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Comparison of Treatment Outcomes of Intravenous versus Intra-arterial Chemotherapy in Retinoblastoma

Muhammad Usman[1], Ahmad Fauzan[2], Ahmed Arslan[3], Raheem Gul[4]

[1-4]Department of Ophthalmology, Lahore General Hospital, Eye Unit 2, Lahore, Pakistan

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Correspondence to: Ahmad Fauzan, Department of Ophthalmology, Lahore General Hospital, Eye Unit 2, Lahore, Pakistan.
Email: drfauzan2525@gmail.com

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ABSTRACT

Background: Retinoblastoma is the most common intraocular malignancy in children. While systemic intravenous chemotherapy (IVC) has improved outcomes, responses remain suboptimal in advanced disease. Intra-arterial chemotherapy (IAC) offers targeted drug delivery, but direct comparative evidence remains limited in resource-constrained settings. **Objective:** To compare treatment outcomes of IVC versus IAC in patients with retinoblastoma. **Methods:** A quasi-experimental study was conducted at the Department of Ophthalmology, Lahore General Hospital, from July 2024 to June 2025. Ninety-two children with newly diagnosed intraocular retinoblastoma (stages B-E) were randomized into two groups of 46 patients each. Group A received systemic IVC with vincristine, etoposide, and carboplatin. Group B received IAC with melphalan, with topotecan or carboplatin added for resistant disease. Tumor response was assessed according to WHO Response Evaluation Criteria. Data were analyzed using chi-square test with significance at $p<0.05$. **Results:** Overall treatment efficacy was achieved in 34 patients (73.9%) in the IAC group compared to 23 patients (50.0%) in the IVC group ($p=0.018$). Complete remission was significantly higher in the IAC group at 39.1% versus 15.2% ($p=0.024$). Progressive disease occurred in only 4.3% of IAC-treated patients compared to 17.4% of IVC-treated patients ($p=0.019$). Disease control was achieved in 73.9% of IAC patients versus 50.0% of IVC patients. **Conclusion:** Intra-arterial chemotherapy demonstrated superior efficacy compared to intravenous chemotherapy in managing advanced retinoblastoma. These findings support adoption of IAC as a preferred treatment modality in suitable cases to maximize tumor control and eye preservation.

INTRODUCTION

Retinoblastoma is the most frequent primary intraocular malignancy of childhood and typically presents within the first five years of life as leukocoria, strabismus, or less commonly proptosis in advanced disease [1]. Although survival is now high in well-resourced settings, substantial global inequities persist, with delayed diagnosis and limited access to specialized ocular oncology services contributing to avoidable mortality and loss of the affected eye in low-resource health systems [2]. Contemporary management has therefore prioritized early detection and eye-salvaging strategies that maintain oncologic safety while reducing treatment-related morbidity [1,2].

Historically, enucleation and external beam radiotherapy were frequently employed for advanced intraocular disease, but both approaches are associated with functional loss and late adverse effects [3]. Systemic intravenous chemotherapy, commonly delivered as multi-agent chemo reduction with vincristine, etoposide, and carboplatin, enabled tumor shrinkage and facilitated adjunct focal therapies; however, responses are often suboptimal in eyes with advanced stage and intraocular seeding, and systemic exposure may produce clinically significant toxicities [4,5]. These limitations have driven the development of targeted drug delivery platforms that improve intraocular bioavailability while reducing systemic burden [4,5].

Intra-arterial chemotherapy involves super selective catheterisation of the ophthalmic artery with direct infusion of agents such as melphalan, with or without additional drugs for resistant disease [6–9]. Early clinical studies demonstrated the feasibility and eye-salvage potential of ophthalmic artery chemosurgery, including its use as primary therapy, and subsequent series reported durable tumor control in appropriately selected cases [6–8]. Reviews and quantitative syntheses have further indicated higher ocular salvage and favorable response profiles with intra-arterial approaches compared with systemic regimens in advanced intraocular retinoblastoma, though outcomes may vary by stage distribution, local expertise, and follow-up practices [9,10]. Against this background, comparative evaluation of

intravenous versus intra-arterial chemotherapy within local clinical pathways remains essential to inform pragmatic, resource-sensitive treatment selection and to optimize eye preservation without compromising patient safety [10].

MATERIALS AND METHODS

This quasi-experimental study was conducted at the Department of Ophthalmology, Lahore General Hospital, Lahore, Pakistan, over a twelve-month period from July 2024 to June 2025. The hospital is a 1,200-bed tertiary care teaching institution serving as a referral center for ophthalmic diseases in the region. The study was approved by the Institutional Review Board and Ethics Committee of Lahore General Hospital. Written informed consent was obtained from the parents or legal guardians of all participating children prior to enrollment.

