PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy of calcium dobesilate in treating Chinese patients with mild to moderate non-proliferative diabetic retinopathy (CALM-DR): protocol for a single-blind, multicenter, 24-armed cluster-randomized, controlled trial
AUTHORS	Hu, Hao; Liu, Jiang; Wang, Duolao; Qiu, Shanhu; Yuan, Yang; Wang, Fenghua; Wen, Liang; Song, Qi; Sun, Zi-lin

VERSION 1 – REVIEW

REVIEWER	Mwangi, Nyawira London School of Hygiene and Tropical Medicine
REVIEW RETURNED	10-Nov-2020

GENERAL COMMENTS	Well done for planning this research. I have enjoyed reading the protocol. Ensure you have access to good statistical support. How will you ensure that whole clusters do not drop out of the study?

REVIEWER	Simo, Rafael Universitat Autònoma de Barcelona
REVIEW RETURNED	23-Nov-2020

GENERAL COMMENTS	This is just a protocol. I don't think that this information without any result merits to be published in a journal such as BMJ Open.

REVIEWER	chanbour, wassef clinic du levant, ophthalmology
REVIEW RETURNED	03-Mar-2021

GENERAL COMMENTS	This is an interesting study protocol, however it needs few adjustments before being considered for publication: 1) The name of the study should be defined clearly (CALM-DR): is not clear 2) Add to the secondary endpoint the type of diabetes (type 1 and 2 have different progression of DR) 3) The study is not single blinded: the patients will know that they are in the observation group and they will meet in the clinics and see other patients in the treatment group. Either the single blinded should be removed from the protocol or the control group should be given a placebo (which I believe is the best option to avoid bias). 4) Titles and sub-titles are not well defined, please use numbers 5) Authors state in Page 18: ''DME is defined by hard exudates in the presence of microaneurysms and blot hemorrhage within 1-disc diameter from the foveal center or the presence of focal photocoagulation scars in the macular area. Clinically significant

	macular edema (CSME) is considered present when the macular edema is within 500 µm of the foveal center or if focal laser photocoagulation scars are present in the macular area.'' The true definition are: -DME is defined as retinal thickening or hard exudates at least one disc diameter to the center of the macula -Clinically significant macular edema (CSME), introduced by the Early Treatment Diabetic Retinopathy Study (ETDRS), is defined as DME meeting at least one of three criteria: thickening at or within 500µm of foveal center, hard exudates within 500µm of foveal center with adjacent thickening, or at least one disk diameter of thickening with part of it located within one disc diameter of foveal center. Receiving laser treatment is an exclusion criteria for the study, the DME and CSME definitions cannot include photocoagulation scars. 6) authors should state the expected start and end date of the study (which month and which year).

REVIEWER	Leila, Mahmoud Research Institute of Ophthalmology
REVIEW RETURNED	11-Mar-2021

GENERAL COMMENTS	The authors targeted a very interesting aspect in management of DR and monitoring the effect of CaD in halting its progression. I fully agree with the authors that this medication if proven effective would by very valuable in low-income countries where anti-VEGF medication and vitreoretinal surgery are either inaccessible or come at unaffordable cost for a wide range of population. Looking forward to the results of this study.

REVIEWER	George, Simon Regional Institute of Ophthalmology, Ophthalmology
REVIEW RETURNED	17-Mar-2021

GENERAL COMMENTS	I would like to mention some of my suggested corrections to the submitted protocol 1) In the Abstract a. It is mentioned that " Calcium dobesilate has been recommended to treat diabetic retinopathy …….. ". Is there a standard reference for this recommendation ? Without a standard recommendation, it will be better to rewrite the sentence as " Calcium dobesilate has been used in the treatment of diabetic retinopathy ……. ". b. It will be better to write strengths of the study (points 1 and 2) and limitations of the study (points 3 and 4 will now become points 1 and 2) as 2 separate subheadings instead of a single heading strengths and limitations of the study. 2) Ethics a. Does all 24 hospitals included in this protocol come under the jurisdiction of the of Human Ethics Committees Zhongda Hospital of South Eastern University? If any of the 24 hospitals (included in this study) is outside the Zhonda hospital Human Ethics Committees' jurisdiction, approval will be needed from that hospital's Human Ethics Committee . b. In the funding section, it is mentioned that the authors have not declared any specific grant for this research. Who meets the expenses for the laboratory investigations and the one year supply of Calcium dobesilate tablets ? If there is a sponsor for the research, the sponsor details can be mentioned in the protocol.

