Acta Ophthalmologica

Acta Ophthalmologica 2014

Review Article

System review and meta-analysis on photodynamic therapy in central serous chorioretinopathy

Jinlan Ma,[1] Nana Meng,[1] Xiaoyi Xu,[2] Fang Zhou[2] and Yi Qu[1]

[1]Department of Heallth Care, Qilu Hospital of Shandong University, Jinan, China
[2]Department of Ophthalmology, Qilu Hospital of Shandong University, Jinan, China

ABSTRACT.

Purpose: **To evaluate the effect of photodynamic therapy (PDT) on central serous chorioretinopathy (CSC) compared with laser therapy and intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) drugs, and to find the maximum treatment effect with minimal dose and fluence of PDT.**

Methods: **A systematic electronic search was conducted in Feb 2013 in PubMed, Embase, ISI Web of Knowledge and the Cochrane library. The main outcome factors were compared in best-corrected visual acuity (BCVA), central macular thickness (CMT) and resolution of subretinal fluid (SRF). Meta-analysis was performed when it is appropriate. The comparisons were designed into four groups: group 1, PDT versus laser photocoagulation; group 2, PDT versus intravitreal injection of anti-VEGF drugs; group 3, half-dose verteporfin PDT versus placebo; group 4, half-fluence PDT versus full-fluence PDT.**

Results: **We retrieved nine reports of studies including a total of 319 patients. In group 1, the summary result indicated that PDT was superior in resolution of SRF ($p = 0.005$) than laser photocoagulation. In group 2, PDT could resolute SRF ($p = 0.007$) and decrease CMT ($p = 0.002$) more rapidly than intravitreal injection of anti-VEGF drugs. In group 3, half-dose PDT was effective in improving BCVA ($p < 0.00001$), decreasing CMT ($p = 0.001$) and resolving SRF ($p < 0.001$). In group 4, half-fluence PDT was effective and could significantly decrease the hypoxic damage which was caused by PDT ($p < 0.001$).**

Conclusion: **PDT is a promising therapy for CSC patients and the parameters of PDT can be adjusted to obtain the maximum treatment effect with minimal adverse effects.**

Key words: central serous chorioretinopathy – meta-analysis – photodynamic therapy – system review – verteporfin

Acta Ophthalmol. 2014: 92: e594–e601

doi: 10.1111/aos.12482

Introduction

Central serous chorioretinopathy (CSC) is characterized by choroidal hyperperfusion and neurosensory retinal detachment secondary to focal retinal pigment epithelium (RPE) lesions (Gass 1967). The main pathogenic mechanism is believed to be focal or diffuse breakdown of the outer blood retinal barrier resulting from the defect in the barrier function and impairment in the resorptive capacity of the retinal pigment epithelium, which are considered to be secondary to the choroidal vascular changes (Pryds & Larsen 2012). The disturbances in choroidal circulation was proved by Indocyanine green (ICG) angiography and optical coherence tomography (OCT), which indicate that abnormalities of the choroidal vasculature may be an important element of CSC that includes hyperpermeability and venous congestion (Yang et al. 2013; Tan et al. 2014). CSC was reported to affect mostly young patients, between the ages of 20 and 45 years (Gass 1967; Gilbert et al. 1984; Yannuzzi et al. 1984), especially in men with a so-called type A personality (Yannuzzi 1987).

Common symptoms of CSC are decreased vision with visual distortion (metamorphopsia), altered colour vision, and black or grey areas or scotomas, and prolonged after-images. Most episodes of CSC are self-limiting and usually resolve spontaneously within 3–4 months (Yannuzzi 1987). However, in approximately 30% to 50% of cases, there may be recurrence, and patients may even experience irreversible and severe visual loss because of chronic neurosensory retinal detachment and RPE atrophy (Levine et al. 1989).

Therapy for this disorder has never been established clearly on the basis of its efficacy and safety. The current therapeutic strategies involve laser photocoagulation and intravitreal injection of anti-vascular endothelial growth factor (VEGF) drugs, including bevacizumab and ranibizumab. The well known treatment of laser photocoagulation to the site of leakage on the fluorescein angiography (FA) shortens the duration of macular detachment in

patients with CSC; however, it has the disadvantages of causing RPE damage and sometimes iatrogenic choroidal neovascularization (CNV) (Chan et al. 2008a,b). Several drugs with different mechanisms of action have been examined over the years (Tatham & Macfarlane 2006; Meyerle et al. 2007; Nielsen et al. 2007; Caccavale et al. 2009), among which anti-VEGF was a newer one, may be beneficial to the choroidal vascular hyperpermability in CSC (Lee et al. 2011).

Recently, several studies (Chan et al. 2008a,b; Reibaldi et al. 2009) reported that indocyanine green angiography (ICGA)-guided PDT with verteporfin leads to anatomic and functional improvement. At the beginning, it adopted standard parameters and standard dose of verteporfin, as described in Treatment of age-related macular degeneration with photodynamic therapy study (The TAP-study group 1999). However, complications appeared in some cases subsequently, including RPE atrophy and juxtafoveal CNV (Cardillo Piccolino et al. 2003; Chan et al. 2003). Patients with CSC usually have relatively good baseline visual acuity (VA), thus it is important to minimize the potential retinal toxicity during treatment while maintaining the treatment effects. Some studies reported the treatment of CSC with modified PDT parameters, including reduced dose of verteporfin or reduced fluence of irradiation, could minimize possible side effects (Lai et al. 2006; Chan et al. 2008a,b; Reibaldi et al. 2009; Lee & Kim 2011).

