Fluorescein *Versus* Indocyanine Green Angiography-Guided Primary Photodynamic Therapy for Treatment of Central Serous Chorioretinopathy: A Systematic Review with Meta-Analysis

Terapia Fotodinâmica Primária Guiada por Angiografia Fluoresceínica *Versus* Angiografia com Verde de Indocianina para o Tratamento da Coriorretinopatia Serosa Central: Uma Revisão Sistemática com Meta-Análise

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ABSTRACT

INTRODUCTION: We aimed to systematically review the evidence comparing the use of fluorescein angiography (FA) *versus* indocyanine green angiography (ICGA) as a guide to primary photodynamic therapy (PDT) for central serous chorioretinopathy (CSC).

METHODS: PubMed, Web of Science, Scopus, and Cochrane Library databases were searched for all relevant studies published from inception to May 26th, 2024. Studies comparing the clinical outcomes of primary PDT guided by FA versus ICGA for eyes with chronic CSC were included. Main outcomes were best-corrected visual acuity (BCVA), central macular thickness (CMT), subfoveal choroidal thickness (SFCT) and subretinal fluid (SRF) resolution. A meta-analysis was performed using a random-effects model.

RESULTS: Of 451 abstracts, 3 were found eligible, enrolling 179 eyes of 170 CSC patients treated with PDT, 82 of which were guided by FA and 97 by ICGA. In all studies, BCVA improved and CMT and SCFT reduced with PDT, regardless of the angiography used as reference, when compared with baseline. The meta-analysis revealed no significant difference between FA versus ICGA-guided PDT in BCVA (MD -0.01 [-0.07, 0.05] logMAR, p=0.71), CMT (MD -5.76 [-43.67, 32.15] µm, p=0.77) and SFCT (MD 16.00 [-8.81, 40.82] µm, p=0.21) changes. Complete SRF resolution in the last follow-up visit was noticed in 70%-100% of patients (83.3%-100% for FA *versus* 70.8%-100% for ICGA).

CONCLUSION: The evidence produced so far suggests that FA and ICGA-guided half-dose PDT are similarly effective and safe in treating chronic CSC.

KEYWORDS: Central Serous Chorioretinopathy; Fluorescein Angiography; Indocyanine Green; Photochemotherapy.

RESUMO

INTRODUÇÃO: O nosso objetivo foi rever de forma sistemática a evidência que compara a utilização da angiografia fluoresceínica (FA) versus a angiografia com verde de indocianina (ICGA) como guia para a terapia fotodinâmica (PDT) primária na coriorretinopatia serosa central (CSC).

MÉTODOS: Foram pesquisadas as bases de dados PubMed, Web of Science, Scopus e Cochrane Library para todos os estudos relevantes publicados desde a sua criação até 26 de maio de 2024. Foram incluídos estudos que compararam os resultados clínicos da PDT primária guiada por FA *versus* ICGA em olhos com CSC crónica. Os principais desfechos analisados foram a acuidade visual corrigida (BCVA), a espessura macular central (CMT), a espessura coroideia subfoveal (SFCT) e a resolução do fluido sub-retiniano (SRF). Foi realizada uma meta-análise com um modelo de efeitos aleatórios.

RESULTADOS: De 451 resumos identificados, 3 estudos foram considerados elegíveis, envolvendo 179 olhos de 170 doentes com CSC tratados com PDT, dos quais 82 guiados por FA e 97 por ICGA. Em todos os estudos, observou-se melhoria da BCVA e redução da CMT e da SCFT com a PDT, independentemente do tipo de angiografia utilizada como referência, quando comparadas com os valores basais. A meta-análise não revelou diferenças significativas entre a PDT guiada por FA e por ICGA na alteração da BCVA (DM -0,01 \[-0,07, 0,05] logMAR, p=0,71), CMT (DM -5,76 \[-43,67, 32,15] µm, p=0,77) e SFCT (DM 16,00 \[-8,81, 40,82] µm, p=0,21). A resolução completa do SRF na última visita de seguimento foi observada em 70% a 100% dos doentes.

CONCLUSÃO: A evidência disponível até ao momento sugere que a PDT com meia-dose guiada por FA ou por ICGA é igualmente eficaz e segura no tratamento da CSC crónica.

PALAVRAS-CHAVE: Angiografia Fluoresceínica; Coriorretinopatia Serosa Central; Terapia Fotodinâmica; Verde de Indocianina.

