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Effectiveness of Selective Intra-Arterial Chemotherapy for Patients with Retinoblastoma: A Meta-Analysis

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Research Article

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ABSTRACT

Purpose: Given the high rates of globe survival, Intra-Arterial Chemotherapy (IAC) was regarded as a novel therapeutic approach for Retinoblastoma (Rb) patients with wide application as primary or secondary management globally for retinoblastoma.

Methods: In this met-analysis we summarized the most recent evidence regarding the efficacy of IAC in the therapeutic management of retinoblastoma. We conducted systemic search on electronic databases including PubMed, Google scholar, EMBASE, and the Web of Science (WoS) till November 2021 for published studies investigating the efficacy of IAC treatment among patients with Rb.

Results: A total of 39 observational studies were eligible for inclusion in this meta-analysis comprising 2604 treated eyes and 3112 patients. The enucleation rate in the selected studies ranged between 0% to 43.7%, with an estimated pooled overall effect size of 0.52 (95%CI: 0.41 to 0.66, p<0.0001). Twenty seven studies (2310 eyes) reported the rate of globe salvage with a range of 30 to 100%. The estimated overall effect size for the percentages of eyes achieved globe salvage was 2.41 (95% CI: 1.6 to 3.63, p<0.0001). The pooled overall effect size of metastatic disease proportion and mortality rate were 0.03 (95% CI: 0.03 to 0.03, p<0.0001) and 0.05 (95 %CI: 0.04 to 0.05, p<0.0001), respectively.

Conclusion: Intra-arterial based treatment for retinoblastoma is an efficacious option according to retrospective trials. IAC treatment also reduced the need for enucleation with low metastasis rates; however, the lack of evidence from the literature warrants further well-designed high-level randomized controlled studies.

INTRODUCTION

Retinoblastoma (Rb) is an intraocular tumor that primarily affects children worldwide. About 8000 cases are diagnosed with retinoblastoma every year across the world with life-threatening and devastating consequences [1]. Since the emergence of ophthalmic artery chemosurgery, the delivery of chemotherapy directly through the intra-arterial route has become first-line treatment at various tertiary ocular centers globally, with both primary and salvage therapy [2]. This approach helped in saving advanced cases of Rb that would have been formerly enucleated [3]. Approximately 80% of advanced Rb cases categorized as group D and E according to the International Classification for Retinoblastoma (ICRB) have had enucleation prior to the era of IAC therapy [4].

The direct application of IAC therapy minimized ototoxicity and neurotoxicity side effects associated with systemic chemotherapy [5]. Although IAC has showed high efficacy regarding globe salvage rates worldwide, the rate of metastasis among Rb patients treated with IAC still undetermined. In 2016, Yousef and colleagues published a systematic review which investigated the evidence for IAC use in patients with Rb [6]. Since then, replicated studies have been conducted. However, most reports of patient cohorts were without adequate level of quality in the retrieved comparative data with discrepancy in sample capacities resulting in troublesome critical assessment of complications and outcomes [7]. Therefore, we aimed to evaluate the present studies and provide an updated summary concerning the clinical efficacy of IAC among patients with Rb, especially those with advanced disease. This meta-analysis is anticipated to provide evidence with high quality to benefit physicians in their clinical practice [8,9].

MATERIALS AND METHODS

The current investigation was carried out in accordance with an established protocol contingent on the statement of meta-analysis of studies in the epidemiology.

Search strategy and selection of studies

The included studies reported at least one of the following ocular outcomes: enucleation rate or globe salvage, metastasis incidence, or death following the treatment of Rb with IAC. We also included studies reporting the outcomes of combined IAC and Intravitreal Therapy (IVT).

Only conducted human research studies in all languages were included. The size or type of study did not limit inclusion. Review articles, editorials, and studies without a level of connection were all removed. The study search protocol is illustrated in Table 1.

Table 1. Search strategy for each electronic database.

