis, and is as follows: First, intramuscular diuretic injection is administered at an age-dependent dose thirty minutes prior to IV chemotherapy injection. Second, the fundus and vitreous are examined under the operative microscope equipped with a prismatic fundus contact lens (Fig. 1a) to select a tumor-free site with no vitreous seeding 3.5-5 mm from the limbus (in case of repeat IV, a site is selected at a meridian different from those of previous injections) for IV injection. Third, the conjunctiva is (a) punctured with a needle approximately 1-1.5 mm away from the desired site of scleral puncture and (b) displaced gently above the intravitreal entry point (Fig. 1b). Fourth, the sclera is punctured with a 31G needle to form an obliquely perpendicular scleral injection channel (Fig. 1c). Fifth, the 0.1-mL cytostatic solution is prepared extempore by dissolving in 0.9% NaCl at the dilution dependent on indication, and, with the position of the needle in the vitreous cavity controlled to avoid lens trauma and contact with the lens, the solution is slowly injected into the vitreous. Sixth, the needle is promptly removed, and the site of injection is treated by tamponade with a cotton swab (Fig. 1c). Seventh, the antibiotic solution is injected beneath the conjunctiva at the site of injection until a bead is formed (Fig. 1d). Eighth, the eye is carefully shaken with a forceps in all directions for 30 to 60 seconds to enable even distribution of the cytostatic in the vitreous. Ninth, sterile dressing is put on the eye and not changed till the next day postoperative review.

The number of IV injections per eye ranged from 1 to 13. There were no perioperative or postoperative complications. In addition, there were no signs of extrabulbar tumor spread, recurrence in the orbit, or remote metastasis during follow-up after intravitreal chemotherapy.

An example case is described below demonstrating the efficacy of the developed IV chemotherapy procedure.

Example case

A 16-month child underwent surgery for advanced T3 retinoblastoma of the right eye at the Department of Pediatric Eye Disorders, the Filatov institute. The eye was enucleated by high-frequency electric welding (HFEW) using the methodology developed at the Department of Pediatric Eye Disorders [14], and a locomotor stump of the ocular prosthesis was formed using the Ecoflon orbital implant. Histology of the enucleated right globe showed retinoblastoma with no invasion, and the left eye was healthy.

At 10 months, examination of the left eye under anesthesia showed multifocal retinoblastoma (six tumor foci varying in size), including a protruding grey white focus, about 4 disc diameters (DD) in size, at 2 o'clock, and small grey foci at 3, 3.30, 4, 10 and 10.30 o'clock positions, at the site of the superior temporal vascular arcade. Teller acuity was 0.13 OS. The intraocular pressure (IOP) was 18 mm Hg OS (Fig. 2a).

The diagnosis was changed to bilateral retinoblastoma, with anophthalmia OD and multifocal retinoblastoma at stage T2N0M0 OS. The treatment included three courses of combination multiagent chemotherapy using the methodology developed at the department [15]. These included (a) three IVitC with melphalan at a dose of 10 µg with concurrent 3-drug (carboplatin, etoposide, and vincristine (CEV)) chemoreduction and (b) further consolidation therapy in the form of 10 µg intravitreal melphalan and laser photocoagulation of tumor foci using the methodology developed at the department [16]. Totally, the infant received four IVitC at various meridians from 10.30 to 12.30 o'clock positions.

The treatment resulted in complete regression of tumor foci and formation of flat atrophic pigmented scars, with the appearance compatible with type 4 RB regression pattern (Fig. 2b). The infant was followed up for 29 months. At present, the disease state is stable and visual acuity is 0.7.

Discussion

Best practice for safe IVitC includes a number of measures. Preoperative diagnostic assessment should include meticulous ophthalmoscopic examination and sonographic examination to localize tumor foci, assess dissemination of vitreous seeds, and select a tumor-free site with no vitreous seeding for IV injection [2, 6, 7, 15, 17]. Next, measures should be taken to prevent tumor cell dissemination during IVitC.

The IVitC technique for RB developed by Munier and colleagues [13] appears to be the closest to ours and is described briefly below. First, they create a transient hypotony by an anterior chamber paracentesis, aspirating the same volume (0.1-0.15 mL) as the one to be injected into the vitreous. Second, a 32G needle mounted on a tuberculin syringe is 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. Third, upon removal of the needle three cycles of freeze and thaw cryoapplications are given at the injection site. Finally, the eye is carefully shaken with a forceps in all directions to enable even distribution of the drug in the vitreous.

We believe that the IVitC technique of Munier and colleagues has the disadvantages as follows. First, the technique includes additional intraocular manipulation (anterior chamber paracentesis) in an eye with an intraocular tumor. This makes the intravitreal injection technique more difficult due to ocular hypotony and anterior shift of the iridolenticular diaphragm, leading to changes in the intraocular topography. Second, numerous IVitC-related paracenteses contribute to a decrease in anterior chamber depth, formation of anterior synechiae, anterior chamber angle closure, and potential development of secondary glaucoma. Third, introducing the injection needle perpendicularly to the surface of the globe may result in reflux from the vitreous cavity. Fourth, three cycles of freeze and thaw cryoapplications given at the injection site will result in an increase both in the operative time and in postoperative inflammation, creating the conditions for local thinning of the sclera, which is especially relevant to the case of repeated IV injections. Finally, three scleral cryoapplications at the pars plana ciliaris may lead to further ciliary atrophy and progressive progressive hypotony, especially in repeated injections.

