Intra-Arterial Chemotherapy for Retinoblastoma: Four-Year Results from Tertiary Center in India

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Keywords

Eye · Tumor · Retinoblastoma · Intra-arterial chemotherapy · India

Abstract

Background: There are limited reports of intra-arterial chemotherapy (IAC) for retinoblastoma (RB) from developing world. **Objectives:** In this study, we report our 4-year experience of IAC for RB from India. **Methods:** Retrospective, interventional case series. Primary outcome measures included tumor regression, vitreous seeds and subretinal seeds control, and globe salvage. Secondary outcome measures were best-corrected visual acuity and treatment complications. **Results:** Fifteen eyes underwent 53 IAC procedures over mean 28.6 ± 13.8 months (range 10–51 months). IAC was employed as primary ($n = 6$) or secondary ($n = 9$) chemotherapy. Following IAC, complete regression of main tumor was seen in 7 eyes (47%) and partial regression in 3 (20%) eyes. Enucleation was done in 5(33%) eyes. Globe salvage rates were achieved in 1 eye (100%) in group B, 2 eyes (67%) in group C ($n = 3$), 6 eyes (67%) in group D ($n = 9$), and 1 eye (50%) in group E ($n = 2$). Following IAC, Kaplan-Meier survival curve showed 93% globe survival rate at 1 year, 76% at

2 years, and 66% at 3, and 4 years. **Conclusion:** IAC has enhanced globe salvage rates in eyes with RB. Multicenter studies with longer follow-up are necessary to better understand outcomes in the long term.

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Introduction

Intra-arterial chemotherapy (IAC) for retinoblastoma (RB) involves the direct delivery of chemotherapeutic agents into the ophthalmic artery (OA). This approach is aimed at increasing drug delivery along with reduction of systemic side effects. IAC was first introduced by Reese et al. [1], which involved direct delivery of chemotherapeutic agent into the carotid artery. Yamane et al. [2] described the technique of “Selective ophthalmic artery infusion” wherein, via a transfemoral approach, they positioned a microballoon catheter in the internal carotid artery, just distal to the orifice of OA. This technique was not truly selective since there are multiple arterial branches proximal to the origin of the OA into which the chemotherapeutic agent could flow. The technique of direct intra-arterial OA infusion was pioneered by Abramson et

al. [3]. Using fluoroscopy and roadmapping, they selectively catheterized the OA by placing a microcatheter directly at the ostium of the OA [4]. This technique was the first truly selective delivery of chemotherapeutic agents into the OA. Chawla and Singh [5] have recently highlighted the challenges in the treatment of RB in the developing world in view of rapidly evolving and ever-changing management modalities. There are few reports on initial experience with intra-arterial, periocular, and intravitreal chemotherapy from India [6–10]. Enucleation rates have steadily declined as higher rates of globe salvage can now be achieved using various forms of chemotherapy [11]. In this study, we report our initial 4-year experience of IAC as a primary or a secondary treatment for RB.

Materials and Methods

This is a retrospective, interventional case series including 15 eyes of 15 patients with RB treated by IAC at the Oncology Service of Sankara Nethralaya/Medical Research Foundation, Chennai between November 2013 and 2017. Institutional Review Board (Ethics subcommittee, Vision Research Foundation, Chennai) approval was obtained prior to the study. Written informed consent was taken from the parents of all patients after a detailed explanation of the risks and potential benefits of treatment. The tenets of the Declaration of Helsinki were adhered to. The International Classification of Retinoblastoma (ICRB) was used to classify the tumors in the affected eyes [12]. The study included subjects with unilateral or bilateral Group B to E RB. Data collection included demographic details, details of presenting features, clinical findings, management, complications, and outcomes. Relevant family history was noted. History of past ocular and systemic treatment was taken. Primary outcome measures included tumor regression, vitreous seed (VS) and subretinal seed (SRS) control, and globe salvage. Secondary outcome measures included best-corrected visual acuity and treatment complications.