Some papers have already reviewed the efficacy and safety of PDT in CSC, most of them support PDT is a promising therapy for CSC, but there were no exact conclusion (Mennel et al. 2007; Ross & Mohamed 2011; Karim & Adelman 2013). Herein we performed a meta-analysis to quantify the effect of PDT in CSC compared with laser photocoagulation and intravitreal injection of anti-VEGF drugs, and to evaluate the efficacy and safety of half-dose verteporfin and half-fluence PDT in the treatment of CSC.

Methods

Search strategy and inclusion criteria

Two researchers independently searched the literature in four databases: the Cochrane Library, the PubMed database, ISI Web of Knowledge and EMBASE until February 2013. The search used the following keyword strings: 'central serous chorioretinopathy', 'photodynamic therapy', 'anti-VEGF therapy' and 'laser photocoagulation' in various combinations. To increase sample size, we included both randomized control trials (RCTs) and observational studies. Meanwhile, some studies were collected by manual searching. Because of appearing twice, or focusing on other outcomes based on the same study group, the duplicated publications were removed. In the beginning PDT has been extensively studied as a potential therapeutic option for chronic cases, but today PDT is also used in acute CSC. This treatment is effective for both chronic and acute CSC. In this study, 63 patients of Chan (Chan et al. 2008a,b) were diagnosed as acute CSC (duration of the symptoms was <3 month), other 256 patients of this study were chronic CSC (duration of the symptoms was >3 month).

Inclusion criteria

Studies were included if they (i) compared PDT with other therapies or compared different parameters of PDT; (ii) were RCTs or observational studies with at least 4-weeks' follow-up and (iii) contained sufficient information of treatment.

Data extraction

The following information was extracted by two investigators independently from published reports with a standardized protocol and reporting form: first author's last name, year of publication, study design, country of origin, the number of enrolled eyes, mean age and gender of patients, follow-up information.

Outcome measures

The primary outcomes measured for the meta-analysis included best-corrected visual acuity (BCVA) in log MAR; change in central macular thickness (CMT) from baseline; and complete resolution of subretinal fluid (SRF). The secondary outcomes were the incidence of adverse events including CNV and choriocapillaris nonperfusion during interventions. CMT was measured manually using the retinal thickness mode and was defined as the distance between the surface of RPE and the outer surface of the neurosensory retina at the fovea. Choriocapillaris nonperfusion was defined as described by Michels et al. (2006): Grade 0, no effect on choriocapillaris in early and late stage of ICGA; Grade I, no significant choriocapillaris nonperfusion in early stage of ICGA and discrete hypofluorescence in late stage of ICGA; Grade II, moderate nonperfusion of the

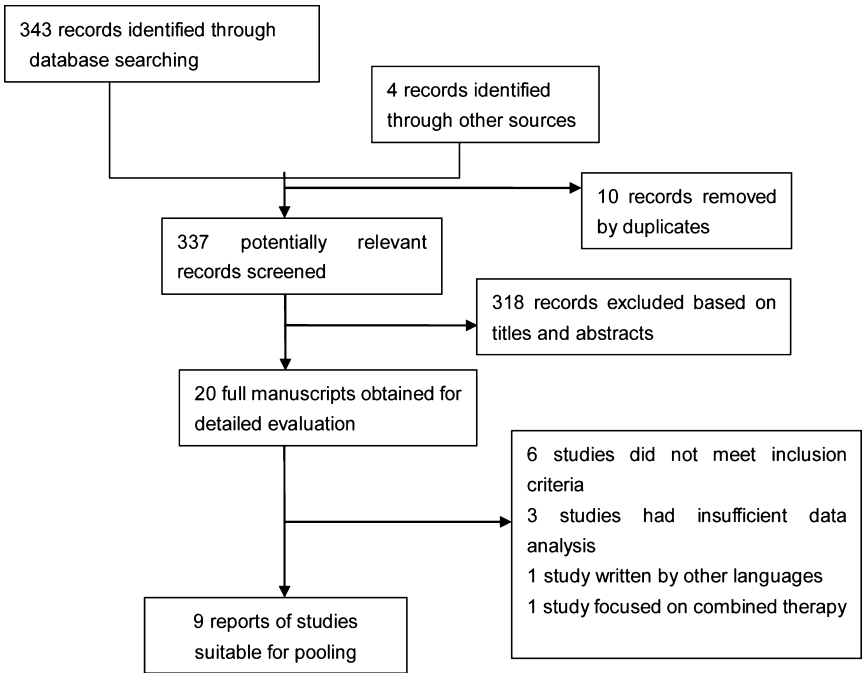

Fig. 1. Flow diagram demonstrates the study selection process.

Table 1. Characteristics of involved trials.