	3) Protocol a. There are lot of grammar/spelling mistakes in the protocol. For example, • In abstract dosage of the drug is written as 500 mg trice daily instead of thrice daily. • correct use of punctuation marks like comma. In the second paragraph of the introduction, comma is used frequently in the sentences. • In inclusion criteria it is mentioned willing to attend this trial. Better to mention willing to participate in the trial. • In exclusion criteria it is mentioned being in pregnancy , being with unstable conditions .It will be better to avoid using ‘ being in “. Please go through the whole protocol and correct the mistakes in grammar /proper use of English words. b. Since it is planned to include only patients with mild and moderate diabetic retinopathy in this protocol, patients receiving laser treatment, cyrocoagulation or vitrectomy are automatically excluded from the protocol. c. Patients who are taking drugs that may have effect on DR in the last one month are excluded in this study. Please specify the names of these drugs. d. Sample size calculation – the proportion of patients with two step progression of DR was taken as 16.2 % from the study by Lim LS (reference publication no.31).However this progression rate is for a sample population that included patients with no DR, minimal NPDR, mild NPDR, moderate NPDR, severe NPDR and PDR. The patients with mild and moderate NPDR (studied in this submitted protocol) constituted only 37.7 % of this sample population. It will be better to contact the authors of the reference publication (Reference no.31) and find out the two step progression of DR for the mild and moderate NPDR population of the study. In addition, the laboratory parameters of the study population in the reference publication no.31 was not monitored in between during the one year study period (unlike the submitted protocol where the parameters will be monitored and kept normal). So the 16.2 % progression value used in the sample size calculation may be higher than the actual progression value for only mild and moderate DR patients on regular monitoring. e. One year period for the trial may be too short to detect DR progression in mild and moderate NPDR patients with well controlled laboratory parameters. f. I feel a double blind trial with use of placebo would be better than a single blind trial. For the submitted single blind protocol to provide correct results without bias ,it will be very important to ensure that the staff interpreting the retina photograph and the data should be blind about the hospital from which the data was sent and the patients’ details.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Nyawira Mwangi, London School of Hygiene and Tropical Medicine, Kenya Medical Training College

Comments to the Author:

Well done for planning this research.

I have enjoyed reading the protocol.

Ensure you have access to good statistical support.

How will you ensure that whole clusters do not drop out of the study?

Response

Thank you for this comment. We added text to clarify how to avoid dropping out of whole clusters (lines 312-323).

Reviewer: 2

Dr. Rafael Simo, Universitat Autònoma de Barcelona

Comments to the Author:

This is just a protocol. I don't think that this information without any result merits to be published in a journal such as BMJ Open.

Response

According to the editor, publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicized. This can help prevent unnecessary duplication of work and will hopefully enable collaboration.

Reviewer: 3

Dr. wassef chanbour, clinic du levant

Comments to the Author:

This is an interesting study protocol, however it needs few adjustments before being considered for publication:

1) The name of the study should be defined clearly (CALM-DR): is not clear

Response

Agreed. An explanation for the abbreviation (CALM-DR) was added at the be beginning of the "Methods and analysis" (lines 117-119).

2) Add to the secondary endpoint the type of diabetes (type 1 and 2 have different progression of DR)

Response

Excellent point. Studies have shown that subtle but significant functional and structural changes may occur very early in type 1 diabetes. Therefore, for patients with type 1 diabetes, we add an additional repeat test at 9 months (line 169 and table 1).

3) The study is not single blinded: the patients will know that they are in the observation group and they will meet in the clinics and see other patients in the treatment group. Either the single blinded should be removed from the protocol or the control group should be given a placebo (which I believe is the best option to avoid bias).