A comprehensive ophthalmic examination was performed under anesthesia. Details of the ophthalmic examination, ancillary and systemic investigations were noted. Documentation of retinal findings was done with fundus drawing and fundus photography with RetCam camera (Massey Industries, Dublin, CA, USA) during examination under anesthesia. The IAC catheterization procedure, chemotherapy dosing, and follow-up schedule were followed as per established protocol, as described in our previous reports [3, 4]. The chemotherapeutic agents used included melphalan (5 or 7.5 mg) and/or topotecan (1 mg). As a protocol, we routinely plan at least 3 cycles of melphalan in all cases at monthly interval. The patients were then followed up at monthly interval and IAC was repeated as and when deemed necessary [3, 4].

As a learning process over the years, there have been some technical changes and modifications of IAC technique. Arterial access: we use ultrasound guidance and 5 French micropuncture kit (Cook medical, Bloomington, IN, USA) to access the common femoral artery. Following this, we place a 5 French radial sheath

(Radifocus, Terumo, Tokyo, Japan) in the common femoral artery. Cost-effective changes to the guide catheter and microcatheter: We use a 5 French vertebral catheter (Cook medical, Bloomington, IN, USA) to access the internal carotid artery and connect it to closed heparinized infusion system. We use Progreat microcatheter (Terumo, Tokyo, Japan) to access the OA. It saves a significant amount of procedural cost by reducing the cost of guiding catheters and microcatheters meant for neuro-interventional procedures. With our combination of catheters, we did not find any case of thromboembolism, significant vasospasm, and stroke in our series. Access for delivery of chemotherapeutic drug: In most of the cases, the microcatheter is positioned at the ostium of the OA, and a selective angiogram is performed with contrast to verify placement, angioanatomy, and choroidal blush, indicating proper flow to the eye. If the ostium of OA is of small size, appropriate changes to infusion including ICA osteo-proximal pulsatile infusion of drug are performed after confirming preferential flow with contrast. If there is variant anatomical supply from external carotid artery, the microcatheter is super-selectively introduced to the supplying artery, commonly, the middle meningeal artery. Infusion of chemotherapeutic agent: chemotherapeutics are diluted in 30 mL of normal saline and manually injected in a pulsatile fashion over 30 min to disrupt laminar flow and allow dispersion of drug to the supplied vascular territory. Hemostasis after sheath removal: After completion of the procedure, hemostasis of the femoral artery is achieved with manual pressure. Children are observed for 12 h in a specialized unit and then discharged home. Vasospasm prevention: We use nimodipine 1 mg in the saline infusion for catheter flushing to avoid vasospasm of the intracranial vessels as well as the internal carotid artery. Radiation dose reduction: We use radiation dose-reduction strategies including using minimal angiographic runs, road map techniques, and appropriate shielding to reduce the radiation dose to children. Procedural support: The procedure is done in the catheterization laboratory suite of a tertiary care pediatric hospital with round the clock availability of consultants from other specialities in case of emergency.

Results

At baseline, mean age of the patients was 30.4 months (range 11–94 months). All 15 patients had sporadic RB. Table 1 provides an overview of demographic details, baseline tumor characteristics, and history of prior treatment. Mean duration of symptoms at presentation was 9.1 weeks (median 3, range 0–48 weeks). Eyes were classified as Group A ($n = 0$), Group B ($n = 1$), Group C ($n = 3$), D ($n = 9$), and Group E ($n = 2$). At baseline, mean tumor base was 17.1 mm (median 18, range 6–24 mm), and the mean tumor thickness was 7.4 mm (median 8.2, range 2.6–11.5 mm). VSs were present in 12 eyes with involvement of 1 quadrant ($n = 1$), 2 quadrants ($n = 5$), 3 quadrants ($n = 1$), or all 4 quadrants ($n = 5$). SRSs were present at baseline in 6 eyes involving 2 quadrants ($n = 2$), 3 quadrants ($n = 2$), or all 4 quadrants ($n = 2$). Optic nerve was visible in 7 eyes, partially visible in 1 eye, and obscured

Fig. 1. Fundus photo shows group D tumor managed with primary IAC, before (a) and after (b) treatment.