Database	Search strategy
Pubmed, Chemosurgery Procedures, and Retinoblastoma	1. "intra-arterial, " (MeSH Terms) OR "chemosurgery procedures" (All Fields) OR "retinoblsatoma" (All Fields) 2. "enucleation "(MeSH Terms) OR "globe salvage" (All Fields) OR "metastasis" (All Fields) OR "mortality" (All Fields) 3. 1 and 2

Embase	1. 'intra-arterial chemotherapy'/exp OR chemosurgery procedures/exp OR ' retinoblsatoma'/exp 2. ' enucleation'/exp OR 'ICBG'/exp OR 'globe salvage'/exp OR 'metastasis'/exp OR 'mortality'/exp 3. 1 and 2
Cochrane Library	1. (intra-arterial chemotherapy): ti,ab,kw OR (chemosurgery procedures): ti,ab,kw OR (retinoblsatoma):ti,ab,kw (Word variations have been searched) 2. (enucleation): ti,ab,kw OR (globe salvage):ti,ab,kw OR (metastasis): ti,ab,kw or (mortality):ti,ab,kw (Word variations have been searched) 3. 1 and 2

The articles which fulfilled the following criteria were integrated into the present meta-analysis:

1. Well-designed studies either prospective study, or a retrospective study.
2. The designated target population was patients with retinoblastoma
3. The procedure of intervention approach was the treatment of Rb using IAC.
4. The investigation included outcomes of IAC treatment either alone or combined with IVT.

The exclusion criteria included:

1. Published Case reports, abstracts, editorials, reviews articles, studies with languages other than English, and studies with small sample size (less than 10 subjects).
2. Studies with missing or incomplete data
3. Research studies designed with objectives other than the examination of IAC outcomes in Rb patients.
4. Studies with methods other than IAC treatment.

Identification

Firstly, we searched electronic engines including, Embase, Google scholar, PubMed, Cochrane Library, and OVID till November 2021, using a combination of selected terms and keywords related to intra-arterial chemotherapy, chemosurgery procedures, and retinoblastoma, as illustrated in Table 1. All selected research publications were gathered into a single EndNote file, with duplication omission [10]. The titles and abstracts were examined to exclude publications that didn't report the effect of intra-arterial chemotherapy among patients with Rb on enucleation rate, globe salvage, metastasis, and mortality rate. The retrieved studies were investigated for relevant data.

Screening

The following study and participant-related properties were summarized onto a pre-designed form with following items: the first author's last name, timeframe, region, year of publication, and type of target population, study protocol, subject's number, demographical data, and applied clinical treatment properties. Additionally, the assessment period is related to quantitative and qualitative techniques of evaluation, information resource, and

outcomes' assessment, and statistical analysis of Odds Ratio (OR), with a 95% CI of associations. We assessed the quality of the selected non-randomized controlled trials by two authors independently.

In case of a study's eligibility according to the inclusion criteria and the aforementioned guidelines, information was retrieved individually by two of the authors. In case of a disagreement, the final decision was taken by the corresponding author. When there was variability in retrieved data from one of the trials data were extracted separately. For the assessment of bias in the retrieved studies; studies were appraised by two of the authors who independently evaluated the procedural quality of the selected trials.

The risk of bias

For bias risk and procedural quality evaluation, the tool of Cochrane risk-of-bias was applied for randomized-trials version 2 (RoB 2). In terms of bias evaluation criteria, studies were evaluated individually and assigned to one of the following risks of bias listed below: If quality standards were fully met, then the study identified as a low risk of bias. If the quality requirements (one or more) were only partially met or were unclear, the publication was deemed to be assigned to the moderate risk of bias category. Or high: if the standards were not fulfilled, or not comprised, the publication was deemed to be in the high risk of bias category. Any inconsistencies were resolved by re-investigating the original article.

