Author's response to reviews

Title: Changes of Intraocular Pressure after Pharmacologic Pupil dilation

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Version: 2 Date: 25 July 2012

Author's response to reviews: see over
Major Compulsory Revisions

1. In the abstract and in the conclusion paragraph of the Discussion section, it is stated that the IOP increase could be caused by a reduction in outflow facility. To make this conclusion, outflow facility should have been measured. Are tonography data available? If not, then reword the conclusion.

We changed the paragraphs as below.

In Abstract (line 53~54)

Dilation of pupil significantly elevated IOP incidentally. The flare which goes out through the trabecular meshwork may have an effect on IOP. To clarify, further evaluation is needed.

In conclusion paragraph of Discussion section (line 192 ~ 193)

According to the results of this present study, pupil dilation caused an elevation of IOP that may be explained by crowding of protein (flare) into the trabecular meshwork.

2. Other than IOP, there are no diurnal baseline measurements (without dilation) of the other parameters. 24 hour fluctuations in several of these parameters (CCT and ACD for example) do exist. Therefore it is difficult to separate the 24 hour fluctuations from the changes due to dilation. Please provide a discussion of how the authors are confident that the post dilation differences are not confounded by 24 hour fluctuations.

We agree with your opinion. We couldn’t control all the effective factors. Ocular parameters, such as corneal thickness and shape, anterior chamber depth, and axial length are also known to undergo significant diurnal change. ACD can be affected by many external influences such as near vision or distance vision, so it is difficult to measure the diurnal effect. Read SA et al. showed there are small amount of diurnal variation in corneal shape and thickness. Corneal state can be changed as epithelial edema by repeated applying the eyedrops and IOP may be undermeasured. We add the contents as below.(line 183 ~ 189)
There are some limitations in this study. Ocular parameters, such as corneal thickness and shape (24,25), anterior chamber depth (26), and axial length (25) are known to undergo significant diurnal change. We didn’t control these factors. Angle and ACD can be affected by many external influences such as near vision or distance vision, so it is difficult to measure the diurnal effect. Also corneal thickness may be changed as epithelial edema by repeated applying the eyedrops and IOP may be undermeasured. This can affect decreased IOP of late diurnal measurement but it is difficult to calculate the cushion effect by epithelial edema. Further study is needed.


3. As this is a study of pupil dilation, the pupil size should be reported. Is there any correlation between size of pupil and IOP effect? Does pupil size change with repeated application of Mydrin?

We did not measured diurnal pupil size of every hour. We just measured before and 2 and 8 hours after pupil dilation. We added as below.

Mean pupil diameter increased from 2.975 ± 0.498 mm to 6.725 ± 0.717 mm 2 hours after dilation and 6.793 ± 0.616 mm after 8 hours, but it was not statistically significant.(p>0.05) There was no significant variation of pupil size in both time interval.(p>0.05)
Minor Essential Revisions

4. Line 42: add “pupil” before “dilation”.

We added.

5. Line 83. Separating baseline from experimental IOPs by up to 3 months may introduce variability that may not exist otherwise. There are seasonal changes in IOP. This should be discussed briefly in the Discussion section.

We added as below.(line 189~191)

IOP may change as either diurnal variation or seasonal change. Qureshi IA et al. reported IOP tend to increase in winter.[27] The longest time interval of IOP measurement among the patients were 3 months and it may affect the variability.


6. Line 140. Please clarify what is meant by “4 to 6 hours after dilation”. This could be interpreted as dilation was maintained for 4 to 6 hours after application of the Mydrin or it could mean 4 to 6 hours after dilation was no longer present.

We changed the sentence as below.(line 141 ~ 143)

IOP was found to be significantly increased at 4 hours and 6 hours after pupil dilation during preserving pharmacologic mydriasis, and slowly decreased after that time.

7. Line 142. Please clarify the meaning of “outflow rates”. Does this mean the rate of flow through the trabecular meshwork (ul/min) or the trabecular outflow facility (ul/min/mmHg)?

We corrected that as “outflow rate through the trabecular meshwork”.(line 147)
8. Line 147. Aqueous inflow cannot be different from aqueous outflow. What goes in must come out or the eye would blow up or shrink to a raisin. This sentence should be reworded.

