META-ANALYSIS OPEN ACCESS

The Effectiveness of Sub-Threshold Laser Versus Spironolactone for the Treatment of Central Serous Chorioretinopathy: A Systematic Review and Meta-Analysis

Amber Khalid [1], *Aveen Fatima* [1], *Quratulain Saleem* [1]
[1]*Department of Ophthalmology, Ziauddin University, Karachi, Pakistan.*

ABSTRACT

Background: The purpose of this systematic review and meta-analysis was to evaluate the efficacy of sub-threshold laser versus spironolactone for the treatment of central serous chorioretinopathy (CSCR).

Methods: A comprehensive search was conducted using PubMed, Cochrane, EMBASE, and Google Scholar for randomized controlled trials, comparative and individual studies on spironolactone and sub-threshold laser in the treatment of CSCR. This search was performed according to PRISMA guidelines, covering studies published from January 2010 up to August 2024. Studies published were selected based on inclusion criteria, including patients with CSCR≥ 3 months and outcomes such as best corrected visual acuity (BCVA), sub-retinal fluid resolution (SRF), and central macular thickness (CMT). Studies other than RCTs or those without relevant outcome measures were excluded from the meta-analysis. Data synthesis was conducted using RevMan 5.4.1, effective sizes were presented as Mean difference (MD) with a 95% confidence interval. Heterogeneity was assessed using the I^2statistic. The risk of Bias for each study was conducted using the revised Cochrane Risk of Bias Tool for RCTs.

Results: 8 studies, comprising 371 eyes, met the inclusion criteria. Spironolactone demonstrated a significant reduction in SRF at the 3rd and 6th month follow-up as compared to sub-threshold (MD= -27.93, 95% CI -41.61 to -14.06, P< 0.0001). The sub-threshold laser was more effective in reducing SRF at 6th month (MD= -41.61, 95% CI -69.21 to-12.90, P=0.004). No statistical difference was found between the 2 treatments for BCVA improvement. The sub-threshold laser was seen more effective in reducing CMT in the 6th month (MD= 47.99, 95% CI 31.20 to 64.77, P< 0.00001). Heterogeneity was substantial in some outcomes, indicating variability across the studies (I^2> 75%).

Discussion: Spironolactone appeared more effective in reducing SRF in CSCR, while sub-threshold laser showed greater efficacy in reducing CMT. Both treatments offer benefits, but further larger-scale, multi-center trials are required to address the observed heterogeneity and long-term efficacy.

Systematic Review Registration: PROSPERO ID: (CRD42024596399).

Keywords: Central Serous Chorioretinopathy, Spironolactone, Sub-Threshold Laser.

Corresponding Author:
Dr. Amber Khalid,
Department of Ophthalmology,
Ziauddin University, Karachi, Pakistan.
Email: dr.arain@gmail.com
ORCID: https://orcid.org/0000-0002-2135-089X
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INTRODUCTION

Central Serous Chorioretinopathy (CSCR) is characterized by the accumulation of serous fluid beneath the neurosensory retina, leading to a localized serous detachment [1]. The exact pathogenesis of CSCR is not fully understood but is believed to result from hyper-permeability of choroid and dysfunction of retinal pigment epithelium (RPE), which comprises of the blood-retinal barrier and leads to accumulation of sub-retinal fluid (SRF) [2]. CSCR is often associated with stress, and corticosteroid use and predominantly affects young men aged 30-50 years [3]. The prevalence of CSCR in males has been seen to be 9.9/10,000, six times higher than in women, 1.7/10,000. Patients usually experience symptoms such as blurred vision, central scotoma, and visual distortion [4]. CSCR can be characterized as acute and chronic, each with distinct progression and treatment strategies[5]. Acute CSCR is referred to as a condition that resolves within 3- 6 months and vision returns to normal in 80% of cases with recurrence seen in 50% of cases. 15% of the cases in CSCR follow the chronic course which persists for more than 12 months [6].

The diagnostic investigations include Optical Coherence Tomography (OCT) to assess the accumulation of fluid and Fundus Fluorescein Angiography to identify the area of leakage [7]. The acute CSCR often resolves spontaneously within 2-3 months, chronic CSCR requires intervention to prevent long-term visual impairment. The treatment includes photodynamic therapy, sub-threshold laser, anti-vascular endothelial growth factor injection (VEGF), and oral mineralocorticoid drugs [8]. The first line approach in mild or first-time cases is observation with lifestyle modification, including stress reduction, discontinuation of steroids, stopping smoking, and control of blood pressure [9].