Table 1. Four-year results of IAC for retinoblastoma: patient demographics, disease characteristics, and prior treatment details at baseline

S. no.	Age at diagnosis, months	Gender	Baseline BCVA	Hereditary pattern	Laterality	ICRB classification	Fellow eye	Systemic treatment prior to IAC
1	32	Male	F & F	Sporadic	Bilateral	Group D	Group A regressed	VEC × 1
2	8	Female	F & F	Sporadic	Unilateral	Group E	No RB	VEC × 6
3	13	Female	F	Sporadic	Bilateral	Group B	Enucleated	VEC × 6
4	36	Male	CSM	Sporadic	Bilateral	Group C	Enucleated	VEC × 6
5	24	Male	F & F	Sporadic	Bilateral	Group D	Enucleated	Nil
6	16	Male	CSM	Sporadic	Bilateral	Group D	Enucleated	VEC × 7
7	48	Male	6/7.5 (Lea symbols)	Sporadic	Bilateral	Group C	Enucleated	VEC × 11
8	11	Male	F & F	Sporadic	Bilateral	Group D	Group C regressed	VEC × 3
9	20	Male	No F	Sporadic	Unilateral	Group D	No RB	Nil
10	28	Male	CSM	Sporadic	Bilateral	Group D	Group D regressed	VEC × 3
11	30	Female	No F	Sporadic	Unilateral	Group C	No RB	Nil
12	24	Male	No F	Sporadic	Unilateral	Group D	No RB	Nil
13	15	Female	F	Sporadic	Unilateral	Group D	No RB	Nil
14	3	Female	6/18 (Snellens)	Sporadic	Bilateral	Group E	Enucleated	VEC × 9
15	11	Male	No F	Sporadic	Unilateral	Group D	No RB	Nil

BCVA, best-corrected visual acuity; ICRB, International Classification of Retinoblastoma; IAC, intra-arterial chemotherapy; IVC, intravenous chemotherapy; RB, retinoblastoma; F, fixates; F & F, fixates and follows; CSM, central, steady and maintained; VEC, vincristine, etoposide, carboplatin.

due to tumor overhang in 7 eyes. Exudative retinal detachment secondary to the tumor was present in 6 eyes. Extent of exudative retinal detachment ranged from 15 to 100% in 15 eyes. Six eyes had a single tumor at presentation. Of the remaining 9 eyes that had multiple tumors,

the number of tumors per eye ranged from 2 ($n = 5$), 3 ($n = 2$), 4 ($n = 1$), or 5 ($n = 1$). Mean proximity of tumor to optic disc was 1.5 mm (median 0, range 0–16 mm) and to the foveola was 2.1 mm (median 0, range 0–20 mm). IAC was employed as either primary ($n = 6$; Fig. 1) or sec-

Fig. 2. Fundus photo shows group D tumor managed with secondary IAC, before (a) and after (b) treatment.

ondary ($n = 9$; Fig. 2) modality of therapy. Except one eye, all patients who received secondary IAC had bilateral RB at presentation. Nine of 15 patients had bilateral RB. Of these, fellow eye of 6 patients underwent primary enucleation for Group E tumor (Table 1). Prior treatment with intravenous chemotherapy using vincristine, etoposide, and carboplatin was as follows: 1 cycle ($n = 1$), 3 cycles ($n = 2$), 4 cycles ($n = 1$), 6 cycles ($n = 2$), 7 cycles ($n = 1$), 9 cycles ($n = 1$), and 11 cycles ($n = 1$). Local treatments prior to initiating IAC-included cryotherapy ($n = 10$), transpupillary thermotherapy ($n = 5$), external beam radiotherapy ($n = 1$), and combination intravitreal chemotherapy with melphalan and topotecan ($n = 1$; Case 9).

Tumor characteristics before IAC, treatment details, ocular complications, and outcomes are mentioned in Table 2. Each eye received mean 3.53 IAC sessions (median 3; range 1–5 sessions). Additional systemic chemotherapy included vincristine, etoposide, and carboplatin for 2 cycles ($n = 2$), 3 cycles ($n = 1$), 5 cycles ($n = 1$), 6 cycles ($n = 3$), or 8 cycles ($n = 1$). Local therapy included cryotherapy ($n = 14$), transpupillary thermotherapy ($n = 11$), and combination intravitreal chemotherapy with melphalan and topotecan ($n = 7$). At the recent most follow-up after IAC, complete regression of the main tumor was seen in 7 eyes (46.7%) and partial regression in 3 eyes (20%). Enucleation was performed in 5 (33.3%) eyes dur-