Statistical analysis

The estimated Odds Ratio (OR) and 95% Confidence Interval (95% CI) by the continuous or dichotomous technique with a fixed or random-effect model were estimated. We estimated the I^2 index and ranged between 0% and 100%. The I^2 index value around 0% was interpreted as no heterogeneity, while I^2 index values of 25% was interpreted as low heterogeneity. The percentages of 50% and 75% were interpreted as moderate and high heterogeneity, respectively. If the I^2 was more than 50%, we applied the random-effect; if it was less than 50%, we applied the fixed-effect. The subgroup analysis was performed as defined before using the stratification of the original calculation per result category. A p-value for discrepancies amongst subgroups of less than 0.05 reflected statistical significance. The Egger regression test for bias assessment was quantitatively measured (bias was present if $p \leq 0.05$), and qualitatively, by visual inspection of funnel plots of odds ratios logarithm against the standard errors. The calculated p-values were 2-tailed. Reviewer Manager (RevMan) version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Denmark) was used to calculate all measurements and perform graphs.

RESULTS

A total number of 614 potential articles were retrieved initially through search engines (Figure 1). After full text assessment and review, 39 studies till 2021 fulfilled the inclusion criteria and were integrated in this meta-analysis [11]. The selected trials involved a total number of 2604 treated eyes. Most of the included studies were retrospective (n=35), and only four studies were prospective. The sample size of the selected studies ranged from 10 to 500 patients with retinoblastoma at the beginning of the trial. Chemotherapeutic agents used in the studies included melphalan, carboplatin and topotecan. All studies reported indications for IAC among patients with retinoblastoma. The main features of the included studies are summarized in Table 2.

Figure 1. Flow chart of the search strategy and selection of the studies.

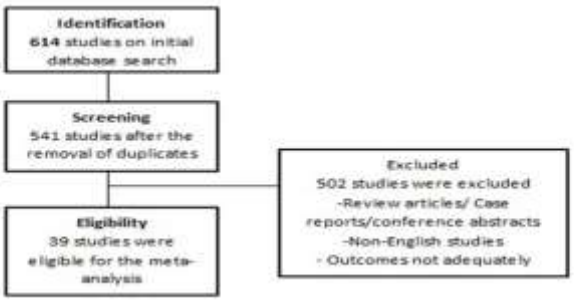


Table 2. Baseline characteristics of the selected studies.

Author's name, year	Country, study design	Number of treated eyes	Unilateral eye disease (%)	Age in months (median, range)	Classification (No. of eyes)	Sessions no. median (range)	Follow-up (months)	Chemotherapy
Abramson, 2010 et al., [12]	USA, Retrospective	28	82%	11(3-88)	(RE), RE V (25), RE IV (1), RE III (1), RE II (1)	3.2(1-6)	15(3-37)	Melphalan, Topotecan, Carboplatin
Gobin, et al., 2011 [13]	USA, Retrospective	91					13	Melphalan, Topotecan, Carboplatin, Methotrexate
Munier, et al., 2011 [14]	Switzerland Retrospective	13					7	Melphalan
Peterson, et al., 2011 [15]	USA, Retrospective	17	38	18(9-32)	D(17)	1.4(1-2)	8.6(3-12)	Melphalan (7.5 mg)
Suzuki, et al., 2011 [16]	Japan, Retrospective	408	39		A(5), B(130), C(30), D(216), E(18)	3.7(1-18)	79(58)	Melphalan (5.0-7.5 mg/m^2 body surface area)
Marr, et al., 2012 [17]	USA, Retrospective	26	4	18(0-62)	26 B(1), C(2), D(17), E(6)	2.3(1-4)	14(1-43)	Carboplatin, Topotecan, Melphalan
Muen, et al., 2012	UK, prospective	15	NA	17(11-150)	NA	01-Mar	9(3-16)	Melphalan