INTRODUCTION

Central serous chorioretinopathy (CSC) is a disorder of the pachychoroid spectrum that affects predominantly young to middle-aged men with emmetropic or hyperopic eyes, usually presenting with unilateral involvement in the acute phase.[1] With increasing age, the gender predilection decreases and there is a higher likelihood of bilateral involvement, diffuse retinal pigment epitheliopathy, and secondary macular neovascularization (MNV).[1,2] Main symptoms include decreased visual acuity, metamorphopsia, relative scotoma, and micropsia.[1] Its pathophysiology is complex, and appears to affect Ruysch's complex, composed by choriocapillaris, Bruch's membrane and retinal pigment epithelium (RPE).[3] On fundoscopy, solitary and localized neurosensory retinal detachments and serous pigment epithelial detachments (PEDs) can be found.1 Changes at the level of RPE and choriocapillaris are evident on ocular angiography. The "ink-blot" and "smoke-stack" patterns are characteristic images on fluorescein angiography (FA), whereas indocyanine green angiography (ICGA) demonstrates choroidal hyperpermeability, delayed choroidal filling, and dilation of the vortex vein ampulla.[4-6]

The most common type is acute CSC, which resolves spontaneously within 4-6 months in most cases. In chronic CSC, defined by duration over 6 months, treatment is usually indicated as diffuse RPE abnormalities and damage, with broad areas of non-resolving serous subretinal fluid (SRF) are commonly seen.[1] Bilateral or recurrent disease, vision-demanding occupation, or the request for faster vision recovery are also indications for intervention.[7] Current treatment modalities include oral mineralocorticoid antagonists, high-density subthreshold micropulse laser (HSML) treatment, conventional thermal laser targeting extrafoveal RPE leakage foci, and photodynamic therapy (PDT).[3] The standard protocol for PDT is performed with 6 mg/m^2 of verteporfin, an irradiance of 600 mW/cm^2, a fluence of 50 J/cm^2, a duration of 83 seconds (s), and a diode laser at a wavelength of 600-689 nm.[8] Despite its effectiveness, several complications have been described after PDT, including RPE atrophy, choriocapillaris ischemia, exudative maculopathy, and secondary MNV.[9] To avoid such complications, modified protocols have been proposed, with the most used being half-dose (3 mg/m^2 of verteporfin) and half-fluence (light energy 25 J/cm^2) protocols. PLACE[10] and SPECTRA[11] trials demonstrated the effectiveness of half-dose PDT for CSC treatment and its superiority to HSML and eplerenone, respectively. In both trials, the area to be treated was determined by the hyperfluorescent areas of leakage seen on mid-phase ICGA to avoid undertreatment as ICGA usually reveals more extensive abnormalities compared to FA.[10,11] Theoretically, a FA-guided PDT could lead

to a less extensive treatment with lower energy used, which may result in a lower chance of choroidal ischemia or RPE damage.[12] The effectiveness of FA-guided PDT with several strategies, including conventional, half-dose, half-fluence, half-time, and multispot, has been demonstrated.[12-14] Some studies compared FA *versus* ICGA-guided PDT for chronic CSC[15-18] but a synthesis of those results has yet to be made. This work aims to fill that void in the literature with a systematic review of the evidence produced so far.

METHODS

We conducted a systematic review with meta-analysis following the guidelines presented by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[19] The protocol was not registered.

SEARCH STRATEGY AND STUDY SELECTION

PubMed, Web of Science, Scopus, and Cochrane Library databases were searched for all relevant studies published from inception to May 26th, 2024. Search terms used are detailed in Suppl. Table 1. References of relevant articles were hand-searched, and a forward citation search was performed.

Search results were screened independently by Title/Abstract by two authors (A.F. and B.C.V.) to exclude duplicates and studies not meeting inclusion criteria using Rayyan.[20] Studies selected in the screening phase underwent a full-text review by the same authors. Disagreements during the process were solved by consensus. The primary aim of the studies was to compare the anatomic and functional outcomes of primary PDT guided by FA *versus* ICGA for eyes with chronic CSC. Patients with previous treatments for CSC, macular neovascularization, or other ocular diseases were excluded. The clinical outcomes of interest included: i) best-corrected visual acuity (BCVA); ii) central macular thickness (CMT); iii) subfoveal choroidal thickness (SFCT); iv) SRF resolution. No restrictions were placed on the age of participants, device, PDT protocol, software, time or country of origin during the search process.

DATA COLLECTION PROCESS

Data were extracted into a purposely built form. The authors were contacted to retrieve any missing information or clarify any doubts. Our primary outcomes were BCVA,

Table 1. Baseline characteristics of the population and description of PDT features.