ing the course of treatment (Cases I, II, IX, XI, and XII); case I due to dense vitreous hemorrhage after fourth IAC session; cases II, IX, XI, and XII due to development of recurrence of tumor. Twelve eyes had active VS at baseline, of which 7 eyes (58.3%) showed complete regression. Six eyes had SRS at baseline, of which 3 (50%) showed complete regression after the last IAC session. In our study, we achieved globe salvage in 100% of group B, 67% of group C, 67% of group D, and 50% of group E eyes. Following IAC, Kaplan–Meier survival curve showed 93% globe survival rate at 1 year, 76% at 2 years, and 66% at 3, and 4 years (Fig. 3a). Kaplan–Meier survival curve following IAC shows 62% visual acuity preservation better than 6/60 (Fig. 3b). Mean follow-up duration was 28.6 (± 13.8) months (range 10–51 months).

Complications related to therapy were graded according to the Common Terminology Criteria for Adverse Events, version 5.0 guidelines. The complications were as follows – Grade 2 posterior subcapsular cataract ($n = 2$), grade 1 vitreous hemorrhage ($n = 2$), grade 3 vitreous hemorrhage ($n = 1$), grade 3 optic nerve disorder ($n = 2$), other eye disorders (branch retinal vein occlusion [$n = 1$], sclerosed retinal vessels [$n = 1$], iris atrophy with posterior synechiae [$n = 1$]), transient OA narrowing ($n = 2$), grade 1 allergic skin reaction ($n = 1$), grade 1 forehead skin pigmentation ($n = 1$). Transient hematological changes

Table 2. Four-year results of IAC for retinoblastoma: Treatment details and outcomes