[18]								
Thampi, et al., 2013 [19]	USA, Retrospective	20	38	15(7-63)	A(1), B(4), C(2), D(11), E(2)	NA	15(1-29)	Melphalan
Venturi, et al., 2013 [20]	Italy Retrospective	41					13	Melphalan
Ghassemi, et al., 2014 [21]	Iran, Retrospective	24	58	39(14-120)	NA	NA	17(3-36)	Melphalan ± Topotecan
Shields, et al., 2014 [22]	USA, Retrospective	70	63	20(4-392)	B(1), C(4), D(17), E(14)	3(1-6)		Melphalan ± Topotecan+carboplatin
Taich, et al., 2014 [23]	Argentina, Retropsective	27					11.7	Melphalan and Topotecan
Parareda, et al., 2014 [24]	Spain, prospective	12	73	21(7-51)	D	2.6(1-5)	29.5(6-57)	Melphalan (3-5 mg)
Akyuz, et al., 2015 [25]	Turkey Retrospective	56					11.9	Melphalan
Ong, et al., 2015 [26]	Taiwan, Retrospective	17	42	18(2-50)	B(3), C(1), D(1), E(12)	3(1-6)	22(5-43)	
Abramson, et al., 2016 [27]	USA Retrospective	120					36	Melphalan, Topotecan, Carboplatin, Methotrexate
Chen, et al., 2016 [28]	China, Retrospective	13			B(2), D(9), E(2)	2.6(2-4)	28(9-65)	Melphalan (0.5 mg/kg) Topotecan (0.5-1.0 mg)
Leal-Leal, et al., 2016 [29]	Mexico, prospective	11	100	22.6(12-36)	B(2), C(5), D(4)		14.3(1.8-28)	Melphalan (4 mg) Topotecan (1 mg)
Michaels, et al., 2016 [30]	USA, Retrospective	19	88	29(5-192)	C(3), D(15), E(1), 5(2-10)			Melphalan or Topotecan
Tuncer, et al., 2016	Turkey, Retrospective	24	77	NA	D		29(6-55)	Melphalan

[31]								
Chen, et al., 2017 [32]	China, Retrospective	107	33	20(4-95)	B(11), C(11), D(56), E(29)	3.1(2-5)	9.1(1-26)	Melphalan (0.5 mg/kg) Topotecan (1 mg)
Fabian, et al., 2017 [33]	UK, Retrospective	64	33	11(0.6-144)	D	55(11-156)	38.7	Melphalan
Munier, et al., 2017 [34]	Switzerland, Retrospective	25	100	33.5 ± 25.9				Melphalan (2.8-7.5 mg)
Reddy, et al., 2017 [35]	UK, Retrospective	9						Melphalan topotecan
Rishi, et al., 2017 [36]	India, Retrospective	10	20	26(11-59)	B(1), C(2), D(6), E(1)	3.8(3-5)	21	Melphalan, Topotecan
Francis, et al., 2018 [37]	USA, Retrospective	436	38	13.4(0.1-195)	A(3), B(42), C(45), D(208), E(85)		26.5(0-119.7)	Melphalan, Topotecan, Carboplatin
Funes, et al., 2018 [38]	Argentina, Retrospective	97				4(1-14)	48.7(12-79)	Carboplatin
Hua, et al., 2018 [39]	China, Retrospective	84	65	16(4-96)	D(36), E(48)		14.2(3-28)	Melphalan, Topotecan
Kiratli, et al., 2018 [40]	Turkey, Retrospective	30			D	2.6	4.0(1-16)	melphalan (5-7.5 mg), Topotecan (1 mg)
Rojanapor n, et al., 2019 [41]	Thailand, Retrospective	27					32	Melphalan, Topotecan, Carboplatin
Hassan, et al., 2019 [42]	Egypt, Retrospective	30					14.2(6-20)	Melphalan
Liu, et al., 2020 [43]	Malaysia Retrospective	14					17	Melphalan,Top otecan, Carboplatin
Oto, et al.,	Turkey,	21						Melphalan

2020 [44]	Retrospective							
Rishi, et al., 2020 [45]	India, Retrospective	24					28.6	Melphalan Topotecan
Gonzalez, et al., 2021 [46]	Colombia, Retrospective	100	39	8.70(4.53-18.55)	A(1), B(10), C(27), D(51), E(11)		29(16-59)	Melphalan ± Topotecan
Li, et al., 2021 [47]	China, Retrospective	73					7	Melphalan, Topotecan, Carboplatin
Linde and Mustak, 2021 [48]	South Africa, Retrospective	25					47	Melphalan ± Topotecan
Oporto, et al., 2021 [49]	Chile, Retrospective	35					36.5	Melphalan, Topotecan
Shields et al., 2021 [50]	USA, Retrospective	341						Melphalan Topotecan Carboplatin