In cases requiring treatment, pharmacological treatment has shown promising results. Mineralocorticoid receptor antagonists like Eplerenone and Spironolactone help to reduce choroidal hyperpermeability and promote fluid reabsorption [10]. Other options include Rifampin, which increases choroidal metabolism, and Mifepristone, a glucocorticoid receptor antagonist under investigation for treatment of CSCR [11]. For persistent and chronic cases, laser and photodynamic therapy (PDT) are effective treatment modalities. The half–dose PDT with verteporfin remains the effective option for the treatment option for chronic CSCR, as it reduces the choroidal hyper-permeability and improves the retinal functional with minimal collateral damage[12]. Focal laser photocoagulation can be applied to the extra foveal leakage site to accelerate resolution. Sub-threshold laser therapy, such as micro pulse laser, has emerged as a safer alternative to traditional laser photocoagulation, as it minimizes retinal damage by delivering a non-continuous energy pulse to stimulate RPE repair without causing visible burns. This technique is particularly useful in cases where the leakage site is closer to fovea [13].

In some cases, intravitreal anti-vascular endothelial growth factors (VEGF) like Ranibizumab and Aflibercept may be beneficial, especially when choroidal neovascularization is present [14]. The prognosis of CSCR is generally favorable but chronic cases require aggressive management to achieve optimal visual outcome. Regular follow-up is essential to assess the treatment response [15]. There has been limited research available on this topic both in Pakistan and internationally with no existing Meta-analysis. The absence of comprehensive evidence leads to uncertainty in clinical decisions. The meta-analysis aimed to assess the efficacy of sub-threshold versus Spironolactone for the treatment of CSCR. Specifically, the analysis seeks to determine which treatment options results in better visual outcomes and complete resolution of sub-retinal fluid with lesser side effects, thereby guiding clinical decision-making for managing CSCR effectively.

METHODS

Study Design

A systematic review and meta-analysis of randomized studies were conducted following the 2020 "Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines"[16]. For all practical and analytic aspects of the study, we were adherent to the Cochrane recommendation. The study protocol was registered on PROSPERO (ID: CRD42024596399) before the commencement of the research[17].

Inclusion Criteria

The inclusion criteria were based on adults ≥ 18 years diagnosed with central serous chorioretinopathy (CSCR) ≥ 3 months, confirmed by clinical examination and imaging (Optical coherence tomography, Fundus Fluorescein Angiography). Chronic CSCR is defined as a persistent of symptoms. All retrospective and prospective clinical trials published in English and approved by appropriate ethical approval committees were included. Both comparative studies (directly comparing sub-threshold laser and spironolactone) and separate studies (evaluating either intervention independently) were included. Studies must involve sub-threshold laser with parameters wavelength 577nanometer, spot size 100-300 microns, 50-200 millivolt power, 100-500 millisecond pulse duration, and 1-5% duty cycle. Studies must involve spironolactone with a dosage of 50-60 mg/day in divided doses twice or thrice a day. Comparative studies must include sub-threshold versus spironolactone including dosages and all parameters as separate studies, there should be clear information about the parameters and dosage. Studies must include all the following outcomes related to the effectiveness of treatment: Visual acuity assessment was done by using Snellen's chart/ log MAR, and retinal fluid resolution and central macular thickness was measured by OCT with a minimum of 3 months follow-up.

Exclusion Criteria

Studies with participants with secondary CSCR (such as steroid-induced), individuals with significant comorbid ocular conditions which affect outcomes such as glaucoma, hypertensive retinopathy, Diabetic retinopathy and age-related macular degeneration) were excluded from the meta-analysis. Case reports, reviews, comparative studies assessing different treatment options, studies involving individual or comparative therapies that do not follow the intervention protocol, using different wavelength lasers, using different sub-threshold laser parameters or using different doses of drugs were not included. Studies that do not assess the outcome on each follow up visit or missed some outcome. Studies published in a language other than English and ones with a high risk of bias, as determined by quality assessment tools, were excluded.

Literature Search Strategy

A PRISMA-based search strategy employing Boolean operators and the PICO (Patient, Interventional, Control, and Outcome) framework was implemented across online databases including PubMed, Cochrane, EMBASE, and Google Scholar. The Boolean operators OR and AND were used to connect various synonymous MeSH (Medical Subject Headings) terms. The search terms included effectiveness of sub-threshold versus spironolactone for the treatment of central serous chorioretinopathy, Role of sub-threshold laser in the treatment of CSCR, and Efficacy of Spironolactone for the treatment of CSCR. All relevant RCTs were selected for our meta-analysis from January 2010 up to August 2024, without applying any filters based on language, publication date, author's name, and institute or country of publication. Additionally, the search was broadened by employing backward snowballing to explore the references of the article that initially met our predefined selection criteria. A comprehensive overview of the search strategy is outlined in **Table 1**.