Studies	Study design	Countries	No. of eyes (*n*)	Mean age (years)	I Interventions	Results of BCVA	Results of CMT	Results of SRF resolution	Adverse effects
Maruko et al. (2010)	Retrospective comparative case series series	Japan	20	57.0 ± 8.2	Half-dose PDT versus laser photocoagulation	Baseline: 0.37 ± 0.4/ 0.1 ± 0.25 1 month: 0.27 ± 0.35/ 0.06 ± 0.21	Baseline: 389 ± 106/ 345 ± 127 1 month: 330 ± 103/ 340 ± 124	1 month: 6/3	NA
Lim et al. (2011)	Prospective comparative case series comparative	Korea	26	45.7 ± 7.3	Half-dose PDT versus laser photocoagulation	Baseline: 0.14 ± 0.16/ 0.22 ± 0.18 1 month: 0.07 ± 0.13/ 0.04 ± 0.07	Baseline: 348.5 ± 101.5/ 352.1 ± 98.7 1 month: 197.6 ± 58.1/ 200.6 ± 64.2	1 month: 13/7	NA
Lee et al. (2011)	Retrospective comparativenonrandomied comparative	Korea	29	48.2 ± 7.8	PDT versus intravitreal injection of anti-VEGF drugs	Baseline: 0.37 ± 0.15/ 0.32 ± 0.28 3 months: 0.19 ± 0.18/ 0.18 ± 0.26	Baseline: 332 ± 87/ 290 ± 85 3 months: 171 ± 27/ 219 ± 74	3 months: 12/9	NA
Bae et al. (2011)	Prospective randomized pilot study	Korea	16	48.9 ± 7.6	PDT versus intravitreal injection of anti-VEGF drugs	Baseline: 0.30 ± 0.37/ 0.38 ± 0.25 3 months: 0.18 ± 0.27/ 0.18 ± 0.22	Baseline: 74.1 ± 56.0/ 26.3 ± 50.6 3 months: −35.4 ± 44.5/ −23.1 ± 56.5	3 months: 6/2	NA
Semeraro F et al. (2012)	Randomized control trials	Italy	22	35.2 ± 6	PDT versus intravitreal injection of anti-VEGF drugs	Baseline: 1.1 ± 02/ 1.2 ± 0.2 9 months: 0.9 ± 0.2/ 0.8 ± 0.3	Change from baseline 114 ± 42/127 ± 36	NA	NA
Chan et al. (2008a,b)	Prospective double-masked clinical trial	China	63	41.0 ± 6.7	Half-dose Verteporfin PDT versus Placebo	Baseline: 0.16 ± 0.19/ 0.11 ± 0.12 3 months: 0.00 ± 0.11/ 0.08 ± 0.11 12 months: −0.05 ± 0.09/ 0.05 ± 0.17	Baseline: 456 ± 223/ 452 ± 218 3 months: 165 ± 82/ 309 ± 182 12 months: 161 ± 65/ 278 ± 192	1 month: 31/4 3 months: 35/8 12 months: 37/1112	NA
Wu et al. (2011)	Randomized control trials	China	34	41.9 ± 6.4	Half-dose Verteportin PDT versus Placebo	Baseline: 0.15 ± 0.14/ 0.12 ± 0.11 12 months: −0.03 ± 0.08/ 0.11 ± 0.21	Baseline: 486 ± 240/ 418 ± 163 12 months: 160 ± 47/ 262 ± 124	12 months: 23/4	NA
Reibaldi et al. (2010)	Multicentre prospective, masked, nonrandomized clinical trial investigatormasked, nonrandomized cl	Italy	42	49.2 ± 6.8	Half-fluence PDT versus full-fluence PDT full-fluence	Baseline: 0.46 ± 0.2/ 0.43 ± 0.1 1 month: 0.28 ± 0.17/ 0.27 ± 0.12 3 months: 0.22 ± 0.2/ 0.27 ± 0.1 12 months: 0.16 ± 0.18/ 0.25 ± 0.2	Baseline: 315 ± 95/ 324 ± 83 1 month: 174 ± 32/ 198 ± 73 3 months: 168 ± 40/ 194 ± 81 12 months: 161 ± 34/ 173 ± 81	1 month: 22/17 3 months: 21/15	3 months: 2/12 high gradesof nonperfusion (>grade II)
Shin et al. (2011)	Multicentre retrospectivecomparison study	Korea	67	49.8 ± 7.5	Half fluence PDT versus full-fluence PDTFull fluence	Baseline: 0.34 ± 0.27/ 0.46 ± 0.42 1 month: 0.26 ± 0.28/ 0.38 ± 0.38 3 months: 0.18 ± 0.32/ 0.23 ± 0.41 12 month: 0.17 ± 0.32/ 0.21 ± 0.39	Baseline: 291.5 ± 78.6/ 307.2 ± 96.6 1 month: 175.0 ± 55.1/ 164.1 ± 60.8 3 months: 165.2 ± 22.6/ 156.4 ± 23.4 12 months: 164.9 ± 20.9/ 154.4 ± 23.6	1 month: 31/32 3 months: 33/33	3 months: 3/10 high gradesof nonperfusion (>grade II)

BCVA = Best-corrected visual acuity in log MAR; CMT = central macular thickness in μm, SRF; = subretinal fluid; NA = not available.

choriocapillaris in early stage of ICGA; Grade III, significant nonperfusion of the choriocapillaris in early stage of ICGA; and Grade IV, nonperfusion of larger choroidal vessels in early stage of ICGA. Choroidal nonperfusion herein was defined as >Grade II.