	Guide	Ebrahimiadib *et al* 2023 Iran		Hayashida *et al* 2020 Japan		Moodi *et al* 2024 Iran	
		Value	*p*	Value	*p*	Value	*p*
Eyes, n	FA	12	-	29	-	41	-
	ICGA	24		32		41	
Male, n (%)	FA	9 (75%)	0.777	20 (69%)	0.370	31 (76%)	1.00
	ICGA	19 (79%)		26 (81%)		31 (76%)	
Age, y	FA	44 ± 5	0.865	52.7 ± 10.6	0.440	41.44 ± 7.61	0.996
	ICGA	44 ± 10		55.0 ± 12.0		41.56 ± 8.77	
BCVA, logMAR	FA	0.34 ± 0.26	0.132	0.058 ± 0.166	0.330	0.21 ± 0.19	0.764
	ICGA	0.56 ± 0.43		0.026 ± 0.181		0.20 ± 0.21	
Duration of symptoms, mo	FA	NR	-	7.0 ± 7.3	0.840	6.42 ± 8.80	**0.033**
	ICGA	NR		9.8 ± 15.1		18.14 ± 24.05	
CMT, µm	FA	340 ± 115	0.650	344.5 ± 147.2	0.470	375.33 ± 98.69	0.876
	ICGA	332 ± 107		342.1 ± 97.7		385.63 ± 140.73	
SFCT, µm	FA	338±38	0.251	400.5 ± 109.0	0.640	456.27 ± 124.85	0.205
	ICGA	363±60		414.2 ± 106.1		524.25 ± 138.78	
PDT spot size, µm	FA	2777 ± 1048	**0.023**	2898.3 ± 705.7	**< 0.01**	3397.56 ± 1557.00	0.966
	ICGA	6016 ± 4503		4993.8 ± 333.1		3387.80 ± 1636.18	
PDT spot numbers, n	FA	1.42 ± 0.90	**0.016**	NR	-	1.39 ± 0.59	0.951
	ICGA	2.50 ± 1.59		NR		1.37 ± 0.49	
Compatible leakage areas, %	-	68%	-	NR		NR	
PDT protocol	-	Half-dose		Half-time		Half-dose	
PDT total energy, J/cm²	FA	3283 ± 2520	**0.012**	NR	-	NR	-
	ICGA	5933 ± 3657		NR		NR	
Follow-up time, mo	FA	4		12		6.36 ± 6.32	0.55
	ICGA					6.96 ± 5.82	

BCVA, best-corrected visual acuity; CMT, central macular thickness; FA, fluorescein angiography; ICGA, indocyanine green angiography; mo, months; NR, not reported; PDT, photodynamic therapy; SFCT, subfoveal choroidal thickness

CMT and SFCT. Data extracted included study setting (first author, publication, year); participants' characteristics (age, gender, eyes included and symptoms duration); angiographic and PDT features (protocol, spot size and number, and energy); SRF change, and re-treatments); complications; and main outcomes. Main outcomes measures were retrieved at baseline and in the last follow-up visit reported.

QUANTITATIVE ANALYSIS

Meta-analysis of continuous outcomes was conducted for studies reporting raw data of the main outcomes with the Cochrane Collaboration's Review Manager (RevMan) software (Version 5.3) with weighting by the inverse variance approach. Random-effects model was chosen due to potential differences in study design and demography. A mean difference (MD) effect measure was used as visual acuity was assessed uniformly between studies and the same OCT machine, Spectralis OCT system (Heidelberg Engineering, Heidelberg, Germany) was resourced for all studies. For each main outcome, the change (mean ± standard deviation (SD)) associated with the PDT was retrieved and used or meta-analytical purposes. For studies reporting the values before and after PDT, we performed a difference of means and calculated the SD as recommended.[21] Between-study heterogeneity was assessed using the I^2 statistic and the Cochran Q statistic. An $I^2 > 60\%$ and a Cochran Q statistic p-value < 0.1 were considered to represent substantial heterogeneity.[22,23] Following Cochrane Guidelines,[24] meta-regression was not performed as there were fewer than ten studies for each OCT parameter that was meta-analyzed.

Risk of bias in individual studies and sensitivity analysis

Two reviewers (AF and RJV) independently evaluated the risk of bias for each eligible study using the ROBINS-I tool.[25,26] Any disagreement was solved by consensus.

A sensitivity analysis was conducted with an $I^2 > 60\%$. Funnel plots were used to assess publication bias.

RESULTS

LITERATURE SEARCH

The study selection process of the 3 eligible studies is shown in a flow diagram (Fig. 1). The literature search process yielded 451 abstracts, of which 314 were unique. Five met the inclusion criteria after a Title/Abstract screening, and their full text was retrieved and assessed for eligibility. Two studies were excluded due to the lack of treatment[27] and enrollment of patients with MNV.[18] No previous systematic reviews on this specific issue were found.

STUDIES, POPULATION AND TREATMENT CHARACTERISTICS

Table 1 summarizes the characteristics of the studies and the patients enrolled. All studies were interventional and

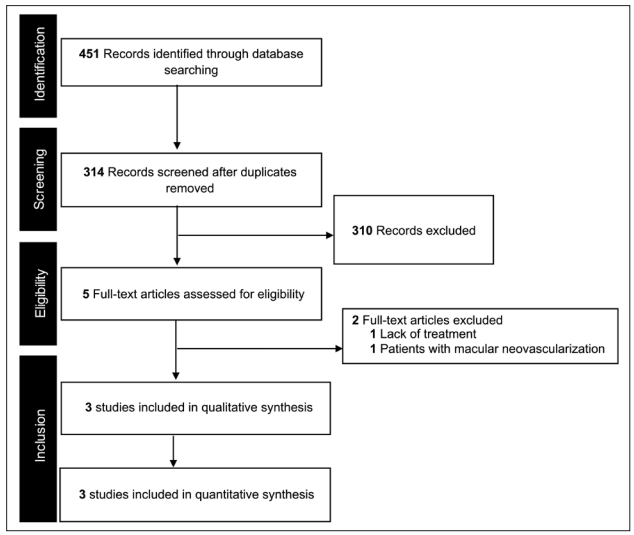

Figure 1. Flow chart of the search strategy.