Study Selection

The literature screening was conducted using Rayyan AI, a web-based application designed to assist in systematic reviews and meta-analysis18. A redundancy check was implemented to exclude duplicate articles from the dataset. The remaining articles were meticulously screened by two independent authors (AK and AF) based on their titles and abstracts to ensure they met the defined selection criteria. Any discrepancies were thoroughly discussed and resolved with input from a third author (QS).

Data Extraction

Research and participant characteristics were extracted into an Excel sheet, including study framework, population characteristic, sample size, group-specific participant count, general patient's characteristics, follow- up and outcome. This data was verified by two independent authors (AK and AF). Any discrepancies were addressed through discussion and consensus with a third reviewer (QS).

Study Quality Assessment

Two reviewers (AK and AF) separately evaluated the robustness of the shortlisted studies using the revised Cochrane Risk of Bias Tool for RCTs[19]. They analyzed studies based on the method used for generating allocation sequence, randomization of participants, and handling of missing data. Any discrepancies were resolved through consensus.

Data synthesis

The data synthesis was conducted using RevMan 5.4.1 software, provided by the Cochrane Collaboration[20]. Our meta-analysis included two RCTs comparing the efficacy of sub-threshold laser and Spironolactone treatment[21,22]. Due to the limited amount of comparative data, the analysis was supplemented by incorporating six additional RCTs: three focusing on sub-threshold laser alone, [23, 24, 25], and three assessing Spironolactone alone [26, 27, 28]. Data from each outcome were entered to generate forest plots. To provide a standardized control for comparison, the control group data from

the Sinawat 2020 study were used for spironolactone in the sub-threshold laser-only studies and for sub-threshold laser in the spironolactone-only studies. For each outcome, BVCA, CMT, SRF, Risk Ratio (RR), and Mean difference (MD) were calculated and presented using a forest plot. The meta-regression was expressed as a coefficient (COeff) with corresponding P-values. A random-effect model was employed for the meta-analysis and meta-regression, pooling the risk ratio along with a 95% confidential interval. Statistical significance was defined as a P-value of < 0.05. Heterogeneity was evaluated using the Higgin'SI^2 test, with the value of I^2= 25-50% considered mild, 50-75% moderate, and >75% indicative of substantial heterogeneity. Sensitivity analysis was applied to the subgroups to ensure the reliability of the outcomes.

Risk of Bias

The risk of bias for included studies was evaluated using the Cochrane Risk of Bias tool for randomized controlled trials. The assessment focused on study design, adherence to the intended intervention, handling of missing outcome data, outcome measurement, and the selection of reported results. Each study was rated as having low risk, moderate, or high risk of bias based on these domains. For studies with unclear methodology, additional information was sought where possible to clarify potential biases.

RESULTS

The search identified 194 records, out of which 19 were duplicates and 4 were in non-English language. 154 of the remaining were considered irrelevant due to different treatment strategies used for comparison. This resulted in 17 records being retrieved in full text for eligibility assessment. After comprehensive evaluation 8 studies were found eligible and included for quantitative analysis. An overview of this process is provided in the PRISMA Chart **(See Figure 1)**.