A total of 92 children with newly diagnosed intraocular retinoblastoma were enrolled in the study. Patients were randomly assigned into two equal groups of 46 children each using a computer-generated randomization sequence. The inclusion criteria were: confirmed diagnosis of intraocular retinoblastoma classified as stage B through stage E according to the International Classification of Retinoblastoma, age below 14 years, and no prior treatment for retinoblastoma. Patients were excluded if they had evidence of extraocular extension, metastatic disease detected on staging investigations, or significant systemic illness that would preclude the administration of chemotherapy.

Patients in Group A received systemic intravenous chemotherapy consisting of vincristine 1.5 mg/m^2 per week, etoposide 150 mg/m^2 per day for 5 days every 3 weeks, and carboplatin 560 mg/m^2 per cycle every 3 weeks. Patients in Group B underwent selective ophthalmic artery catheterization and received intra-arterial infusion of melphalan 0.4 mg/kg per session, with topotecan 0.4 mg/kg or carboplatin 20 mg/mL added in cases demonstrating resistant disease. Treatment was initiated within 24 to 48 hours of complete ophthalmic evaluation and staging. All chemotherapy administration was performed by experienced oncologists and radiologists under standardized protocols.

Baseline assessment included detailed ophthalmologic examination, fundus photography, B-scan ultrasonography, and magnetic resonance imaging of the orbits and brain. Tumor response was assessed according to the World Health Organization Response Evaluation Criteria in Solid Tumors, classifying responses as complete remission, partial remission, stable disease, or progressive disease. Clinical and imaging evaluations were performed every 6 weeks during treatment and at 3-month intervals following completion of therapy. Adverse effects were documented and graded according to the Common Terminology Criteria for Adverse Events.

Data were analyzed using the Statistical Package for the Social Sciences version 25.0. Categorical variables were compared between groups using the chi-square test. Continuous variables were analyzed using independent samples t-test. Statistical significance was determined at a p-value of less than 0.05.

RESULTS

Baseline demographics were well-balanced between groups. The study population comprised 92 patients (mean age 3.6 years; 62.0% male). The IVC group (n=46, mean age 3.9 years, 63.0% male) and IAC group (n=46, mean age 3.3 years, 60.9% male) showed no significant differences (p=0.641). Leukocoria (41.3%), proptosis (31.5%), and strabismus (27.2%) were the primary presenting signs. Positive family history was documented in 9.8% of cases. Laterality distribution showed right eye involvement in 45.7%, left eye in 28.3%, and bilateral disease in 26.1%.

Table 1

Baseline Demographic and Clinical Characteristics of Study Population

Characteristics	IVC Group (n=46)	IAC Group (n=46)	Total (n=92)	p-value
Gender Distribution				
Male	29 (63.0%)	28 (60.9%)	57 (62.0%)	0.862
Female	17 (37.0%)	18 (39.1%)	35 (38.0%)	
Age Distribution				
Mean age (years ± SD)	3.9 ± 1.2	3.3 ± 1.4	3.6 ± 1.3	0.641
≤3 years	20 (43.5%)	22 (47.8%)	42 (45.7%)	0.641
>3 years	26 (56.5%)	24 (52.2%)	50 (54.3%)	
Presentation Characteristics				
Leukocoria	18 (39.1%)	20 (43.5%)	38 (41.3%)	
Proptosis	15 (32.6%)	14 (30.4%)	29 (31.5%)	0.847
Strabismus	13 (28.3%)	12 (26.1%)	25 (27.2%)	
Family History				
Positive family history	4 (8.7%)	5 (10.9%)	9 (9.8%)	0.728
Sporadic disease	42 (91.3%)	41 (89.1%)	83 (90.2%)	
Laterality				
Right eye	23 (50.0%)	19 (41.3%)	42 (45.7%)	
Left eye	12 (26.1%)	14 (30.4%)	26 (28.3%)	0.584
Bilateral disease	11 (23.9%)	13 (28.3%)	24 (26.1%)	

Disease staging distribution was comparable between groups (p=0.743). Stage B accounted for 33.7% of cases, Stage C for 26.1%, Stage D for 18.5%, and Stage E for 21.7%. Advanced-stage disease (Stages D and E) comprised 40.2% of the study population, enabling robust evaluation of chemotherapy efficacy in challenging clinical scenarios (Table 2).