longitudinal, one being prospective[16] and the other two retrospective,[15,17] and all were published since 2020. A total of 179 eyes of 170 CSC patients were enrolled and treated with PDT, 82 of which were guided by FA and 97 by ICGA. Most patients were middle-aged males with a mean duration of symptoms of over 6 years (not reported in one study[16]). In Moodi *et al*,[17] patients submitted to ICGA-guided PDT had a significantly longer duration of symptoms compared with the FA-guided PDT group. Baseline BCVA, CMT and SFCT were not significantly different between groups. Two studies[15,16] reported that a larger spot size was used when ICGA served as a guide and, one of those studies,[16] also described a higher number of spots and a higher total amount of energy spent during ICGA-guided PDT. The other study[17] did not find any difference in the spot size or number between angiography types. Two studies[16,17] applied a half-dose PDT, whereas the other opted for a half-time protocol.[15]

QUANTITATIVE ANALYSIS OF CLINICAL OUTCOMES OF PDT

Table 2 presents the clinical outcomes of PDT and Fig. 2 depicts the forest plot of the meta-analysis.

In all studies, BCVA improved and CMT and SCFT reduced with PDT, regardless of the angiography used as reference, when compared with baseline. The meta-analysis revealed no significant difference between FA *versus* ICGA-guided PDT in BCVA (Fig. 2A; MD -0.01 [-0.07, 0.05] logMAR, p=0.71), CMT (Fig. 2B; MD -5.76 [-43.67, 32.15] µm, p=0.77) and SFCT (Fig. 2C; MD 16.00 [-8.81, 40.82] µm, p=0.21) changes. All analyses presented low to moderate heterogeneity (I^2 = 0%, 0% and 43%, respectively). Complete SRF resolution in the last follow-up visit was noticed in 70%-100% of patients (83.3%-100% for FA *versus* 70.8%-100% for ICGA). In Moodi *et al*,[17] all patients had a full SRF resolution with a single treatment and without recurrence after a mean follow-up of over 6 months. Hayashida *et al*[15] described a lower rate of complete SRF resolution at 3 months (72% *versus* 94%, p=0.04) and high-

Table 2. Clinical results of PDT.

	Guide	Ebrahimiadib *et al* 2023 Iran			Hayashida *et al* 2020 Japan			Moodi *et al* 2024 Iran		
		Baseline	Follow-up	*p*	Value	Follow-up	*p*	Value	Follow-up	*p*
BCVA, logMAR	FA	0.34 ± 0.26	0.14 ± 0.13	**0.005**	0.058 ± 0.166	−0.065 ± 0.126	**< 0.01**	0.21 ± 0.19	0.07 ± 0.13	**< 0.001**
	ICGA	0.56 ± 0.43	0.43 ± 0.47	**0.001**	0.026 ± 0.181	−0.064 ± 0.178	**< 0.01**	0.20 ± 0.21	0.06 ± 0.17	**< 0.001**
	P*	0.132	0.160		0.330	0.500		0.764	0.700	
CMT, µm	FA	340 ± 115	195 ± 37	**0.002**	344.5 ± 147.2	−163.9 ± 127.6	**< 0.01**	375.33 ± 98.69	235.73 ± 31.40	**< 0.001**
	ICGA	332 ± 108	207 ± 74	**0.001**	342.1 ± 97.7	-158.9 ± 102.0	**< 0.01**	385.63 ± 140.73	235.59 ± 33.22	**< 0.001**
	P*	0.650	0.478		0.470	0.860		0.876	0.564	
SCFT, µm	FA	338±38	277 ± 44	**0.001**	400.5 ± 109.0	−49.6 ± 34.5	**< 0.01**	456.27 ± 124.85	377.63 ± 103.13	**< 0.001**
	ICGA	363±60	274 ± 48	**0.001**	414.2 ± 106.1	−50.3 ± 45.7	**< 0.01**	524.25 ± 138.78	389.57 ± 120.62	**0.018**
	P*	0.251	0.10		0.640	0.900		0.205	0.108	
Complete SRF resolution, n (%)	FA	10 (83.3%)		-	28 (97%)		-	41 (100%)		-
	ICGA	17 (70.8%)			32 (100%)			41 (100%)		
	P*	0.414			0.480			-		
Recurrence and/or persistence of SRF, n (%)	FA	-		-	10 (34%)		-	0 (0%)		-
	ICGA	-			4 (13%)			0 (0%)		
	P*	-			**0.04**			-		
Re-treatment, n (%)	FA	1 (8.3%)		-	5 (17.2%)		-	0 (0%)		-
	ICGA	1 (4.2%)			2 (6.3%)			0 (0%)		
	P*	-			0.140					

Asterisk (*) indicates the *p*-value for FA *versus* ICGA comparison. Dagger (†) indicates the *p*-value for the change (baseline *versus* follow-up).