Quality assessment

The methodological quality of eligible studies was assessed with criteria adapted from guidelines for the evaluation of articles on prognosis (Verhagen et al. 1998). The criteria included enrolment of unselected patients undergoing PDT or other treatments; a clearly defined inception cohort; more than 90% patients completed planned follow-up.

Intervention arms

To quantify the efficacy and safety of PDT, we conducted the comparisons into four groups, the first two groups focused on the effect of PDT compared with other treatments, the next two groups focus on the safety of PDT with modified parameters. Group 1, PDT versus laser photocoagulation (Maruko et al. 2010; Lim et al. 2011); group 2, PDT versus intravitreal injection of anti-VEGF drugs (Bae et al. 2011; Lee et al. 2011; Semeraro et al. 2012); group 3, half-dose verteporfin versus placebo (Chan et al. 2008a,b; Wu et al. 2011); group 4, half-fluence PDT versus full-fluence PDT (Reibaldi et al. 2010; Shin et al. 2011). All studies mentioned above had various follow-up durations; we assessed outcomes at 1, 3, 6 and 12 months from treatment if the data were available. All data were estimated and displayed by forest plots.

Statistical analysis

Data were processed by RevMan (Version 5.0; The Cochrane Collaboration, Copenhagen, Denmark). For every study, we calculated the mean difference (MD) for the continuous outcome (BCVA and CMT) along with 95% confidence intervals (CIs) by Inverse Variance method. Resolution of SRF and adverse effects were expressed as discontinuous outcomes, the summary odds ratios (ORs) were calculated by Mantel–Haenszel method. The outcome measures were pooled by using the fixed-effect model.

The between-study heterogeneity was tested by the chi-square-based Cochran's statistics and the inconsistency index (I^2) (Higgins et al. 2003), which indicated the proportion of variability across studies due to heterogeneity rather than sample error. Statistically significant heterogeneity was considered present with $P_{heterogeneity} < 0.05$ and $I^2 > 50\%$. Subgroup analysis and asymmetry assessment of the funnel plot for evaluating publication biases was not conducted due to the limited trials involved in the final analysis.

Results

Study characteristics

Figure 1 summarized the selection of reports of eligible clinical trials. We identified 347 potentially eligible literature citations, of which 19 were reviewed as full articles. Nine reports of studies with suitable data were eligible for inclusion with a total of 319 CSC eyes (Chan et al. 2008a,b; Maruko et al. 2010; Reibaldi et al. 2010; Bae et al. 2011; Lee et al. 2011; Lim et al. 2011; Shin et al. 2011; Wu et al. 2011), among which five reports (Chan et al. 2008a,b; Reibaldi et al. 2010; Bae et al. 2011; Wu et al. 2011; Semeraro et al. 2012) were RCTs with good quality scores, the others (Maruko et al. 2010; Lee et al. 2011; Lim et al. 2011; Shin et al. 2011) were comparative case series trials.

The detailed characteristics of the participants from the nine reports were given in Table 1. All subjects' ages ranged from an average of 41–57 years old, the gender was not evenly distributed. The mean follow-up time was from 1 to 12 months and the loss to follow-up was reported as <10%. Clinical heterogeneity was seen in several areas, including specific characteristics of CSC and different treatment protocols.

Summary results of BCVA, CMT, resolution of SRF and adverse events

In group 1, two trials (Maruko et al. 2010; Lim et al. 2011) assessed the efficacy of half-dose verteporfin PDT on CSC compared with laser photocoagulation at 1 month's follow-up.