Response

Thank you for this comment. Cluster randomization trials are experiments in which intact social units or clusters of individuals rather than independent individuals are randomly allocated to intervention groups. Cluster randomization is often used to avoid 'contamination' between those receiving the intervention and those who are not.

Therefore, the reason for the cluster design of this randomized trial is to avoid the intervention group telling the control group about the treatment. Because if this occur, then there is a danger of dilution bias resulting in a Type II error.

Specifically, intervention naturally applied at the cluster level. In an attempt to reduce the 'contamination' effects and bias, hospital was used as the randomization unit. Allocation to either the intervention or the control groups of the trial occurred after hospitals had been recruited. These hospitals are located in 24 different cities in China. The patients in the intervention and control groups would not see each other.

4) Titles and sub-titles are not well defined, please use numbers

Response

Number to the title has been added (line 3).

5) Authors state in Page 18: ‘’DME is defined by hard exudates in the presence of microaneurysms and blot hemorrhage within 1-disc diameter from the foveal center or the presence of focal

photocoagulation scars in the macular area. Clinically significant macular edema (CSME) is considered present when the macular edema is within 500 µm of the foveal center or if focal laser photocoagulation scars are present in the macular area.''

The true definition are:

-DME is defined as retinal thickening or hard exudates at least one disc diameter to the center of the macula

-Clinically significant macular edema (CSME), introduced by the Early Treatment Diabetic Retinopathy Study (ETDRS), is defined as DME meeting at least one of three criteria: thickening at or within 500µm of foveal center, hard exudates within 500µm of foveal center with adjacent thickening, or at least one disk diameter of thickening with part of it located within one disc diameter of foveal center. Receiving laser treatment is an exclusion criteria for the study, the DME and CSME definitions cannot include photocoagulation scars.

Response

You are correct. We have revised it according to your comment (lines 360-368).

6) authors should state the expected start and end date of the study (which month and which year).

Response

Yes, now added: "We will recruit patients between June, 2021, and December, 2021. Follow-up will complete in December, 2022" (lines 121-122).

Reviewer: 4

Dr. Mahmoud Leila, Research Institute of Ophthalmology

Comments to the Author:

The authors targeted a very interesting aspect in management of DR and monitoring the effect of CaD in halting its progression. I fully agree with the authors that this medication if proven effective would by very valuable in low-income countries where anti-VEGF medication and vitreoretinal surgery are either inaccessible or come at unaffordable cost for a wide range of population. Looking forward to the results of this study.

Response

Thank you for your comment.

Reviewer: 5

Dr. Simon George, Regional Institute of Ophthalmology

Comments to the Author:

I would like to mention some of my suggested corrections to the submitted protocol

1) In the Abstract

a. It is mentioned that “Calcium dobesilate has been recommended to treat diabetic retinopathy ……..

“. Is there a standard reference for this recommendation? Without a standard recommendation, it will be better to rewrite the sentence as “Calcium dobesilate has been used in the treatment of diabetic retinopathy ……. “.

Response

We agree and have revised this in the abstract (line 25).

b. It will be better to write strengths of the study (points 1 and 2) and limitations of the study (points 3 and 4 will now become points 1 and 2) as 2 separate subheadings instead of a single heading strengths and limitations of the study.

Response

Thank you for your great suggestion. The

editor thinks that integrating the strengths and limitations into one paragraph meets the requirements of BMJ open.

2) Ethics

a. Does all 24 hospitals included in this protocol come under the jurisdiction of the of Human Ethics Committees Zhongda Hospital of South Eastern University? If any of the 24 hospitals (included in this study) is outside the Zhonda hospital Human Ethics Committees’ jurisdiction, approval will be needed from that hospital’s Human Ethics Committee.

Response

Thank you for your reminding. All these hospitals belong to different regions and have their own ethics committees. The ethics committee of each hospital has conducted an ethics review in their respective hospitals (lines 44-45, and lines 482-483).

b. In the funding section, it is mentioned that the authors have not declared any specific grant for this research. Who meets the expenses for the laboratory investigations and the one year supply of Calcium dobesilate tablets? If there is a sponsor for the research, the sponsor details can be mentioned in the protocol.