BCVA, best-corrected visual acuity; CMT, central macular thickness; FA, fluorescein angiography; ICGA, indocyanine green angiography; mo, months; NR, not reported; PDT, photodynamic therapy; SFCT, subfoveal choroidal thickness.

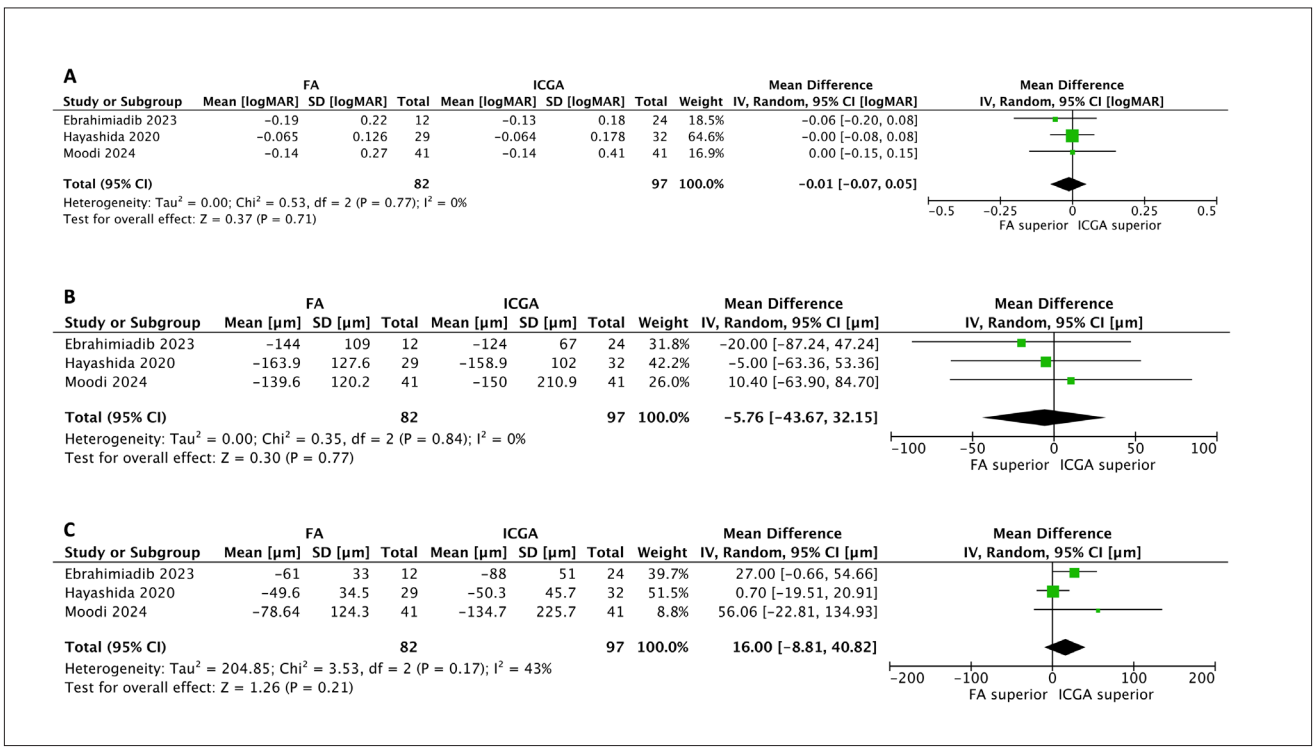

Figure 2. Forest plot of clinical outcomes of FA-guided versus ICGA-guided PDT, namely BCVA (A), CMT (B) and SFCT (C). Mean and standard deviation (SD) are included, with 95% confidence intervals (CIs), heterogeneity scores, and overall effect in an inverse variance (IV) random-effects model. The square size represents the weight attributed to each study based on relative sample size.

er proportion of recurrence and/or persistence of SRF after FA-guided half-time PDT (34% *versus* 13%, *p*=0.04), but no significant differences in treatment success (defined as complete resolution of SRF) at final visit. There were no significant differences in the re-treatment rates.

SAFETY

No complications were described in any study.

BIAS ASSESSMENT

Publication biases were investigated by plotting funnel plots (shown in Suppl. Fig. 1), which revealed a symmetrical distribution of studies about the MD, indicating little to no publication bias or small study bias. Bias analysis was performed in all three studies that were considered eligible and are shown in the Suppl. Fig. 2 and Suppl. Fig. 3.