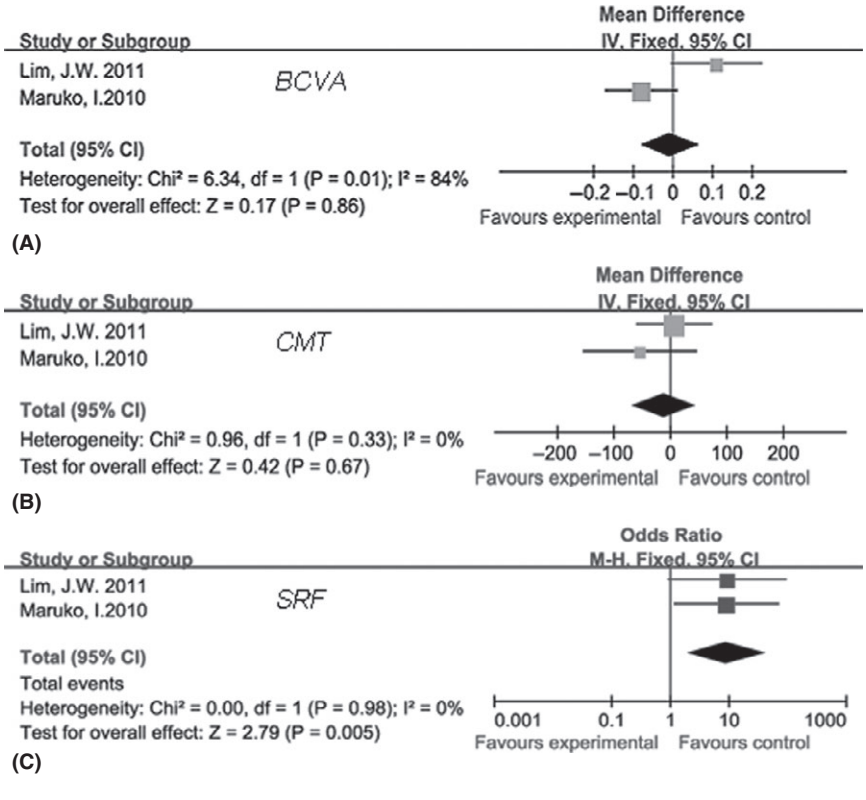

Fig. 2. Summary results of BCVA, CMT and resolution of SRF in group 1. The summary results of comparing PDT with laser photocoagulation at 1 month's follow-up. (A) No significant difference in BCVA was found. (B) No significant difference in CMT was found. (C) PDT was superior to laser photocoagulation in SRF resolution at 1 month's visit.

Figure 2A,B showed no significant difference in the pooled result of BCVA (p = 0.86) and CMT (p = 0.63). Figure 2C presented the resolution of SRF 9.14 fold higher in PDT group than laser photocoagulation group (OR = 9.14; 95%CI: 1.94, 43.10; p = 0.005). Heterogeneity in BCVA was significant ($P_{heterogeneity}$ = 0.01, I^2 = 84%).

Group 2 compared PDT with intravitreal injection of anti-VEGF drugs including three studies which had consistent treatment arms. Lee et al. (2011) and Semeraro et al. (2012) selected bevacizumab while Bae et al. (2011) used ranibizumab as anti-VEGF drugs. The data of follow-up duration only could be extracted at 3 months. No significant difference was found in BCVA (MD = 0.05; 95%CI: −0.07, 0.17; p = 0.45) with no heterogeneity ($P_{heterogeneity}$ = 0.21, I^2 = 37%; Fig. 3A). However, the combined MD in CMT showed a favourable response to PDT (MD = −38.39 μm; 95% CI: −63.21, −13.56; p = 0.002) with no heterogeneity found (Fig. 3B). Complete resolution of SRF was observed in 18 patients (85.7%) accepted PDT and 11 (45.8%) accepted anti-VEGF drugs. The summary OR was 9.18 (95%CI: 1.83, 46.02; p = 0.007), PDT was superior in resolution of SRF (Fig. 3C).

In group 3, both the RCT studies (Chan et al. 2008a,b; Wu et al. 2011) used half-dose (3 mg/m^2) verteporfin PDT as treatment arm compared with placebo (30 ml normal saline) with the rationale that a lower dose verteporfin having less serious collateral damaging effects on the retina and choroid. They both completed 12 months' follow-up, BCVA was significantly improved (MD = −0.16; 95%CI: −0.23, −0.09; p < 0.00001) and CMT kept lower level (MD = −140.75 μm; 95%CI: −224.54, −56.96; p = 0.001) in the treatment group than in the placebo (Fig. 4A,B). Meanwhile the proportion of eyes with complete resolution of SRF showed 18.44 fold higher in the treatment group (95%CI: 4.70, 72.28; p < 0.001) (Fig. 4C). No heterogeneity was found.

Group 4 reported the efficacy and safety of half-fluence (25 J/cm^2) PDT compared with conventional PDT (50J/cm^2, full-fluence) (Reibaldi et al. 2010; Shin et al. 2011). There was no difference in improving BCVA at the