S. No.	IAC cycles	Drugs used for IAC, mg	Disease before first IAC			Disease after last IAC			Disease at last follow-up			Adjunct treatment	Adverse effects	BCVA at last follow-up
			tumor size, mm	VS quad	SRS quad	tumor size, mm	VS quad	SRS quad	tumor size, mm	VS quad	SRS quad			
1	4	IAC #1: M(7.5) + T(1) IAC #2: M(7.5) + T(1) IAC #3: M(7.5) + T(1) IAC #4: M(7.5) + T(1)	5.7 × 3.1	4	3	13.8 × 4.2	4	0	Enuc	Enuc	Enuc	VEC × 5 Cryo × 1 TTT × 2	VH	NA
2	4	IAC #1: M(7.5) IAC #2: M(7.5) + T(1) IAC #3: M(5) + T(1) IAC #4: M(5) + T(1)	20 × 6	0	1	12.8 × 8	4	0	Enuc	Enuc	Enuc	VEC × 2 Cryo × 3 TTT × 2	Nil	NA
3	3	IAC #1: M(5) IAC #2: M(5) IAC #3: M(7.5)	12 × 2	0	0	8.2 × 2	0	0	3 × 1.4	0	0	VEC × 2 Cryo × 7 TTT × 7	Nil	F&F
4	4	IAC #1: M(7.5) + T(1) IAC #2: M(7.5) + T(1) IAC #3: M(7.5) + T(1) IAC #4: M(7.5) + T(1)	12 × 2.3	1	0	5.5 × 1.2	0	0	3 × 1.2	1	0	Cryo × 5 TTT × 4 IVitC × 1	VH	6/36
5	3	IAC #1: M(5) + T(1) IAC #2: M(5) + T(1) IAC #3: M(5) + T(1)	18 × 9.3	2	2	10 × 4.8	4	0	4 × 4.8	0	0	Cryo × 8 IVitC × 2	Diffuse iris atrophy, PSC cataract, posterior synechiae	6/9
6	3	IAC #1: M(5) IAC #2: M(5) IAC #3: M(7.5)	10 × 2.8	4	2	12 × 2.8	0	0	7.5 × 2.9	0	0	Cryo × 9 TTT × 1 IVitC × 6	STBRVO, PSC cataract, sclerosed retinal vessels, Optic atrophy	F&F
7	3	IAC #1: M(5) IAC #2: M(7.5) IAC #3: M(7.5)	14 × 3.7	0	0	10 × 2.3	0	0	10 × 3	0	0	Cryo × 5	Nil	6/24
8	5	IAC #1: M(5) IAC #2: M(5) IAC #3: M(5) IAC #4: M(5) IAC #5: M(5)	20 × 2.6	0	0	20 × 2	0	0	20 × 2	0	0	VEC × 6 Cryo × 6 TTT × 14	Forehead skin pigmentation, ophthalmic artery narrowing (transient)	F
9	5	IAC #1: M(5) + T(1) IAC #2: M(5) + T(1) IAC #3: M(5) + T(1) IAC #4: M(5) + T(1) IAC #5: M(5) + T(1)	20.5 × 9.3	2	0	4.5 × 2.2	0	0	Enuc	Enuc	Enuc	VEC × 6 Cryo × 12 IVitC × 10	Nil	NA
10	4	IAC #1: M(7.5) IAC #2: M(7.5) + T(1) IAC #3: M(7.5) IAC #4: M(7.5) + T(1)	20 × 3.3	0	0	14 × 2.7	2	0	9 × 2	4	0	VEC × 3 Cryo × 9 TTT × 6 IVitC × 2	Ophthalmic artery narrowing (transient)	6/12
11	4	IAC #1: M(5) + T(1) IAC #2: M(5) + T(1) IAC #3: M(7.5) + T(1) IAC #4: M(7.5) + T(1)	14 × 4.9	1	0	12 × 4.5	1	0	Enuc	Enuc	Enuc	Cryo × 3 TTT × 3 IVitC × 3	Nil	NA
12	4	IAC #1: M(7.5) IAC #2: M(7.5) IAC #3: M(7.5) IAC #4: M(7.5)	20 × 9.8	0	2	Enuc	Enuc	Enuc	Enuc	Enuc	Enuc	VEC × 8 Cryo × 8 TTT × 3	Nil	NA
13	4	IAC #1: M(7.5) + T(1) IAC #2: M(7.5) + T(1) IAC #3: M(7.5)	6.8 × 6.2	4	0	4.9 × 4.9	1	0	4.9 × 4.9	4	0	TTT × 6	Nil	F&F
14	3	IAC #1: M(7.5) IAC #2: M(7.5) + T(1) IAC #3: M(7.5) + T(1)	1.1 × 2.4	4	0	Regressed	0	0	Regressed	0	0	Cryo × 3 IVitC × 3	Toxic optic neuropathy	6/36
15	1	IAC #1: M(7.5)	18 × 9.1	1	3	12 × 4	0	0	6 × 1.6	0	0	VEC × 6 Cryo × 4 TTT × 2	VH	F

BCVA, best-corrected visual acuity; IAC, intra-arterial chemotherapy; VS, vitreous seeds; SRS, subretinal seeds; M, melphalan; T, topotecan; PRF, pathologic risk factors; VEC, vincristine, etoposide, and carboplatin; TTT, transpupillary thermotherapy; IVitC, intravitreal chemotherapy; VH, vitreous hemorrhage; NA, not applicable; Enuc, enucleated; F&F, fixates and follows; F, fixates; RD, retinal detachment; PSC, posterior subcapsular cataract; STBRVO, superotemporal-branched retinal vein occlusion.

Fig. 3. a Kaplan–Meier survival curve following IAC shows 93% globe survival rate at 1 year, 76% at 2 years, and 66% at 3 and 4 years. **b** Kaplan–Meier survival curve following IAC shows 62% visual acuity preservation better than 6/60.

included relative pancytopenia ($n = 4$), relative leukopenia ($n = 5$), relative thrombocytopenia ($n = 4$), eosinophilia ($n = 2$), and relative lymphocytopenia ($n = 1$).