Response

Funding was provided by research grant from the Chinese Society of Microcirculation (lines 534-539). For the subjects, China's three basic medical insurances programs currently cover 96.8% of the nation's total population, including medical insurance program for urban employees, insurance program for unemployed urban citizens, and the new rural cooperative medical care system. These insurances can fully cover the medications and examinations needed by the patients.

3) Protocol

a. There are lot of grammar/spelling mistakes in the protocol. For example,

• In abstract dosage of the drug is written as 500 mg trice daily instead of thrice daily.

Response

Corrected (line 35).

• correct use of punctuation marks like comma. In the second paragraph of the introduction, comma is used frequently in the sentences.

Response

Corrected (lines 79-88).

• In inclusion criteria it is mentioned willing to attend this trial. Better to mention willing to participate in the trial.

Response

Corrected (line 178).

• In exclusion criteria it is mentioned being in pregnancy, being with unstable conditions. It will be better to avoid using ‘being in “.

Response

Corrected (line 186).

Please go through the whole protocol and correct the mistakes in grammar /proper use of English words.

Response

Thank you for your careful review. We are very sorry for the mistakes in this manuscript and inconvenience they caused in your reading. The manuscript has been thoroughly revised by a native English speaker, and we hope it can meet the journal's standard.

b. Since it is planned to include only patients with mild and moderate diabetic retinopathy in this protocol, patients receiving laser treatment, cyrocoagulation or vitrectomy are automatically excluded from the protocol.

Response

You are correct. We deleted this exclusion criterion (line 195).

c. Patients who are taking drugs that may have effect on DR in the last one month are excluded in this study. Please specify the names of these drugs.

Response

Names of specific drugs that affect diabetic retinopathy are provided (lines 209-211).

d. Sample size calculation – the proportion of patients with two step progression of DR was taken as 16.2 % from the study by Lim LS (reference publication no.31). However this progression rate is for a sample population that included patients with no DR, minimal NPDR, mild NPDR, moderate NPDR, severe NPDR and PDR. The patients with mild and moderate NPDR (studied in this submitted protocol) constituted only 37.7 % of this sample population. It will be better to contact the authors of the reference publication (Reference no.31) and find out the two step progression of DR for the mild

and moderate NPDR population of the study. In addition, the laboratory parameters of the study population in the reference publication no.31 was not monitored in between during the one year study period (unlike the submitted protocol where the parameters will be monitored and kept normal). So the 16.2 % progression value used in the sample size calculation may be higher than the actual progression value for only mild and moderate DR patients on regular monitoring.

Response

We contacted the corresponding author of Reference no.31 to ask for unpublished result on the progression rate of mild and moderate NPDR. According to the response of the first author, the rate of progression at 12-months follow-up of mild and moderate NPDR was 15.2%. Recalculating the sample size based on this value shows that each group requires 528 samples, and the two groups require a total of 1056 samples. Taking into account an anticipated drop-out rate of 20%, the total sample size will be 1272 patients (636 in each of the two study groups, or 53 in each cluster) (lines 33, 214, 423-424, and 428-431).

We fully agree that the 16.2% used in the sample size calculation may be higher than the actual progression value for mild and moderate NPDR under regular monitoring. However, in contrast to the results from population-based studies, the data from clinical trials is sparse and less convincing. Clinical trials have tended to report outcomes in terms of ≥ 2 or 3-step progression of diabetic retinopathy on the ETDRS grading scale. The UKPDS follow-up[1,2] reported ≥ 3-step progression rates of 29% over 6 years, while the placebo arm of the DIabetic Retinopathy Candesartan Trials (DIRECT)[3] reported a lower rate of 19% over the same time period. In contrast, the rates of ≥ 2-step progression over 3 years in the UKPDS[1,2] of 15% are similar to those reported for the placebo arm of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study[4] of 12%. In additio, a meta-analysis[5] of the rates of progression of diabetic retinopathy found that the progression of two or more steps in different studies ranged from 3% to 20%. Differences in study populations, baseline characteristics, and duration of follow-up, especially in the prevalence and severity of retinopathy, may have contributed to these differences.