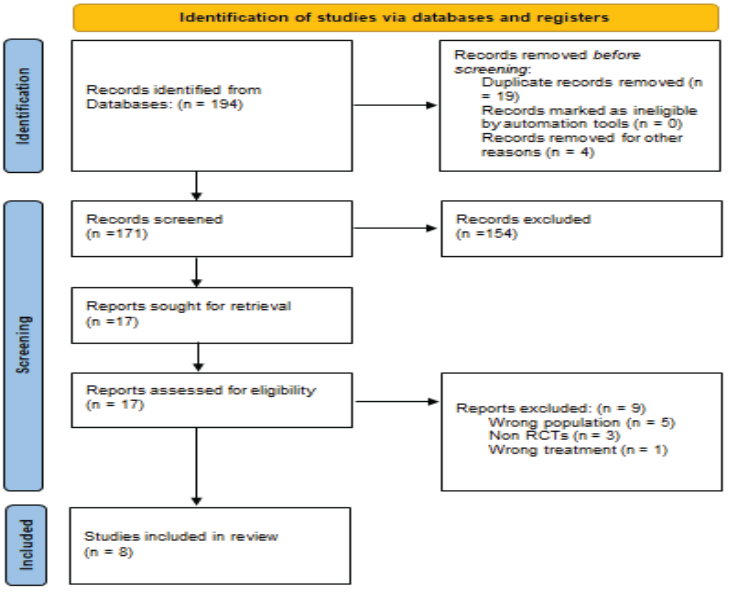

Figure 1: PRISMA Flowchart

Characteristics of Eligible Studies

The 8 eligible studies included in the meta-analysis comprised 371 eyes of chronic CSCR patients. Among these, 204 patients received sub-threshold laser therapy while 167 were treated with Oral Spironolactone. The age and gender distribution of the study groups were consistent across all studies. The average age of patients was found to be 46.96 years. On average, males constituted the majority across all studies, with a male-to-female ratio of 3.39:1. Males accounted for 77.24% of the total population, while females represented 22.76%. The mean follow-up period was 7.82 ± 3.36 months. All the studies included a mean baseline BCVA of 0.31 ± 0.3. Table 1 outlines the baseline characteristics of each study included.

Primary Outcomes

Table 1 : Demographic and clinical characteristics of individual studies

Authors	Treatment	Study type	Duration of Study	Total patients	Mean age	Male	Female	Duration of disease (month)	Duration of treatment (month)	Resolved CSCR	Un-Resolved CSCR
Mercuri 2024	Sub-threshold vs Spironolactone	RCT Retrospective	4 year	Sub-threshold 47 Spironolactone 36	48.95± 9.0	Sub-threshold 43 Spironolactone 36	Sub-threshold 4 Spironolactone 11	12	1.34±0.56	Sub-threshold 73% Spironolactone 66%	Sub-threshold 27% Spironolactone 33%
GOA 2024	Sub-threshold vs Spironolactone	RCT Retrospective	1.5 year	Sub-threshold 35 Spironolactone 29	47.83±9.04	Sub-threshold 35 Spironolactone 29	Sub-threshold 6 Spironolactone 8	17.28± 27.66	≤3	Spironolactone 76.9% Sub-threshold 80.6%	Sub-threshold 19.4% Spironolactone 23.1%
Altine 2021	Sub-threshold	RCT Prospective	1.5 year	39	46.72±8.61	26	13	-	1-3 treatment session 6-9 month	69.2%	30.8%
Isik 2020	Sub-threshold	RCT	3 year	58	42.4±9.9	47	11	5.1± 1	11.4± 8.5	67.2%	32.8%
Uzlu 2021	Sub-threshold	RCT Retrospective	3.5 year	19	48.9± 9.40	13	6	12.5 ± 11.3	3-6	-	-
GAO 2 2024	Spironolactone	RCT Retrospective	1 year	42	46±0.6	29	13	7.16± 2.97	2-6	57.1%	42.9%
Herold 2017	Spironolactone	RCT Prospective	1.6 year	20	47± 6	15	5	5.2±16	1-3.5	75%	25%
Sinawat 2020	Spironolactone vs Control	RCT Retrospective	6 year	Spironolactone 12 Control 15	44.27±8.5	Spironolactone 12 Control 26	Spironolactone 9 Control 15	4.24±1.92	4.85±1.42	66%	44%

The individual data of included studies including demographic information and clinical assessment, treatment option and outcome were shown in **(Table 1).** The study duration ranged from 1 to 6 years. The mean ages were between 42.4 and 48.95 years with predominantly male participants. The sub-threshold laser showed higher resolution rates (66%-80.6%) ass compared to Spironolactone (57.1%-76.9%). Studies with focused on Spironolactone only showed higher unresolved rates as compared to those with Sub-threshold as the only intervention.

Risk of Bias Assessment

Table 2: Risk of Bias Summary Based on Cochrane's Risk of Bias Tool

Study	Randomization Process	Deviations from Intended Interventions	Missing Outcomes Data	Measurements of Outcomes	Selection of Reported Results	Overall Risk of Bias
Mercuri 2024	Some concerns	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
GOA 2024	Low Risk	Low Risk	Low Risk	Some concerns	Low Risk	Low Risk
Altine 2021	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Isik 2020	Low Risk	Low Risk	Low Risk	Some concerns	Low Risk	Low Risk
Uzlu 2021	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
GAO 2 2024	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Herold 2017	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Sinawat 2020	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

The risk of bias for each included study was assessed using Cochrane's Risk of Bias 2 (RoB 2) tool **(Table 2)**. Each study was evaluated across the 5 domains: randomization process, deviations from intended interventions, missing outcomes data, measurements of outcomes, and selection of reported results. They were categorized as having low risk, some concerns, or high risk. The assessment indicated a predominantly low risk in most categories in 87.5% (7) of the studies. However, 12.5% (1) study raised some concerns regarding the randomization process while 25% (2) of the studies showed some concerns in the measurement of outcomes.