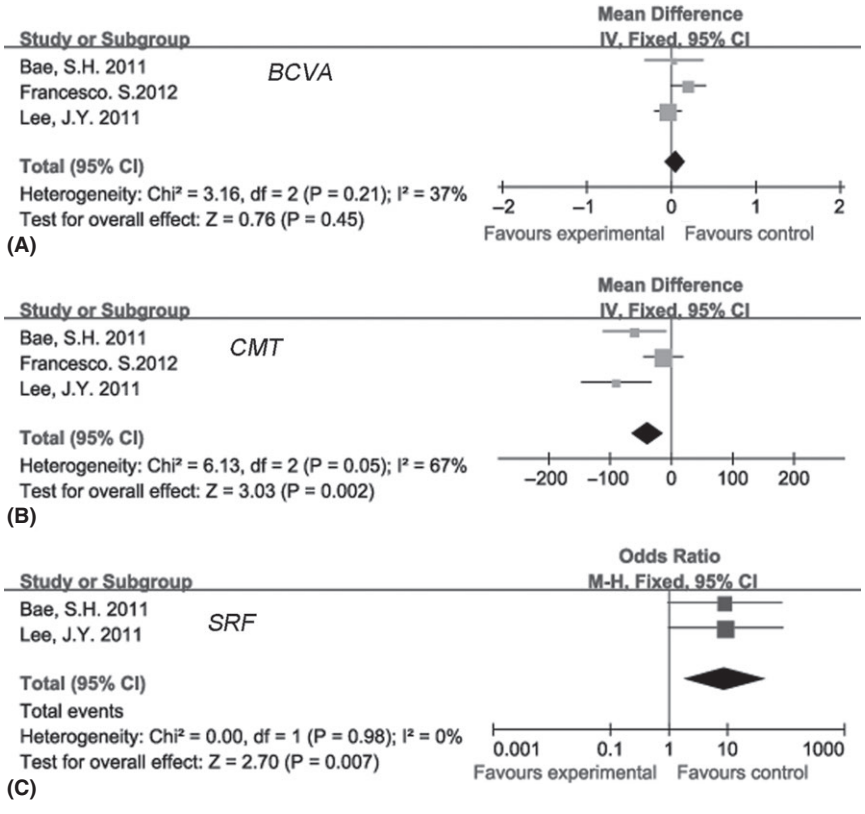

Fig. 3. Summary results of BCVA, CMT and resolution of SRF in group 2. The summary results of comparing PDT with intravitreal injection of anti-VEGF drugs at 3 months' visit. (Chi^2: Chi-square statistic, CI: confidence interval, df: degrees of freedom, I^2: I-square heterogeneity statistic, IV: inverse variance, Z: Z-statistic).

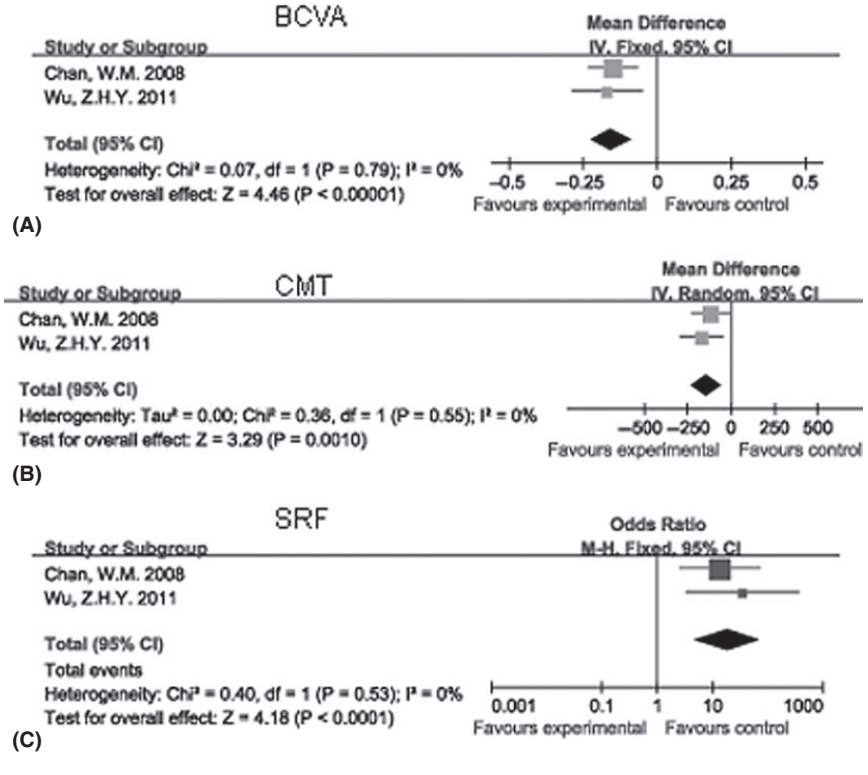

Fig. 4. Summary results of BCVA, CMT and resolution of SRF in group 3: comparing half-dose verteporfin PDT with placebo at 12 months' visit.

