Author's response to reviews

Title: Effects of glaucoma drugs on ocular hemodynamics in normal tension glaucoma: a randomized trial comparing bimatoprost and latanoprost with dorzolamide

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Author's response to reviews: see over
Dear editorial team,

Please find enclosed the revised version of our manuscript entitled: Effects of glaucoma drugs on ocular hemodynamics in normal tension glaucoma: a randomized trial comparing bimatoprost and latanoprost with dorzolamide.

The suggestions of the reviewers were very helpful in further improvement of the manuscript. We followed most suggestions of the reviewers. Please find on the following pages a detailed reply to the comments of reviewers.

We hope to meet your approval for publication of our manuscript in BMC ophthalmology. Please do not hesitate to contact me at any time, if further information is required.

With kind regards,

Oliver Zeitz, M.D.
(on behalf of the authors)
Reply to Alon Harris’ report

on the submission to BMC-ophthalmology entitled “Effects of bimatoprost and latanoprost on ocular hemodynamics in normal tension glaucoma: a randomized trial” by Oliver Zeitz et al.

First of all the authors would like to thank Professor Harris for his comments that were very helpful in revising and restructuring of our manuscript. To aid the reviewer and editors in evaluation our reply, we first repeat the question/comment of the reviewer, (underlined typeface), reply to the comment (plain typeface), and then indicate changes made in the manuscript in bold typeface.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. No mention of potential study pitfalls is given, the discussion and conclusions of the paper need to be re-addressed and a frank and honest discussion should be given including the limitations of only using a single imaging device to measure TOTAL ocular blood flow. These are very important corrections to make before the paper can rest on its conclusions. There is a very good likelihood that the authors did not have an adequate study size (n) and/or sufficient imaging techniques to claim no alterations in flow. The conclusions and discussion should include the study limitations!

We agree with you that the methodological limitations of the study needs to be discussed. We added therefore a paragraph in the discussion on page 8 (last paragraph, cont. on page 9):

“The precise and clinically relevant evaluation of ocular perfusion still poses a great challenge. Quantitative determination of total ocular blood flow with a single method is not possible, but combination of different methods is proposed to give a better approximation. (Rechtman, 2003) This fact limits the explanatory power of this and other studies addressing ocular perfusion in ophthalmological diseases. Aim of the present study was to focus on glaucoma patients and it is hypothesized that glaucoma is associated with a localized disturbance of ocular hemodynamics at the optic disc. The optic disc is supplied with blood by the posterior ciliary arteries. The most reliable method for evaluation of hemodynamics in the short posterior ciliary artery is color Doppler imaging. Blood flow velocity in the short posterior ciliary arteries is influenced on the one hand by the vascular tone of the vessel itself but also by the resistance of the dependent downstream vasculature. Thus blood flow velocities in the short posterior ciliary artery reflect also the hemodynamics at the level of the optic disc. The influence of the tested compounds on perfusion of the entire eye cannot be answered by the present study.”

The conclusions have been restructured and we would kindly like to ask to refer to page 9 in the manuscript to see the modified conclusions.

2. No study power is given to ensure that the number of subjects (n) was sufficient to detect any significant differences which may have occurred.

We added information about our analysis of statistic power (methods, page 6, third paragraph):

“In an a-priori-power-analysis the sample size was calculated. H1 was defined by an increase of flow velocity by 50% and a standard deviation of 35%. This definition was applied because preliminary data indicated a change in that range caused by dorzolamide. To reach a statistic power of more than 0.80 at least n=9 individuals for
PSV and n=8 individuals for EDV per treatment group are required. For power analysis, the tool G*POWER V. 2.0 of F. Faul and E. Erdfelder (University of Bonn; available at http://wwwpsycho.uni-duesseldorf.de/aap/projects/gpower/) was used.”

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

3. Grammar improvements are still needed in the paper, the authors must review their work for grammatical correctness!

The authors apologize for any grammatical incorrectness. We asked a translator to check the manuscript and hope to meet your and the editor’s approval.
Reply to Josef Flammer’s report

on the submission to BMC-ophthalmology entitled “Effects of bimatoprost and latanoprost on ocular hemodynamics in normal tension glaucoma: a randomized trial” by Oliver Zeitz et al.

First of all the authors would like to thank Professor Flammer for his comments that were very helpful in revising and restructuring of our manuscript. To aid the reviewer and editors in evaluation our reply, we first repeat the question/comment of the reviewer, (underlined typeface), reply to the comment (plain typeface), and then indicate changes made in the manuscript in **bold typeface**.

General: Drug studies should, whenever possible, be done by controlled double blind studies. It should be stated in the paper that this was not the case in the present study.

We agree with this comment and added a phrase at the beginning of the methods section (page 4, first paragraph of Methods):

[…]The study was designed as an interventional, randomized, prospective, institutional, single-blinded, controlled, clinical trial. […]

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Methods: Please calculate the resistivity index on CDI. This is a very useful parameter.

We calculated RI as a secondary variable and it is given in the tables 1-4. The tables might be got lost during the submission of our first version. We apologize for that.

Statistics: It is not enough to simply compare first with second examination. It would be even more interesting to test whether the different drugs have different influence on the change over time.