DISCUSSION

PDT is among the most common treatments for chronic CSC, usually indicated for eyes with diffuse choroidal vascular hyperpermeability (CVH) and RPE leakage as HSML is less effective in this scenario.[28] Protocols with modified parameters (fluence, time, or verteporfin dose) have been studied to avoid PDT complications. Currently, half-dose PDT is the most popular option with effectiveness demonstrated in several trials.[10,11,29] Half-time PDT was also shown to be effective despite being a less common approach.[30] In trials, ICGA has been used as the guide to identify the areas of choroidal hyperpermeability to be treated as it allows a better visualization of choroidal vascular changes and, usually, reveals more extensive abnormalities compared to FA.[10,11,30] In this work, we synthesized the evidence comparing the results of FA-guided *versus* ICGA-guided primary PDT for chronic CSC and found no significant differences in BCVA, CMT and SFCT. Half-time FA-guided PDT seems to have less success in complete resolution of SRF after a single session compared to the half-dose protocol.

PDT protocol involves the infusion intravenously of verteporfin (Novartis, Basel, Switzerland), a light-sensitive pigment, that is activated by a diode laser when reaching the eye. This reaction induces the narrowing and remodeling of the choroidal vessels and reduction of choroidal hyperpermeability, which leads to SRF resolution.[16,31] Many specialists apply PDT on the areas of CVH revealed by ICGA, however, this dye is expensive, may not be widely available, and is more time-consuming than FA.[16]

This work enrolled three studies with two groups each (FA and ICGA-guided PDT) presenting well-balanced clinical and demographic characteristics before primary PDT, except for the duration of symptoms in Moodi *et al*.[17] This fact does not seem to have influenced the results, as all patients of this work had full recovery without relapse during follow-up. Two studies[15,16] reported a significant difference in PDT spot size between angiography modalities, with the ICGA-guided spot being wider, as argued in previous trials.[10,11,30] Ebrahimiadib *et al*[16] also reported fewer spots and the resource to lower energy with FA-guided PDT. The same authors compared the treatment areas between FA and ICGA in both treated and fellow eyes. While the areas were compatible in 68% of treated eyes, a substantial disparity of 72% was found in the fellow eyes.[16] This agreement in treated eyes goes in line with the results of Kianersi *et al*,[27] that compared the accuracy of FA in determining the treatment spot for eyes candidates to ICGA-guided PDT. The authors found a correspondence of 78% in site and 74% in size between both exams.[27] Of note, that study enrolled eyes with acute and chronic CSC and found an association between chronic CSC and discrepancy in spot size between exams.[27] These facts highlight that both modalities can demonstrate the areas of interest in symptomatic eyes candidates for treatment. However, FA demonstrates the active leaking spots, a consequence of CVH, while ICGA can show the CVH itself, explaining the differences reported. In addition, eyes with subclinical choroidal changes but no RPE damage may not present pathological features in FA.[16]

Regarding the effectiveness, no difference in BCVA, CMT or SFCT at the last follow-up visit was found when comparing the results of FA *versus* ICGA-guided PDT. However, Hayashida *et al*[15] reported a lower proportion of eyes with complete SRF resolution after FA-guided PDT at 3 months (72% *versus* 94%, *p*=0.04). If not rejected, those patients were submitted to another half-time PDT four or more months after the first session, which led to the lack of differences at 6 and 12 months. Although no significant differences were found regarding recurrence or persistence of SRF, the same authors reported worse results with FA-guided PDT when a composed outcome, recurrence and/or persistence of SRF, was considered.[15] Of note, this was the only study employing half-time PDT. This fact by itself should not justify these results as half-dose and half-time FA-guided PDT have been demonstrated to be similarly effective and safe in treating CSC,[12] but with a lower recurrence rate than reported by Hayashida *et al*.[15] This discrepancy might be related to the longer duration of symptoms in the work by Hayashida *et al*.[15]

The studies hereby revised that used half-dose PDT[16,17] found no differences in the outcomes of interest at any timepoint. Moodi *et al*[17] reported a complete resolution of SRF in all treated eyes. In this work, there was no significant difference in spot size or number between angiography modalities, which means that the same area was covered with the treatment regardless of the guide. The results of Ebrahimiadib *et al*[16] question the benefit of treating areas without overt RPE damage, as FA-guided PDT was as effective as its comparator but with smaller and fewer spots and less energy.[16] Of note, this study had the shortest follow-up period reported (4 months). So, validation of FA-guided PDT with a randomized controlled trial (RCT) of longer duration is warranted. In addition, it needs to be clarified if FA-guided PDT as a primary approach leads to lower energy used and smaller spot size with the same effectiveness and, if so, the specific indications to select the best candidates. The role of both approaches must be assessed for acute and chronic CSC

separately as, despite the same pathophysiology, the choroidal changes and RPE damage are substantially disparate.

The reduction of choroidal hyperpermeability seems to be the key effect of PDT in CSC treatment. As ICGA allows a better visualization of choroidal changes and the main trials comparing CSC treatments used this modality as reference, the authors recommend the resource to ICGA-guided half-dose PDT, whenever possible. If not available, FA-guided half-dose PDT is an adequate alternative as it seems to be similarly effective and safe. In cases of recurrence after PDT guided by FA, referral to centers with ICGA may be a prudent option. Non-invasive modalities, including OCT and OCT-angiography (OCTA), can also be useful in this scenario. Changes of choroidal thickness after PDT have been demonstrated.[32,33] Future research must address the potential association between choroidal thickness measured by OCT, and CVH demonstrated by ICGA, and its potential role to refine the zone of treatment.