Nineteen studies explicitly investigated enucleation events following IAC. The enucleation rate in the selected studies ranged between 0%-43.7%, with the highest rate (more than 50%) in Hua, et al., (2018) study. The estimated overall pooled effect size of enucleation rates was 0.51 (95% CI: 0.42 to 0.63, $p<0.0001$) with considerably high heterogeneity ($I^2=98\%$) as summarized in forest plot (Figure 2). Twenty seven studies with 2,310 treated eyes reported the rate of globe salvage with a range of 30 to 100%. The overall rate was 76.4% for Rb patients received IAC treatment. The estimated overall effect size for the percentage of eyes achieved globe salvage was 2.05 (95%CI: 1.62 to 2.60, $p<0.0001$) with high heterogeneity ($I^2=90\%$) (Figure 3). The rate of metastasis, as reported in seven studies, was approximately 2.4%. The pooled overall effect size of metastatic disease proportion was 0.03 (95%CI: 0.03 to 0.03, $p<0.0001$). The estimated heterogeneity level (I^2) was 61% (Figure 4).

Figure 2. Forest plot of the estimated overall effect sizes of the enucleation rate.

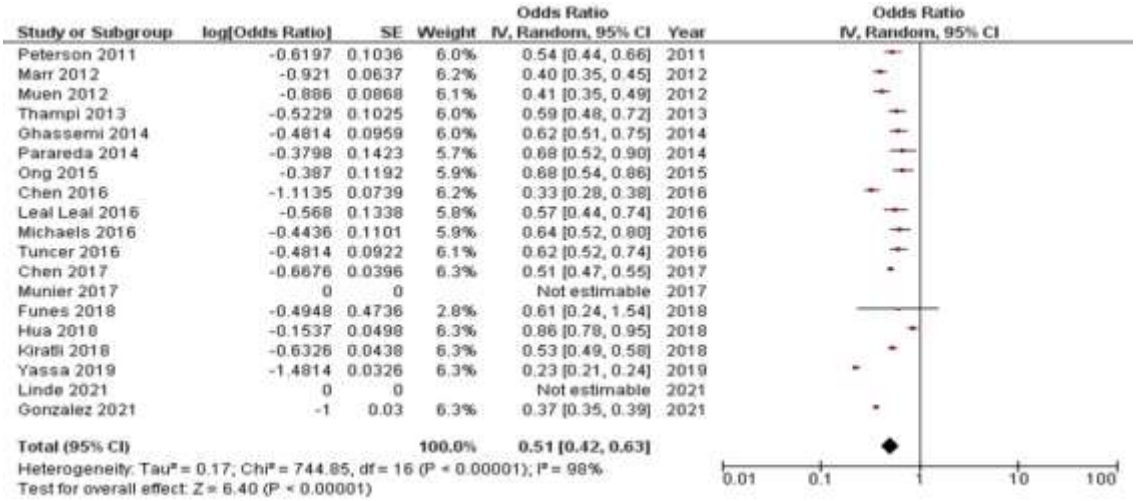


Figure 3. Forest plot of the estimated overall effect size of globe salvage proportions.