In the IVitC technique developed by us (Patent of Ukraine No. 144,595 issued 12.10.2020, Bulletin No. 19) [17], ocular hypotony is achieved by preoperative application of intramuscular injection of a diuretic, whereas reflux from the vitreous cavity is prevented by the following measures: displacing the conjunctiva above the intravitreal entry point; forming an obliquely perpendicular injection channel; treating the site of scleral puncture with cotton swab tamponade and applying antibiotic solution subconjunctivally, which also prevents an infection of the vitreous; and selecting different meridians for repeat IVitC to prevent scleral thinning.

The above measures enable improving the IVitC technique for RB, advancing prevention of tumor cell dissemination during IVitC, and decreasing the risk of perioperative and postoperative complications after IVitC for RB (Table 1). Therefore, compared with the IVitC technique for RB developed by Munier and colleagues [13], our technique has the following distinctive features:

(1) Creating hypotony preoperatively in a non-invasive way;

(2) Preventing reflux from the vitreous cavity by:

(a) Puncturing the conjunctiva with a needle approximately 1-1.5 mm away from the desired site of scleral puncture and displacing it gently above the intravitreal entry point;

(b) Forming an obliquely perpendicular scleral injection channel;

(c) Applying cotton swab tamponade of the site of injection upon removing the needle;

(d) Injecting the antibiotic solution beneath the conjunctiva at the site of injection until a bead is formed;

(3) Decreasing the risk of perioperative and postoperative complications after IVitC for RB due to rejecting the use of additional manipulations (an anterior chamber paracentesis and cryoapplications at the injection site) and selecting a site for repeat IVitC injection at a meridian different from those of previous injections.

Conclusion

The developed IVitC technique for intraocular RB is minimally invasive, easy to use and prevents perioperative and postoperative complications. High ablative capacity was achieved by reducing reflux from the vitreous, and confirmed by the absence of extrabulbar tumor spread, tumor recurrence in the orbit, and remote metastasis.

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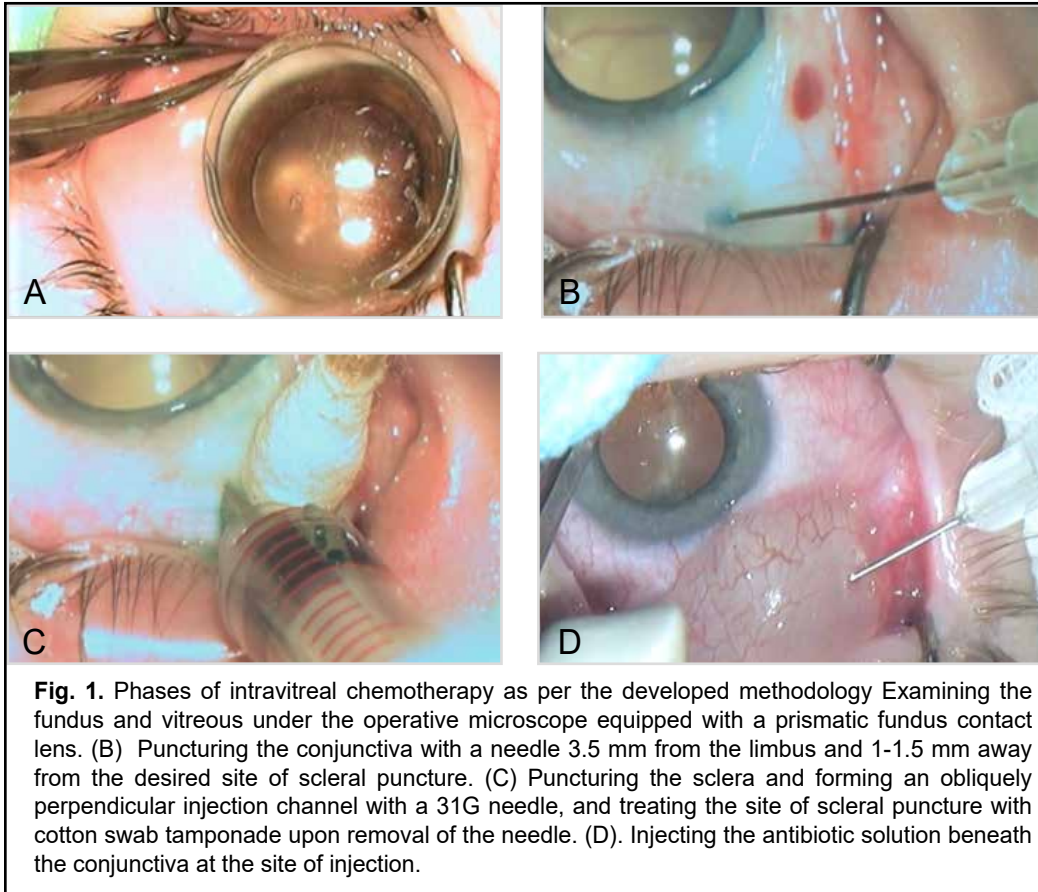
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Table 1. Advantages of the newly developed intravitreal chemotherapy technique for retinoblastoma