Sensitivity Analysis

An analysis of sensitivity was performed for the outcomes with heterogeneity greater than 50% to

assess the impact of individual studies on the overall variability. For BCVA in 3rd month, removing Isik 2020 reduced the heterogeneity (I2) from 92% to 1%, with the recalculated MD showing a slight shift from MD= 0.06, 95%CI-0.12 to 0.24; P=0.53; I^2= 92%) to MD= -0.01, 95%CI-0.07 to 0.05; P=0.42; I^2= 1%) indicating that the study contributed significantly to the observed heterogeneity. Similarly, for CMT at 3rd month, the exclusion of Isik 2020 led to a decrease in heterogeneity from 58.1% to 17%, with the MD changing from (MD -14.47, 95% CI -37.41 -8.46; P= 0.22), I^2= 58.1%) to (MD -1.50, 95% CI -17.92, 14.93; P= 0.30), I^2= 17%) improving the consistency across studies. In the analysis of SRF at 6th, removing month GAO2 within the subgroup reduced the heterogeneity from 83% to 0% with MD going from 97(95%CI 70.48 -123.52; I^2=83), to 48.22(95%CI 9.58 – 86.85; I^2=0), resolving the variability in this outcome. These adjustments demonstrated that certain studies were driving the heterogeneity in results.

All 8 reported studies assessed BCVA, SRF, and CMT at 3 months follow-up as an outcome. For the BCVA comparative studies of sub-threshold laser versus spironolactone no statistically significant effect was observed compared to control (MD=-0.06, 95% CI -0.17 to 0.05; P=0.25; I^2 =0%). Subgroup analysis for sub-threshold laser alone and spironolactone laser alone and spironolactone were not estimable due to insufficient data. The reported mean difference ranged from -0.02 to 0.05 for the Sub-threshold group and 0.04 to 0.13 for the Spironolactone only group with a confidence interval indicating no significant improvement. The low heterogeneity (1^2=0%) suggests consistency across studies, reinforcing that neither treatment is superior in improving BCV at 3 months. **(Figure: 1)**

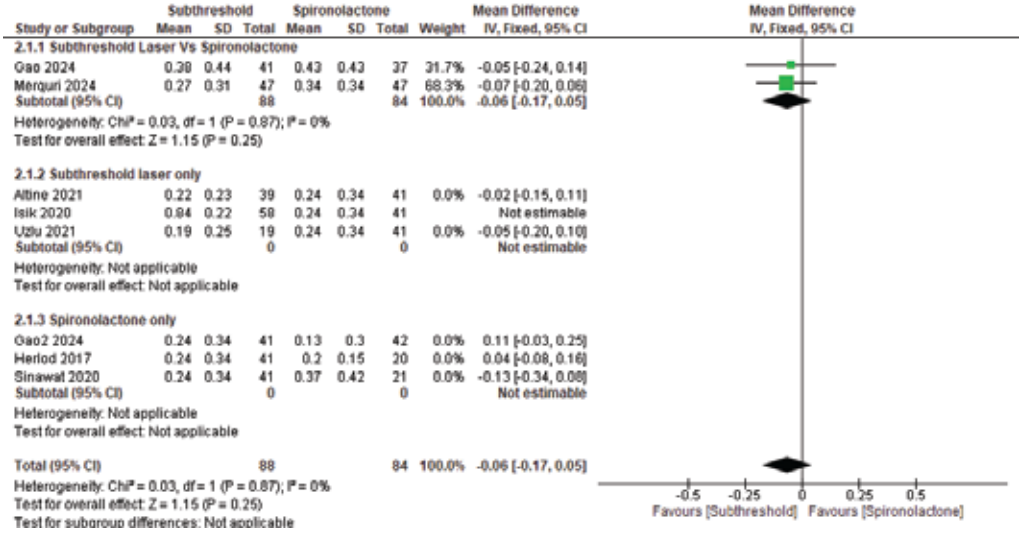

Figure: 1 Forest plot of best corrected visual acuity outcome at 3rd-month green square and their respective lines are the point estimate and 95% confidence intervals per study. Small black diamond showed study subgroups and large diamond represent pooled effect estimate.