Compared to previous studies we chose an extended follow-up period because antiglaucomatous therapy is a long-term therapy. We therefore believe that the long-term effects are more interesting than acute effects after first administration. In the case that there are changes in hemodynamics caused by a certain compound we agree with the suggestion to study the dynamics of this change. The present study is focussed on prostaglandins. Both compounds did not have a significant effect on ocular perfusion after a one month therapy, so that the presented data did not give an adequate starting point to study a time course of changes of ocular hemodynamics.

As the IOP-lowering effect also has an effect on circulation (especially when autoregulation is disturbed) the IOP should be taken into account in a statistical model. This e.g. could be done by using IOP as a covariate.

IOP was lowered on average by 2.5-3.5 mmHg in all study groups receiving an active therapy. This causes a change of ocular perfusion pressure by approximately 5%. Retrobulbar blood flow velocities are proportional to ocular perfusion pressure, which means that a 5% change in ocular perfusion pressure, results in a 5% change in retrobulbar blood flow velocities (if all other parameters affecting retrobulbar blood flow velocities remain stable). The effects we observe with dorzolamide are much higher and this range is the range the present study is focussed on. Thus we believe that the present simple statistic model fits to the hypothesis of this study. The relative low effect of the tested compounds on ocular perfusion pressure was beside of pathophysiological aspects the major argument for performing the present study with NTG patients and not with glaucoma patients starting therapy at much elevated IOP levels.
We added a paragraph to the discussion on the bottom of page 7 (continued at the top of page 8) to clarify that point:

“In the setting of the present study the absolute IOP reduction in relation to ocular perfusion pressure is low and does affect ocular perfusion pressure only by approximately 5%. Retrobulbar blood flow velocities are directly proportional to ocular perfusion pressure. Subsequently, the effect of such a change in intraocular pressure on retrobulbar blood flow velocities is low, particularly compared to the change seen after administration of dorzolamide. Nevertheless, the tendency of an increase of retrobulbar blood flow velocity is visible in all treated groups.”

Results: The term positive control is not very adequate. I would replace this term by putting the name of the drug (dorzolamide). This is also true for the title. You either mention all three drugs or none. You could simply write in the title: The effect of glaucoma drugs on ocular hemodynamics . . .”.

We follow your suggestion and changed the term “positive control” into “dorzolamide group” through the entire manuscript. In addition, we made the following changes:

Title (page 1): “Effects of glaucoma drugs on ocular hemodynamics in normal tension glaucoma: a randomized trial comparing bimatoprost and latanoprost with dorzolamide”

Abstract: According to your suggestion, the entire abstract was re-structured. We would kindly like to ask to refer to page 2 in the manuscript for the modified abstract.

Background (page 4, first paragraph): “[...] The effects were compared with the hemodynamic properties of dorzolamide, which has repeatedly been shown to improve ocular blood flow and can therefore be used as a reference compound for the evaluation of hemodynamic effects of antiglaucomatous eye drops [...]”

Nevertheless, the dorzolamide group has from our point of view the character of a control group, because we wanted to show with these patients, that we are able to detect changes in ocular hemodynamics by CDI and that we can reproduce previously published findings. The essence in our present paper is the results with latanoprost and particularly bimatoprost, as well as the comparison of both. Thus the introduction and discussion remains focussed on these both compounds.

Discussion: You wrote: "While both substances do not improve ocular blood flow to a significant degree, they are both suitable for treatment of normal tension glaucoma". In your results you showed that dorzolamide had a better influence on ocular perfusion. Please discuss the usefulness for NTG treatment in a more neutral way.

With a distance of the couple of weeks while the paper was reviewed by BMC-ophthalmology we totally agree with you, that the conclusion needs to be changed. Please find the modified conclusion on page 9.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

You wrote: "An altered blood flow velocity due to vasoconstricting activity of bimatoprost reported from Allemann and colleagues is not detectable in humans by CDI measurements”. We agree that in-vitro studies can not automatically be extrapolated to humans, even less to glaucoma patients. Nevertheless the fact that both bimatoprost and latanoprost did not significantly improve ocular circulation in these normal tension glaucoma patients, despite a good IOP-lowering effect would rather point in the direction that the drugs themselves are not neutral. If they were neutral, we would rather expect a significant improvement of circulation.
As mentioned above, IOP reduction in a range observed in the present study causes a change of ocular perfusion pressure of 5%, resulting in a change of retrobulbar blood flow velocities by also 5%. This effect is too low to be detected by the present study design and probably also by the CDI method. The tendency of an increase of blood flow velocities can be observed in all treated study groups. This topic is addressed in the inserted paragraph on page 7 (bottom) and 8 (top):

“In the setting of the present study the absolute IOP reduction in relation to ocular perfusion pressure is low and does affect ocular perfusion pressure only by approximately 5%. Retrobulbar blood flow velocities are directly proportional to ocular perfusion pressure. Subsequently, the effect of such a change in intraocular pressure on retrobulbar blood flow velocities is low, particularly compared to the change seen after administration of dorzolamide. Nevertheless, the tendency of an increase of retrobulbar blood flow velocity is visible in all treated groups.”