Cause	Consequences
Administering intramuscular diuretic injection at an age-dependent dose	Non-invasive diuretic-induced dehydration of the vitreous decreases intraocular pressure
Puncturing the conjunctiva with a needle approximately 1-1.5 mm away from the desired site of scleral puncture and displacing it gently above the intravitreal entry point	A “conjunctival vent” is created to prevent reflux from the vitreous
Forming an obliquely perpendicular scleral injection channel	A reduction in the potential for reflux from the vitreous
Treating the injection site with a cotton swab tamponade.	Reflux from the vitreous is transiently prevented
Injecting the antibiotic solution subconjunctivally until a bead is formed	Prolonged blocking of the scleral channel with prevention of an infection of the vitreous
A site for repeat intravitreal injection is selected at a meridian different from those of previous injections	Prevention of scleral thinning in repeat intravitreal chemotherapy injections



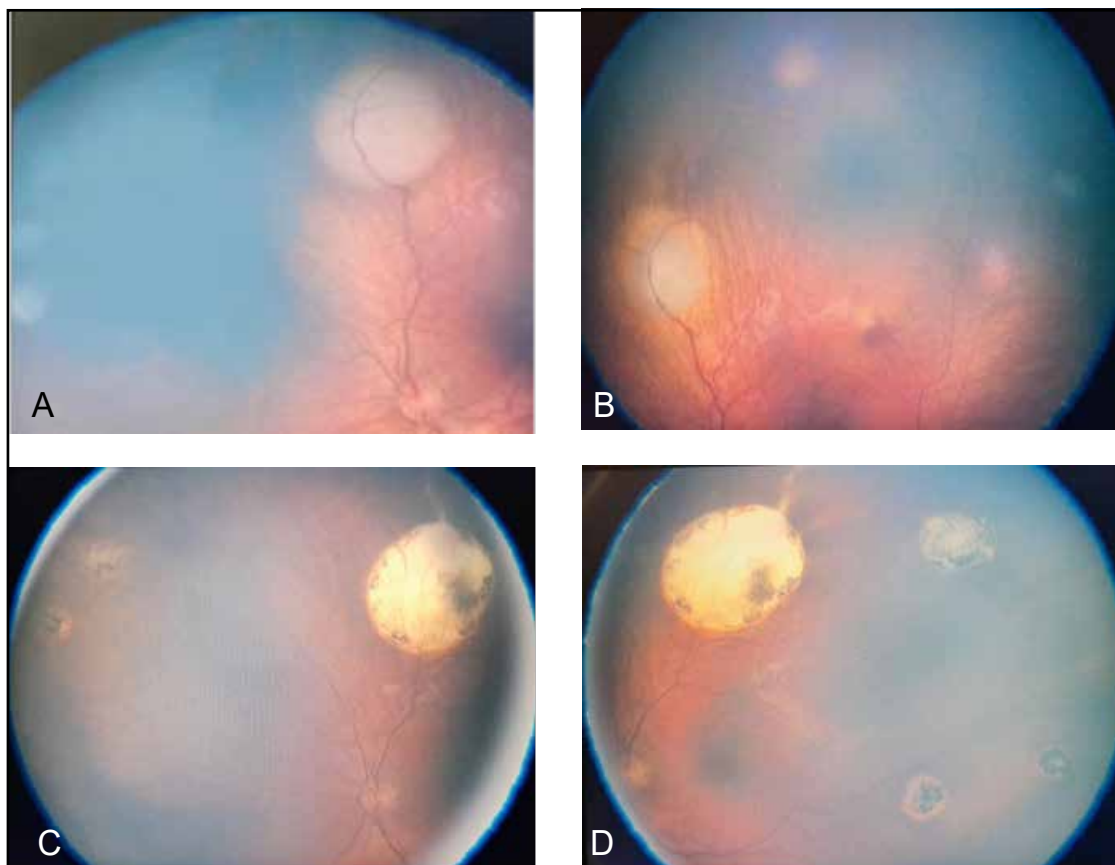


Fig. 2. Photograph of the child's only eye (left eye) with retinoblastoma at stage T2N0M0. (A, B) Before treatment, there were a protruding grey white focus, about 4 disc diameters (DD) in size, at 2 o'clock, and small grey foci at 3, 3.30, 4, 10 and 10.30 o'clock positions, at the site of the superior temporal vascular arcade. (C, D) Complete regression of all tumor foci and formation of flat atrophic pigmented scars, with the appearance compatible with type 4 retinoblastoma regression pattern, at 2, 3, 3.30, 4, 10 and 10.30 o'clock positions, after combination treatment, including three courses of combination multiagent chemotherapy with intravitreal chemotherapy and laser photocoagulation