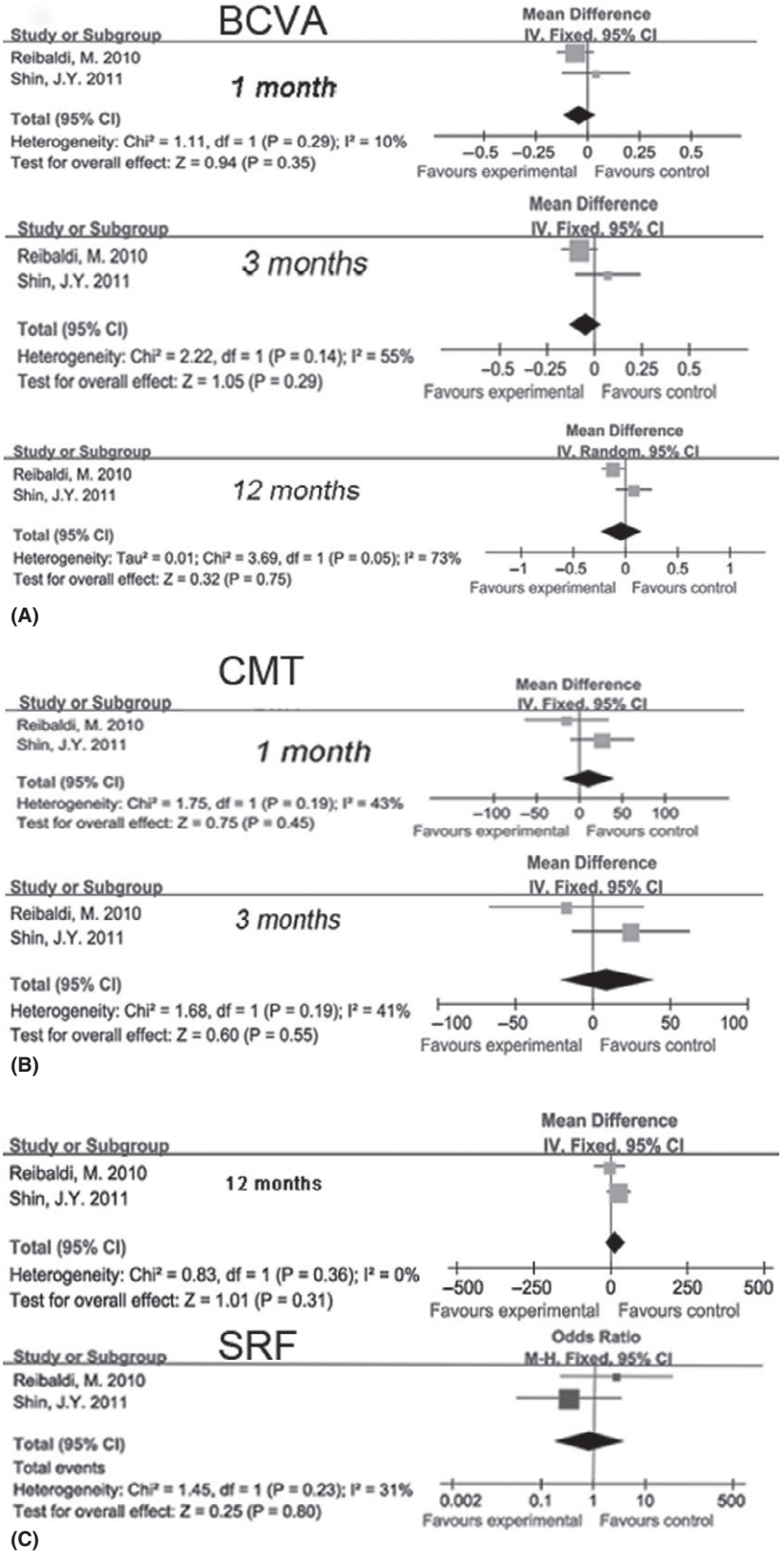

Fig. 5. Summary results of BCVA, CMT and resolution of SRF in group 4: comparing half-fluence PDT with full-fluence PDT at 1, 3 and 12 months' visit.

follow-up of 1 month ($p = 0.30$), 3 months ($p = 0.18$) and 12 months ($p = 0.75$), respectively (Fig. 5A). Similar results were drawn in mean change in CMT ($p = 0.45$; $p = 0.55$; $p = 0.31$), respectively (Fig. 5B). The data of the ratio of eyes with complete resolution of SRF only could be extracted at 1 month's visit and the summary OR was 0.82 ($p = 0.80$) (Fig. 5C). However, 3 months after treatment, choroidal regional no perfusion was more common in the full-fluence PDT than in the half-fluence PDT (OR = 0.09; 95%CI: 0.03, 0.29; $p < 0.001$), which indicated that half-fluence PDT was safer than conventional PDT (Fig. 6).

Discussion

The recommendable treatment option for CSC would be the one that can result in visual improvement, shorten the duration of symptoms, reduce the recurrence rates while have a good safety profile. This study demonstrated that PDT was effective in the treatment of CSC with improving BCVA, decreasing CMT and resolution of SRF, and adverse effects could be avoided via modifying the parameters of PDT.

In this meta-analysis, compared with laser photocoagulation, PDT was noted to be beneficial on the SRF absorption. However, no advantage was found in recover visual and the CMT. It was supposed that PDT induced more widespread alteration in choroidal function than laser photocoagulation which might only affect the local environment around the leakage. Moreover, PDT acted directly on the choriocapillaris which might lead to relatively rapid resolution of SRF accumulation, whereas, laser photocoagulation induced resolution of SRF via remodelling of RPE, then SRF was gradually absorbed by RPE pump (Lim et al. 2011). Furthermore, laser photocoagulation cannot prevent recurrence of the clinical condition because of the possible development of other leakage points. BCVA may be decreased if the leakage site is close to the fovea. It was reported that 2% to 10% risk of developing CNV happened after laser treatment (Reibaldi et al. 2010).

Compared with intravitreal injection of anti-VEGF drugs, PDT was superior in CMT recovery and resolution of SRF. However, no positive finding on BCVA was revealed. PDT was considered as ideal treatment of CSC based on the proposed mechanism of choroidal hypoperfusion. PDT promotes the absorption of SRF by choroidal

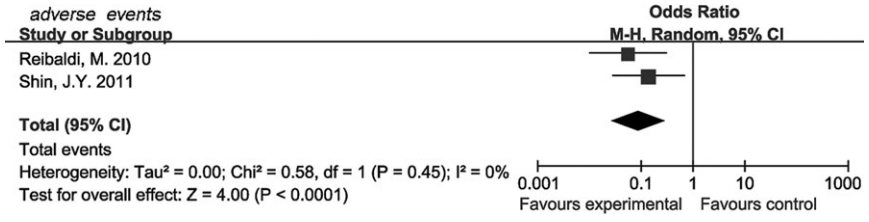

Fig. 6. Summary results of adverse events in group 4. Summary ORs of adverse events along with their associated 95% CIs, comparing half-fluence PDT with full-fluence PDT. Choroidal nonperfusion was more common in the full-fluence PDT group than in the half-fluence PDT group at 3 months' visit.