The forest plot compares the 3-month Sub-retinal fluid (SRF) outcomes between sub-threshold laser and spironolactone treatments. The overall mean difference is −12.62 (95% CI: −39.74 to 14.49), indicating no significant difference between the two interventions (p = 0.36). Subgroup analyses for sub-threshold laser alone and spironolactone alone were not estimable due to insufficient data, with wide confidence intervals suggesting no clear advantage. The reported mean differences ranged widely, from −54.13 to -127.04 for sub-threshold laser only and 11.90 to 37.50 for the spironolactone-only group. Moderate heterogeneity (I^2=52%) indicates some inconsistency among studies, reinforcing that neither treatment demonstrates a clear advantage in reducing CMT at 3 months. **(Figure: 2)**

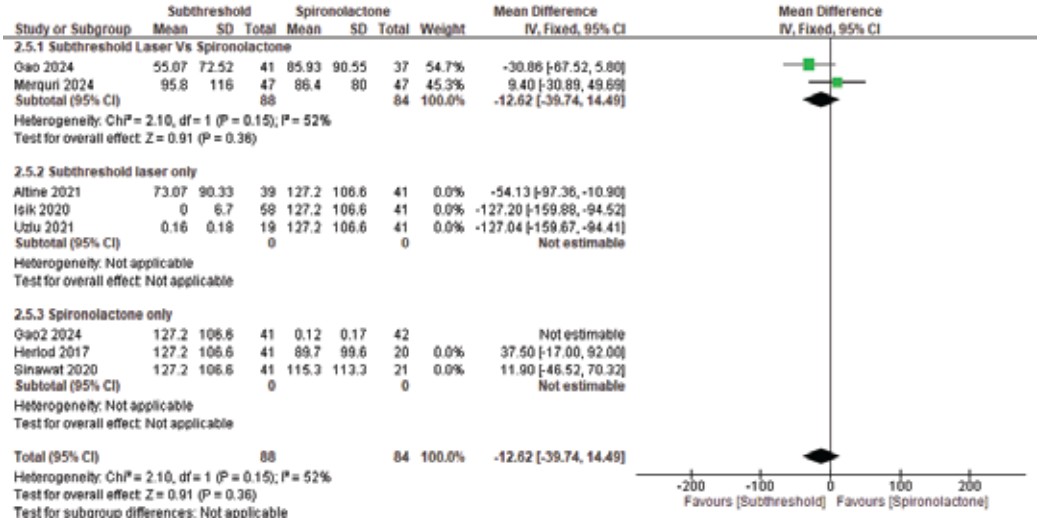

Figure: 2 The Forest Plot of Sub- Retinal fluid outcomes at 3rd month green square and their respective lines are the point estimate and 95% confidential intervals per study. Small black diamond showed study subgroups and large diamond represent the pooled effect estimate. The data was assessed quantitatively on basis of level of fluid present.

The forest plot evaluates central thickness (CMT) at 3 months, comparing sub-threshold laser and spironolactone treatments. The overall mean difference is 7.34 (95% CI: -4.91, 19.59), suggesting no significant difference between the two interventions (p = 0.24). High heterogeneity (I^2 = 74%) indicates substantial variability across studies. Subgroup analysis for sub-threshold laser alone and spironolactone alone was not estimable due to limited data, with wide confidence intervals. The reported mean differences varied widely, from -34.50 to -17.74 for Sub-threshold only and -9.90 to 20.33 for Spironolactone group indicating no significant difference between the two interventions. **(Figure: 3).**

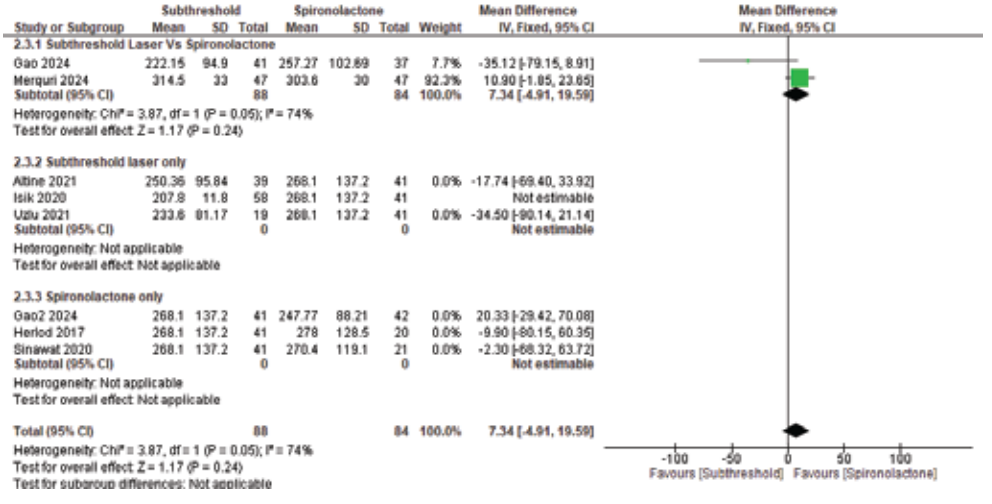

Figure: 3 The Forest Plot of central macular thickness outcome at 3rd month green square and their respective lines are the point estimate and 95% confidential intervals per study. Small black diamond showed study subgroups and large diamond represent pooled effect estimate.