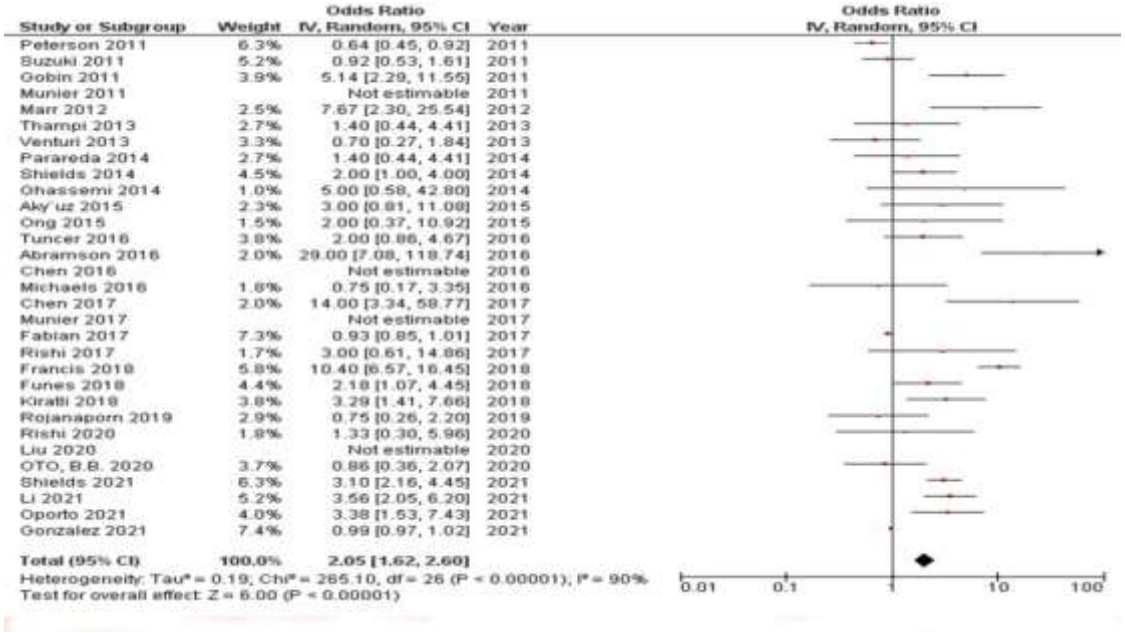
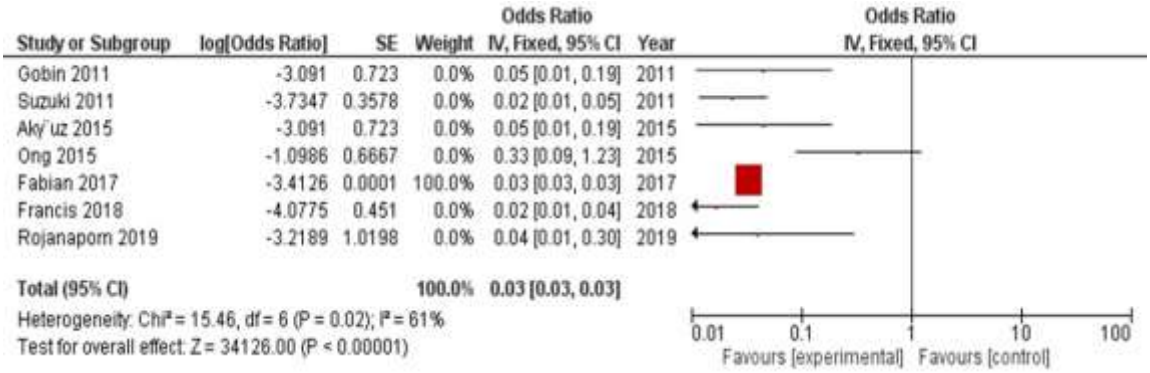
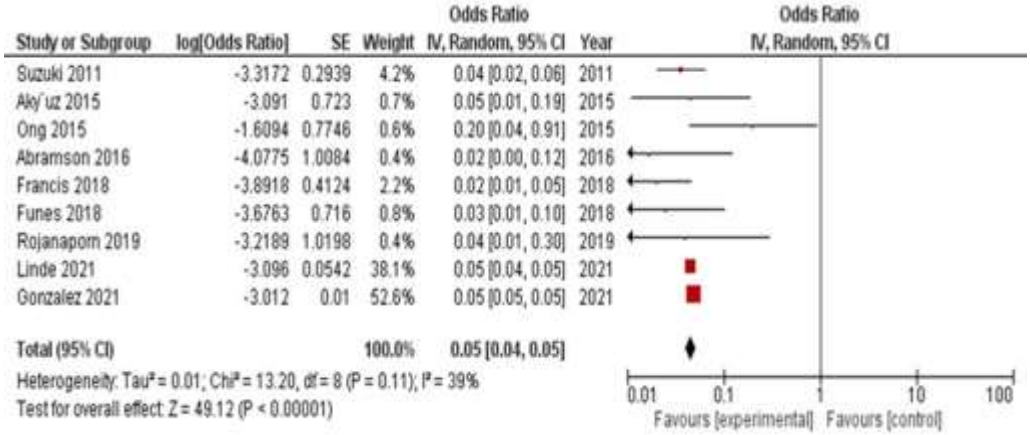


Figure 4. Forest plot of the estimated overall effect size of metastasis proportions.