vascular remodelling and reduction of choroidal hyperpermeability (Chan et al. 2003). However, the role of VEGF in the pathogenesis of CSC was unclear because no study demonstrated increased level of VEGF in CSC. Furthermore, no optimal dose of ranibizumab/bevacizumab for CSC was generally accepted, currently it was based on the results for the management of AMD and may be insufficient for CSC. Nevertheless, PDT has been shown to up-regulate VEGF (Lee et al. 2009). We hypothesized that combination treatment with PDT and anti-VEGF may have a beneficial synergistic effect on CSC. Further studies on combination treatment are needed in the future.

Modifying PDT parameters, including reduced dose of verteporfin or fluence of irradiation, could probably minimize side effects of PDT (Lai et al. 2006; Chan et al. 2008a,b; Reibaldi et al. 2009; Lee & Kim 2011). This meta-analysis demonstrated both half-dose verteporfin PDT and half-fluence PDT had significant advantages on treatment of CSC. Half-dose verteporfin PDT could provide satisfied outcomes on VA, CMT and resolution of SRF. However, Zhao et al. (2009) reported that 30% of full-dose verteporfin might be effective on CSC. The optimal verteporfin dosage for CSC is still under investigated.

Our study showed that both full-fluence and half-fluence PDT treatment options could lead to BCVA improvement and resolution of SRF, which confirmed PDT's efficacy on CSC. Full-fluence of laser irradiation may exceed the necessary to activate the photo sensitizer (verteporfin) and generate single oxygen in the treated area which result in closure of deep choroidal vessels and focal alterations in RPE, finally unwanted damage to the normal tissue formed (Cardillo Piccolino et al. 2003; Chan et al. 2003). It was presumed that choroidal damage may be avoided by an appropriate fluence selection. Our analyses revealed that half-fluence PDT could minimize the deleterious effect on choroid.

In some articles, The authors reported that the choroidal thickness was significantly greater in the affected eye compared with the fellow eye, meanwhile, some studies reported decreases in choroidal thickness after PDT within the areas of leakage and under the fovea in CSC patients, respectively (Pryds & Larsen 2012; Tan et al. 2014). Maruko et al. (2010) used enhanced depth imaging OCT (EDI-OCT) to investigate changes in choroidal thickness in eyes undergoing laser photocoagulation or PDT for chronic CSC. Laser photocoagulation was performed in patients with areas of focal leakage on FA. The result showed PDT was more effective in decreasing choroidal thickness. These observations are intriguing as they may help enhance our understanding of the pathophysiology of CSC and how PDT affects its clinical course. We should focus on the role of choroidal thickness in future study.

The strength within the studies was that the exact definition and measurement of outcomes were fairly consistent and our pooled results should not be biased due to misclassification. Additionally, there was a broad spectrum on follow-up times of involved studies. We unified them and taken into account for this analysis.

The current study has some limitations which may affect the final conclusions. First, it was small sample size with only nine studies involved, subgroup analyses and assessments of publication bias could not be preformed due to small study numbers. Therefore, there may be 'small study effects' overestimating the effect of PDT. Second, some results were limited by heterogeneity in the included trials, which include ethnicity, gender distribution, differences in the treatment protocol and sample size of patients. And it was difficult to explore the potential sources of heterogeneity and bias. Third, various risk factors have been associated with visual outcomes of PDT, disease duration, type of CSC and pigment epithelial detachment. In this study, we did not evaluate all these factors, which can affect the result of our analysis. Fourth, we did not elaborated on the influence of the duration of CSC prior to treatment in this article.

In conclusion, our data demonstrated PDT was superior in SRF absorption than laser photocoagulation and intravitreal injection of anti-VEGF drugs. A promising trend towards usage of half-dose PDT for CSC was elucidated. Moreover, with improvement on BCVA, CMT and resolution of SRF, half-fluence PDT could be safer than standard fluence PDT. Further investigations are required to determine the overall long-time benefits and adverse events of PDT on CSC, multi-centre controlled trials should be conducted to construct standard PDT parameters for CSC therapy.

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Received on August 3rd, 2013.
Accepted on May 18th, 2014.

Correspondence:
Yi Qu
Qilu Hospital of Shandong University
No. 107, Wenhuaxi Road
Jinan 250012
China
Tel: +86 531 82166150
Fax: +86 531 86927544
Email: drquyi@gmail.com

The authors thank the professors whose studies were involved in our meta-analysis and provided useful data to us. The appropriate institutional review boards waived approvals because this research did not involve humans or animals. This research adheres to the Declaration of Helsinki. The authors alone are responsible for the content and writing of the paper. This study was partly supported by Natural Science foundation of Shandong Province (ZR2013HZ003), Scientific & Technologic Project of Jinan (201302025).