To assess the long term outcome of both studies, the 6th month follow-up results for BCVA, SRF and CMT were also analyzed. However due to limited availability of comparative data forest plots could not be utilized for the analysis. In comparative studies (Spironolactone versus Sub-threshold laser) the outcome related to BCVA showed no significant difference (MD: 0.04, 95% CI -0.09 -0.17; P= 0.54), with no heterogeneity reported. In Sub-threshold only group, all 3 studies showed non- significant overall effect (MD; 0.02, 95%CI -0.10 -0.14; P= 0.74; I^2= 0%) showing consistency across the studies with no heterogeneity. For the spironolactone group

no statistically significant difference was found between 3 studies (MD; 0.02, 95% CI-0.01 -0.14; P =0.74; I^2 =47%). In the overall analysis, there was no statistically significant difference between sub-threshold laser and Spironolactone (MD; 0.00, 95% CI -0.07; P= 0.99; I^2=31%, indicating the similarity between two interventions.

An overall statistically significant reduction in SRF level was observed in studies of Spironolactone versus sub-threshold laser (MD; -32.25, 95%CI -48.02- TO -16.48; P<0.00001; I^2=97%). For the comparison between sub-threshold versus Spironolactone, 1 study (Gao2024) reported a mean difference of -30.90(95%CI -68.92 - 7.12), showing no statistical difference between 2 groups and no heterogeneity was reported. In sub-threshold only group all 3 studies showed significant reduction in SRF with mean difference (MD; -129.15, 95%CI -152.05 to -106.25; P<0.00001; I^2=43%). In contrast, for the Spironolactone only group reported a significant mean difference of 97(95%CI 70.48 -123.52, with substantial heterogeneity (I^2=83%). Overall, the analysis demonstrated a significant effect favoring Spironolactone in reduction SRF, although there was high heterogeneity (I^2= 97%) among the studies. The test for subgroup differences was also found significant (P<0.00001; I^2= 98.8%) indicating that the treatment effects differed significant across the analyzed subgroups.

CMT was assessed at 6th month showing statistically significant difference favoring sub-threshold laser was observed as compare to Spironolactone (MD; 47.99, 95% CI 31.20 – 64.77; P<0.001; I^2 =97%). Regarding the sub-threshold versus Spironolactone 1 study (Gao 2024) reported a significant mean difference 200.60; 95% CI 170.82 – 230.38), favoring sub- threshold laser, with no heterogeneity reported (I^2= 0%). In sub-threshold group 3 studies showed a significant difference (MD; -95.61, 95% CI -123.05 to -68.17; P< 0.001; I^2=0%. In contrast, for the spironolactone only group reported mean difference 65.89, 95% CI 34.85 – 95.30; P< 0.001; I^2=0%). Overall, a significant effect in favor of sub-threshold laser was observed, but high heterogeneity (I^2=97%) indicates variability in study results. The test for subgroup difference was also significant (P<0.001; I^2= 99%) suggesting the treatment effect differs across the subgroup analyzed.