Nine studies reported the mortality rate, with an estimated population number of 1896 patients. The overall mortality rate was 1.3%. The pooled overall effect size of mortality was 0.05 (95%CI: 0.04 to 0.05, p<0.0001) with low heterogeneity (I^2=39%) (Figure 5).

Figure 5. Forest plot of the estimated overall effect size of mortality rates.



The Analysis of studies and adjustment for gender, race, and age was not performed because none of the studies included adjusted or stated for the influence of these variables. Egger regression analysis estimates (p=0.84) revealed no publication bias based on visual and quantitative evaluation of the funnel plot. Despite this, most of the included studies for meta-analysis had low quality of procedure due to their limited sample size. None of the studies had selective reporting bias, or inadequate outcome data.

DISCUSSION

Systemic administration of chemotherapy is the standard approach for treatment of most cancer patients including retinoblastoma with high incidence rate of drug associated adverse effects [46]. In 2004, the use of selective intra-arterial ophthalmic chemotherapy was firstly reported by Yamane, et al. [47] for patients with retinoblastoma. Despite its challenging technique of catheterizing small blood vessel, IAC has become the first option for treatment of retinoblastoma with widespread utility throughout the world. Before the application of IAC technique, approximately 80% of Rb cases eventually need enucleation to control the hematogenous spread and the involvement of central nervous system [48].

The present meta-analysis included 39 studies assessing the main clinical outcomes and complications associated with IAC for patients with retinoblastoma. We conducted this meta-analysis to provide an updated comprehensive evidence of the clinical efficacy and utility of IAC by the inclusion of recent studies which adopted various drugs for retinoblastoma management. The results of the current meta-analysis revealed an improved rate of enucleation following intra-arterial chemotherapy among patients with Rb. The efficacy of intra-arterial chemotherapy in globe conservation has been confirmed in many studies. In this meta-analysis, the estimated overall globe salvage was 76.4% with IAC treatment which is consistent with the rates found by Yousef, et al. 2016 [6], in a recent systematic review based on 12 studies. In our results, the estimated overall metastatic rate was 2.4% which is quiet similar to that reported by Yousef, et al., 2016 pooled analysis estimates of about 2.1% (6). Also, Chen, et al., 2018 [49] reported an overall metastatic rate of 2.7% with IAC among patients with advanced retinoblastoma. The presence of an evidence of histopathologic risk features significantly increases the risk metastatic eye disease. This risk considerably decrease to less than 10% in countries with well advanced hospital settings [49,50].

CONCLUSION

To sum up, intra-arterial based treatment for retinoblastoma is an efficacious option according to retrospective trials. IAC treatment also reduced the need for Enucleation with low metastasis rates; however, the paucity of evidence from literature warrants further well designed high-level randomized controlled studies. Despite the potential efficacy and the achieved high rates of globe salvage with IAC treatment, several systemic and ocular complications have been reported. Choroidal/retinal ischemia, detachment of retina in about 25% of patients, retinal atrophy and vitreous hemorrhages were the most commonly reported ocular complications. Retinal detachment and hemorrhages represent clinical complications that are transient and generally self-limiting. Unlike ischemic events, it could result in long-term complications and threaten eye vision. Systemic complications included neutropenia and fever. About 10% of cases required bronchodilator for the management of bronchospasm complications. The limitations of the present meta-analysis include the following: firstly, it is based mainly on retrospective studies without any high-level randomized controlled trials. Secondly, few studies reported the disease progression and survival rates with the lack of adequate follow-up after IAC. Thirdly, a substantial heterogeneity was detected in the reported outcomes, and finally, limited standards for stratifying patients with Rb disease.

Acknowledgments

None.

Disclosure

The author reports no conflicts of interest in this work.

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