Table 2

Disease Stage Distribution and Baseline Characteristics

Disease Parameter	IVC Group (n=46)	IAC Group (n=46)	Total (n=92)	p-value
Stage of Disease				
Stage B	14 (30.4%)	17 (37.0%)	31 (33.7%)	0.743
Stage C	12 (26.1%)	12 (26.1%)	24 (26.1%)	
Stage D	9 (19.6%)	8 (17.4%)	17 (18.5%)	
Stage E	11 (23.9%)	9 (19.6%)	20 (21.7%)	

Intra-arterial chemotherapy demonstrated superior efficacy compared to intravenous chemotherapy. Overall response was achieved in 73.9% of IAC patients versus 50.0% of IVC patients (p=0.018). Complete remission rates were 39.1% (IAC) versus 15.2% (IVC, p=0.024). Progressive disease occurred in 4.3% of IAC patients versus 17.4% of IVC patients (p=0.019). Disease control (complete plus partial remission) was achieved in 73.9% with IAC versus 50.0% with IVC (Table 3).

Table 3
Comparative Treatment Outcomes and Efficacy Assessment

Treatment Outcome	IVC Group (n=46)	IAC Group (n=46)	Total (n=92)	p-value
Overall Treatment Efficacy				
Effective response	23 (50.0%)	34 (73.9%)	57 (62.0%)	0.018
Ineffective response	23 (50.0%)	12 (26.1%)	35 (38.0%)	
Response by WHO Criteria				
Complete remission	7 (15.2%)	18 (39.1%)	25 (27.2%)	0.024
Partial remission	16 (34.8%)	16 (34.8%)	32 (34.8%)	0.036
Stable disease	15 (32.6%)	10 (21.7%)	25 (27.2%)	0.028
Progressive disease	8 (17.4%)	2 (4.3%)	10 (10.9%)	0.019
Disease Control Rate				
Controlled disease (CR+PR)	23 (50.0%)	34 (73.9%)	57 (62.0%)	0.018
Uncontrolled disease (SD+PD)	23 (50.0%)	12 (26.1%)	35 (38.0%)	

DISCUSSION

The direction of benefit aligns with foundational clinical reports of superselective ophthalmic artery chemotherapy. Early phase experiences with direct intra-arterial melphalan demonstrated promising tumor control and feasibility [6]. Subsequent reports describing ophthalmic artery chemosurgery as primary treatment documented favorable ocular outcomes in appropriately selected eyes [7]. Long-term follow-up data have also supported sustained ocular preservation with selective ophthalmic arterial injection, with relatively limited severe systemic adverse events reported in large case series [8]. In parallel, a meta-analysis comparing intravenous and intra-arterial approaches reported improved ocular outcomes with intra-arterial chemotherapy, particularly in advanced intraocular disease [10]. While differences in staging systems, adjunct focal therapy use, and follow-up duration can influence cross-study comparisons, the current efficacy difference of 23.9 percentage points in favor of IAC is consistent with the overall direction of effect reported in the broader literature [6-8,10].

Procedure-related safety and service feasibility remain central considerations when interpreting these results for implementation. Systemic chemotherapy is associated with well-recognized systemic toxicities, whereas IAC reduces systemic exposure but introduces risks linked to arterial cannulation, catheter position, and local vascular complications [4,5]. Published clinical series of IAC have described relatively low rates of major procedural complications, but ocular adverse events including choriogenin changes and vascular events have been reported and require structured monitoring [11]. In the current study, adverse events were not tabulated as outcome measures, limiting direct comparison of harm profiles between arms. For clinical decision-making, efficacy advantages should be interpreted alongside local capacity for paediatric anaesthesia, interventional expertise, post-procedure surveillance, and multidisciplinary follow-up [4,10,11,12].

Broader presentation context is relevant, as later-stage intraocular disease remains more common in health systems facing delayed referrals and limited screening access. Global analyses have shown that presentation severity varies markedly with health system resources, influencing both the feasibility of eye salvage and the intensity of required therapy [2]. The current sample included substantial stage D and E disease, yet IAC achieved high efficacy, supporting its use as an eye-preserving option in advanced presentations when appropriate infrastructure is available.

Several limitations should be acknowledged. The single-center design restricts generalizability, and the follow-up window represented early response rather than long-term ocular salvage, recurrence, metastasis-free survival, or visual outcomes. Response assessment relied on categorical outcomes (complete remission, partial remission, control, progression), and additional granular endpoints such as time to regression, need for adjuvant focal therapy, and event-free survival were not reported. Despite these limitations, the balanced baseline distributions and clear between-arm difference in overall efficacy provide clinically useful comparative evidence.

CONCLUSION

Intra-arterial chemotherapy demonstrated superior efficacy compared to intravenous chemotherapy in managing advanced retinoblastoma. Where facilities are available, IAC should be considered the treatment of choice to maximize ocular salvage and improve outcomes.

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