DISCUSSION

Central serous retinopathy (CSCR) is a common retinal condition characterized by serous detachment of the neurosensory retina [29]. CSCR is caused by a combination of choroidal vascular dysfunction and retinal pigment epithelial impairment [30]. An increase in choroidal permeability and hydrostatic pressure leads to leakage of fluid leakage, while retinal pigment epithelium (RPE) fails to pump out the accumulated fluid, resulting in serous retinal detachment [31]. The CSCR is a multifactorial disease, elevated levels of corticosteroids whether endogenous (stress) or exogenous (medication) play a key role by increasing choroidal permeability and inhibiting RPE function. Systemic factors like hypertension, H. pylori, sleep disturbance and genetic predisposition, smoking, and alcohol may contribute to disease susceptibility [32]. Sub-threshold laser therapy, a non-damaging photo thermal approach, has emerged as a promising intervention to stimulate retinal pigment epithelium healing without causing visible retinal damage[33]. Spironolactone, a mineralocorticoid receptor antagonist, has shown potential in the treatment of CSCR due to its effect on choroidal permeability and fluid regulation. By blocking the mineralocorticoid receptors Spironolactone reduces the choroidal congestion, decreases fluid leakage, and improves RPE function. These both provide safer and more targeted treatment options for CSCR[34]. Patients with CSCR often experience varying degrees of visual disturbance and metamorphopsia [35]. Although the condition is typically self-limiting with a favorable visual prognosis, a significant number of cases exhibit recurrent episodes, while others develop persistent subretinal fluid despite the treatment [36]. Over time these recurrences and fluid persistence can lead to irreversible visual loss or long-term visual impairment[37]. Chronic CSCR may result in retinal pigment epithelium atrophy, causing progressive central vision deterioration [38]. Persistent sub-retinal fluid leads to photoreceptor damage, increasing the risk of permanent vision deficits [39]. In some cases, choroidal neovascularization and sub-retinal fibrosis may develop contributing to reduced visual acuity. Therefore, conducting a long-term follow-up is crucial to understand the underlying factors [40]. This meta-analysis aimed to compare the efficacy of sub-threshold laser therapy and oral spironolactone in the treatment of CSCR> 3 months based on the assessment of BCVA, SRF, and CMT. Our meta-analysis is the 1st of its kind to comprehensively evaluate these treatment modalities in CSCR, highlighting the unique contribution of our work to the existing literature. A rigorous search yields 194 records, ultimately leading to the inclusion of 8 studies and involving 371 eyes, which provide a robust basis for analysis. The analysis revealed that neither treatment demonstrated a statistically significant effect on BCVA at the three-month follow-up. Specifically, comparative studies of sub-threshold versus spironolactone resulted in a standard mean difference of 0.21, indicating no meaningful difference between the 2 modalities. Interestingly, sub-threshold laser therapy alone did

show a statistically significant benefit, but high heterogeneity (I^2= 96%) limits the interpretability of these results. The predominance of male participants (77.24%) and the consistent average age of 46.96 years across the studies suggest that this treatment may primarily target a specific demographic, which should be considered when generalizing findings. In terms of SRF reduction, the results indicated a significant advantage for spironolactone over sub-threshold laser treatment (MD -27.93), with an impressive p-value of< 0.0001 and high heterogeneity (I^2= 96%). Notably, the subgroup analyses highlighted that spironolactone consistency outperformed sub-threshold laser in SRF reduction at the 6th-month mark, further emphasizing the potential of spironolactone as a preferred treatment strategy for this condition. CMT assessment at the 3rd and 6th months received no statistical differences between treatments, indicating that while sub-retinal fluid may be reduced more effectively with spironolactone, it does not necessarily correlate with changes in macular thickness. This dissociation between SRF and CMT responses suggests that different mechanisms may underpin the therapeutic effects of these treatments and indicate that further need to investigate the biological processes. The finding suggests that while both modalities are effective in managing the CSCR, they may serve different therapeutic purposes. The significant reduction in SRF was associated with spironolactone suggesting its utility in managing fluid accumulation, which is often a primary concern in CSCR treatment.

While this meta-analysis provides valuable insight, it is not without limitations. The small number of studies and high heterogeneity observed in several outcomes necessitate caution in interpreting these results. Future research should aim to conduct larger, multicenter controlled trials that address these limitations, with a focus on long-term outcomes, quality of assessments, and potential side effects associated with each treatment. Additionally, exploring the underlying mechanism of action for both treatment modalities could enhance our understanding of their respective role in managing CSCR.

CONCLUSION

In conclusion, while both sub-threshold laser therapy and spironolactone play vital role in the management of CSCR. This meta-analysis advocates for the prioritization of spironolactone based on its superior performance in reducing the CSCR. As our understanding of chronic CSCR evolves, continued research will be essential in refining treatment protocols and enhancing patient care. The findings not only contribute valuable insights to the management of chronic CSCR but also emphasize the need for ongoing research to address the gaps in the literature and improve treatment strategies.

LIST OF ABBREVIATIONS

CSCR: Central serous chorioretinopathy
RPE: Retinal Pigment Epithelium
PDT: Photodynamic Therapy
VEGF: Vascular endothelial growth factor
BCVA: Best corrected visual acuity.
CMT: Central macular thickness
SRF: Sub-retinal fluid
MD: Mean difference
RR: Risk ratio
COeff: Co-efficient
I^2: Heterogeneity

CONFLICT OF INTEREST

None

AUTHORS' CONTRIBUTIONS

AK was responsible for conceptualization, methodology, data collection, writing the original draft, and supervision. **AF** contributed to writing the literature search, data extraction, and analysis. **QS** assisted in writing the literature search, data extraction, and proofreading.

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