This work has some limitations. A small number of studies enrolling a limited number of eyes were revised and two PDT protocols were included. However, despite non-randomized, the studies were well-conducted, enrolling balanced groups of patients, no losses to follow-up, and using the same units for BCVA and the same OCT machine for retinal and choroidal measurements. We were able to summarize and compared the main functional and anatomic outcomes after PDT and to provide recommendations for clinical practice and future research.

CONCLUSION

In summary, the evidence produced so far suggests that FA and ICGA-guided half-dose PDT are similarly effective and safe in treating chronic CSC. Half-time FA-guided PDT seems to have less success in complete resolution of SRF after a single session but without differences in 12-month outcomes (including eyes after retreatment) and re-treatment rates. Thus, FA-guided half-dose PDT might be a good alternative as primary approach if ICGA is not available.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

All authors contributed substantially to the conception and planning of the study; AF, RJV, and BCV collected the data; AF and RJV analyzed the data; all authors were responsible for interpreting the data; AF drafted the manuscript; all authors reviewed the manuscript for critical intellectual content; all authors gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Todos os autores contribuíram substancialmente para a conceção e o planeamento do trabalho; AF, RJV e BCV realizaram a recolha de dados; AF e RJV analisaram os dados; todos os autores foram responsáveis pela interpretação dos dados; AF redigiu o manuscrito; todos os autores reviram o trabalho quanto ao conteúdo intelectual de importância crítica; todos os autores deram a aprovação final da versão a publicar e concordam em ser responsáveis por todos os aspetos do trabalho.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse.

Apoio Financeiro: Este trabalho não recebeu qualquer subsídio, bolsa ou financiamento.

Proveniência e Revisão por Pares: Não solicitado; revisão externa por pares.

ETHICAL DISCLOSURES

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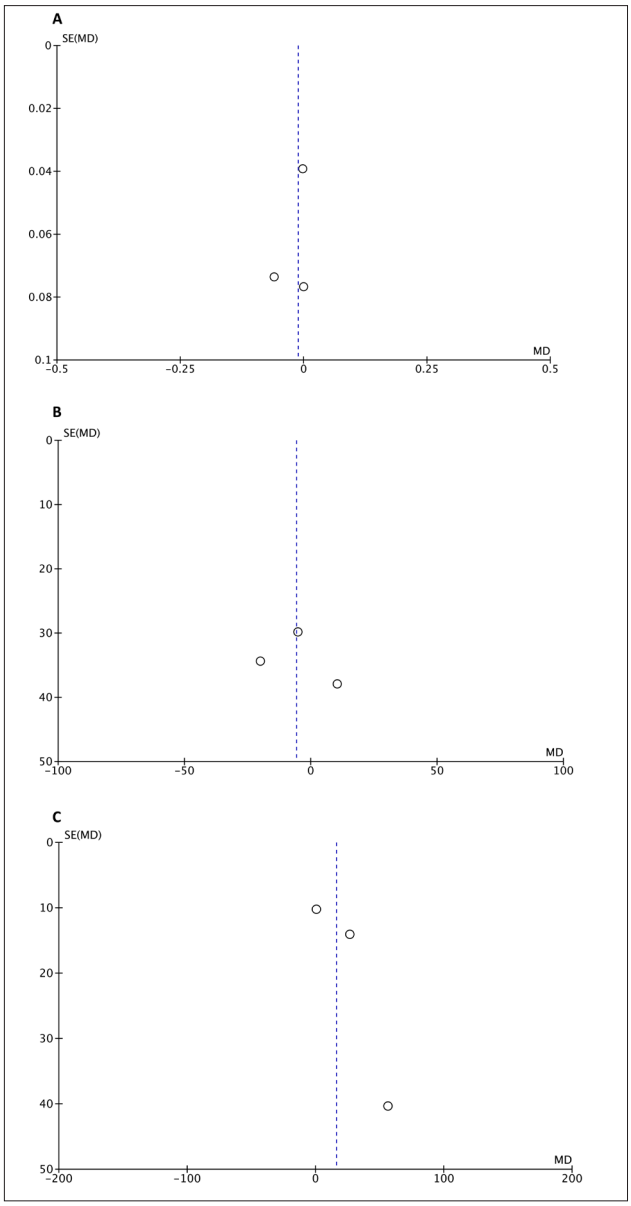
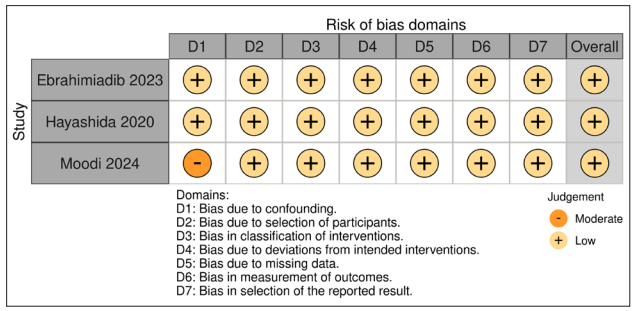
Supplementary Table 1. Search queries.