Therefore, we chose the value of 15.2% as the basis for calculation of sample size.

References

1 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.

2 Stratton IM, Kohner EM, Aldington SJ, et al. UKPDS 50: risk factors for incidence and progression of retinopathy in Type II diabetes over 6 years from diagnosis. Diabetologia 2001;44:156-63 PubMed .

3 Sjølie AK, Klein R, Porta M, et al; DIRECT Programme Study Group. Effect of candesartan on progression and regression of retinopathy in type 2 diabetes (DIRECT-Protect 2): a randomised placebo-controlled trial. Lancet 2008;372:1385-93.

4 Keech AC, Mitchell P, Summanen PA, et al; FIELD study investigators. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. Lancet 2007;370:1687-97 PubMed .

5 Wong TY, Mwamburi M, Klein R, et al. Rates of progression in diabetic retinopathy during different time periods: a systematic review and meta-analysis. Diabetes Care 2009;32:2307-13 PubMed .

e. One year period for the trial may be too short to detect DR progression in mild and moderate NPDR patients with well controlled laboratory parameters.

Response

The one-year treatment period may be too short. However, some studies[1,2,3] have shown that the effect of short-term calcium dobesilate therapy (3 months or 6 months) was statistically significant for diabetic patients with mild and moderate background DR on improving the capillary resistance or on the course of the diabetic retinopathy. In addition, we also assess the progression of mild and moderate NPDR by retinal vessel diameter. The change in retinal vessel diameter can provide additional information regarding the progression of DR[4]. Evaluation by clinical examination, retinal vessel diameter, and fundus photography will help to discover the beneficial effects of calcium dobesilate in this study.

References

1 Benarroch IS, Brodsky M, Rubinstein A, et al. Treatment of blood hyperviscosity with calcium dobesilate in patients with diabetic retinopathy. Ophthalmic Res 1985;17:131-8 PubMed .

2 Vojnikovic B. Doxium (calcium dobesilate) reduces blood hyperviscosity and lowers elevated intraocular pressure in patients with diabetic retinopathy and glaucoma. Ophthalmic Res 1991;23:12-20 PubMed .

3 Benarroch IS, de Salama Benarroch AR, Nano H, et al. Calcium dobesilate as a treatment for capillary fragility in diabetic retinopathy. Ophthalmologica 1974;168:370-5 PubMed .

4 Klein R, Myers CE, Lee KE, et al. Changes in retinal vessel diameter and incidence and progression of diabetic retinopathy. Arch Ophthalmol 2012;130:749-55 PubMed .

f. I feel a double blind trial with use of placebo would be better than a single blind trial. For the submitted single blind protocol to provide correct results without bias, it will be very important to ensure that the staff interpreting the retina photograph and the data should be blind about the hospital from which the data was sent and the patients' details.

Response

Since patients in the intervention group in this study need to purchase drugs by themselves through medical insurance instead of free drugs delivered by researchers, double-blind trials cannot be conducted. However, this will not affect the compliance of the subjects and the feasibility of the research, because China's medical insurance can fully cover the patients' medical expenditures. In fact, the treatment of both the intervention group and the control group belong to the routine management of diabetes.

We agree with the importance of the staff who interpret the retina photographs not knowing from which hospital the photos and patient information were sent. We have revised to clarify (Lines 350-355).

VERSION 2 – REVIEW

REVIEWER	George, Simon Regional Institute of Ophthalmology, Ophthalmology
REVIEW RETURNED	02-May-2021

GENERAL COMMENTS	The author has made the changes to his previously submitted

	protocol, based on the suggestions in my first review. I still feel that rate of progression (15.2% , used in the sample size calculation) at 12-months follow-up of mild and moderate NPDR patients is a high value for patients with well controlled parameters and on regular monitoring (as in this proposed protocol). Since we were not able to obtain a definite progression rate for mild to moderate NPDR patients in well controlled patients at end of one year from other clinical trials, we may assume the rate of progression as 15.2 % but the final results from this study will have to be statistically analyzed to check whether the taken sample size was sufficient or not .The actual rate of progression at the end of 12 months for a well controlled and monitored group can be found out from the control group observation results in this protocol .