Discussion

IAC and IVC continue to be valuable treatment options for globe salvage in eyes with advanced RB [13, 14]. In unilateral, non-germline Groups B–E RB, IAC is now considered as a primary treatment option in selected cases. Secondary IAC is used for treating recurrent tumors, SRs, and VSs [15]. Intravitreal chemotherapy is used for recalcitrant or recurrent VS [15, 16]. Overall globe salvage rate reported in the current study was 67%. Globe salvage rates reported in literature for eyes treated with IAC based on ICRB classification have varied from 55 to 82% [4, 14, 16–20]. We achieved globe salvage in 100% of group B, 67% of group C, 67% of group D, and 50% of group E eyes. A recent meta-analysis compared the globe salvage rates of various studies based on the ICRB classification with different groups of eyes (group B = 100%, group C = 100%, group D = 38.5–100%, group E = 33.3–62.1%) [11]. In the present study, complete regression of the main tumor was seen in 7 eyes (47%) at the final follow-up, whereas Shields et al. [21] found complete response of IAC to the main tumor in 88% (14 of 17 eyes) cases, although they included eyes with only primary IAC. IAC offers the advantage to reduce systemic chemo-

therapy-related complications such as neutropenia, anemia, and secondary neoplasms, decreases the duration of hospital stay, and allows delivery of high-dose chemotherapy directly to the tumor [13, 14]. Reduced systemic absorption also allows the use of melphalan, which has been found to be the most effective chemotherapeutic agent in RB [22]. Concerns with the use of IAC include its efficacy in advanced Group E tumors and recurrence rates in tumors with VS; high economic burden especially in developing countries; rates of useful vision salvage despite globe salvage; and complications.

The choice of treatment for RB in the developing world not only depends on the treating physician's familiarity and experience with procedures such as IAC but also the cost of treatment and the possibility of receiving subsidized care. It is a given that specialized health care is primarily self-paid, with paucity of such facilities in public hospitals, fiscal capping of public health insurance, and restricted coverage of private health insurance among the people. Conversely, in the cultural context, it is highly unacceptable for the parents to have a child lose an eye with enucleation, to the extent of bearing significant financial burden in pursuing treatment for unilateral cases or to the other extreme of entirely giving up on treatment for subjects with advanced bilateral RB. Also, availability of highly specialized care with interventional radiologists, neurosurgeons, pediatric oncologist under one roof is limited to few centers in the country. In this socioeconomic context, private health-care providers in an insti-

tutional setting have devised ways to subsidize care by giving up on doctors' fee, employing innovative techniques for cost reduction, and involving nongovernmental organizations and crowd funding to offset treatment costs. Another technically challenging issue is that of drug compounding that is very different from that practiced in the west. In the absence of compounding pharmacies, the treating physician reconstitutes the drug (Melfalan) and filters it by passing through a 2 µm filter before injecting the calculated dose. However, despite the above challenges, IAC retains its value as an eye salvaging procedure. With the growing awareness of IAC among patients and referring ophthalmologists, the number of patients choosing IAC has been increasing.

Complications in IAC can occur due to the technique of the injection itself; and from the use of a high dose of chemotherapeutic agents that can lead to ocular and systemic toxicity [23]. Fortunately, in our cohort, there has been no instance of stroke, hemiplegia, metastasis, or death in any patient. However, we are aware of unreported adverse events (monoplegia) having occurred in other centers in India (unpublished). This can probably be alluded to "overzealous" attempts in offering a "new" procedure to the patients, without adequate understanding and training. An "interventionalist" who is well-versed with the procedure and has experience with pediatric patients must undertake this responsibility. In our setting, the ocular oncologist examines the child under anesthesia, marks the eye to be treated, and indicates the choice and dosage of drugs to be used. Fortunately, greater experience has led to a higher confidence in the care delivery with IAC.

Our study shows comparable results to that reported in the literature [17, 19]. However, it has its own limitations including those related to its retrospective nature. It is possible that initial results with IAC could be confounded by a learning curve related to the procedure [7]. The use of adjunct intravitreal chemotherapy in the later part of the study could have contributed to improved results [24].

Conclusion

IAC has emerged as a remarkably effective treatment strategy for RB, both as primary and secondary treatment. With growing experience, technical complications are decreasing. Making it more cost-effective can broaden this treatment option even further.

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Statement of Ethics

Subjects (or their parents or guardians) have given their written informed consent. The study protocol has been approved by the research institute's committee on human research.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

P.R.: Conceptualization, data analysis, writing, editing, and revising the manuscript. T.S. and M.S.: Conceptualization, writing, editing, and revising the manuscript. M.S., A.A., and P.C.: Data gathering and data analysis, editing, and revising the manuscript. RR: Data gathering and analysis, editing, and revising the manuscript.

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