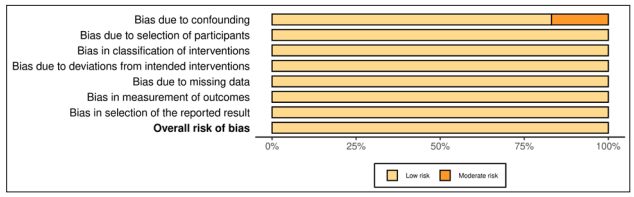
Search database	Dates	Search query
MEDLINE	Inception – May 26th, 2024	1: exp Central Serous Chorioretinopathy/ 2: (central serous adj2 (retinopath$ or chorioretinopath$)).tw. 3: (retinitis adj3 (angiospastic$ or serosa or capillarospastic or capillarospastic or angiosplastic)).tw. 4: (retinopath$ adj3 (angiospastic$ or serosa or capillarospastic or capillarospastic or angiosplastic)).tw. 5: (central$ adj3 (retinitis or serosa)).tw. 6: 1 or 2 or 3 or 4 or 5 7: exp Photochemotherapy/ 8: photodynamic.tw. 9: 7 or 8 10: 6 and 9 11: exp Indocyanine green/ 12: (indocyanine adj3 green).tw. 13: (ICG or ICGA).tw. 14: 11 or 12 or 13 15: exp Fluorescein/ 16: (Fluorescein or FFA).tw. 17: 15 or 16 18: 14 and 17 19: 10 and 18 20: exp Angiography/ 21: angiograph$.tw. 22: 20 or 21 23: 10 and 22 24: 19 and 23
Web of Science	Inception – May 26th, 2024	1: TS=("central serous" NEAR/2 (retinopath? OR chorioretinopath?)) OR TS=(retinitis NEAR/3 (angiospastic? OR serosa OR capillarospastic OR capillarospastic OR angiosplastic)) OR TS=(retinopath? NEAR/3 (angiospastic? OR serosa OR capillarospastic OR capillarospastic OR angiosplastic)) OR TS=(central? NEAR/3 (retinitis OR serosa) 2: TS=(photodynamic) 3: TS=(indocyanine NEAR/3 green) OR TS=(ICG OR ICGA) 4: TS=(Fluorescein OR FFA) 5: TS=(angiograph?) 6: #1 AND #2 AND #3 AND #4 AND #5
Scopus	nception – May 26th, 2024	(TITLE-ABS-KEY ("central serous" PRE/2 (retinopath? OR chorioretinopath?)) OR TITLE-ABS-KEY (retinitis PRE/3 (angiospastic? OR serosa OR capillarospastic OR capillarospastic OR angiosplastic)) OR TITLE-ABS-KEY (retinopath? PRE/3 (angiospastic? OR serosa OR capillarospastic OR capillarospastic OR angiosplastic)) OR TITLE-ABS-KEY (central? PRE/3 (retinitis OR serosa))) AND (TITLE-ABS-KEY (photodynamic)) AND (TITLE-ABS-KEY (indocyanine PRE/3 green) OR TITLE-ABS-KEY (icg OR icga)) AND (TITLE-ABS-KEY (fluorescein OR ffa)) AND (TITLE-ABS-KEY (angiograph?))
Cochrane Library	Inception – May 26th, 2024	#1: MeSH descriptor: [Central Serous Chorioretinopathy] explode all trees #2: central serous near/2 (retinopath* or chorioretinopath*) #3: retinitis near/3 (angiospastic* or serosa or capillarospastic or capillarospastic or angiosplastic) #4: retinopath* near/3 (angiospastic* or serosa or capillarospastic or capillarospastic or angiosplastic) #5: central* near/3 (retinitis or serosa) #6: #1 or #2 or #3 or #4 or #5 #7: MeSH descriptor: [Photochemotherapy] explode all trees #8: photodynamic #9: #7 or #8 #10: MeSH descriptor: [Indocyanine Green] explode all trees #11: indocyanine near/3 green #12: ICG or ICGA #13 #10 or #11 or #12 #14 MeSH descriptor: [Fluoresceins] explode all trees #15 Fluorescein or FFA #16 #14 or #15 #17: MeSH descriptor: [Angiography] explode all trees #18: angiograph* #19: #17 or #18 #20: #13 and #16 and #19 #21: #6 and #9 and #12 and #13 and #16 and #19



Supplementary Figure 1. Funnel plots for the assessed outcomes.



Supplementary Figure 2. Risk-of-bias assessment by ROBINS-I domain for the included studies.



Supplementary Figure 3. Summary of risk of bias across ROBINS-I domains for the included studies.