I agree with your opinion. In general, normal situation, aqueous flow can maintain its balance by autoregulation. We just said about temporary imbalance due to drug. Aqueous outflow may decrease than inflow temporarily when out of balance. It will keep the balance by autoregulation but there may be some gap until its activation which leads to temporal IOP increase. We changed that sentence and added as below.(line 148 ~ 152)

Temporary imbalance of aqueous flow may have an effect on these patients. Also dilation can affect greater anterior chamber depth and the wider contact region between trabecular meshwork and aqueous. There may be small amount of flare before the dilation and only few flare may also occur due to small rubbing between iris and lens when the pupil begin dilation. Thus IOP may not increase after dilation. Further evaluation with large population based study may be needed.

9. Figure 1. Were flare readings collected in the volunteers on the day without dilation? Indicate with an arrow the time that the Mydrin was given. How much of this flare reduction could be attributed to normal diurnal fluctuations?

We evaluated the flare value of control at just before the dilation. We marked it on the figure 1 and corrected the legend of figure 1 as below.(line 289 ~ 292) But diurnal flare variation was not measured so it’s difficult for us to discuss about the effect of diurnal flare variation with our results. We are sorry about this.

Figure 1. Laser flare photometry values. Flare values decreased significantly after dilation and remained low. The arrows indicate the time mydriatics was given. Intraocular pressure(IOP) at 9A.M. is measured before mydriatics instillation. To keep dilated pupil, mydriatics was instilled every 2 hours until 9P.M. just after IOP measurement.
One group studied for diurnal variation of aqueous flare. They suggested that the aqueous flare intensity was found to be higher during the day and lower in the night. Additionally, they suggested that diurnal variation of aqueous protein concentration is mostly attributable to that of aqueous rate. Considering their reports, diurnal flare variation may affect our results, however, the effect may be little because the variation was relatively small and the graph showed double hump shape like as diurnal IOP curve.


10. Figure 2 raises questions similar to above. Were angle width measurements collected in the volunteers on the day without dilation? Indicate with an arrow the time that the Mydrin was given. How much, if any, of the width increase could be attributed to normal diurnal fluctuations?

We evaluated the flare reading of control value at just before the dilation. We marked it on the figure 2. But diurnal angle variation was not measured so it’s difficult for us to discuss about diurnal angle variation with our results. We are very sorry about this. We added that in the limitation section as below.(line 183 ~ 186)

There are some limitations in this study. Ocular parameters, such as corneal thickness and shape [24,25] anterior chamber depth [26], and axial length [25] are known to undergo significant diurnal change. We didn’t control these factors. Angle and ACD can be affected by many external influences such as near vision or distance vision, so it is difficult to measure the diurnal effect.


Discretionary Revisions

11. Figure 3. This figure can be deleted and the text of the legend reported in the Results section.

We removed the figure 3.

We have made the suggested revision. We hope that the Editors and reviewers will now find this revised manuscript suitable for publication.
Minor Essential Revisions:

1. What is the percentage of eyes that developed post-dilation rise in IOP?

There were decrease in 2 eyes and no change in 8 eyes. In 68.9% patients showed significant IOP increase.

We added as below.(line 113 ~ 114)

Diurnal IOP was elevated in 22 eyes (68.9%), decreased in two, and unchanged in eight.

2. How could you explain those who did not develop any IOP rise according to the proposed mechanism?

There can be imbalance between aqueous inflow and outflow according to the various personal reactions to dilating eyedrops. Aqueous inflow seems to have decreased to a greater extent than aqueous outflow in these patients. Also dilation may affect greater anterior chamber depth and the wider contact region between TM and aqueous. There may be small amount of flare before the dilation and only few flare may occur due to small rubbing between iris and lens at dilated state. Thus IOP may not increase after dilation. However, we didn’t find out reasonable proof in our study. Further evaluation with large number of subjects may be needed. We added as below.(line 150 ~ 154)

Temporary imbalance of aqueous flow may have an effect on these patients. Also dilation can affect greater anterior chamber depth and the wider contact region between trabecular meshwork and aqueous. There may be small amount of flare before the dilation and only few flare may also occur due to small rubbing between iris and lens when the pupil begin dilation. Thus IOP may not increase after dilation. Further evaluation with large population based study may be needed.
3. Where there any pseudoexfoliation patients?

We didn’t include the pseudoexfoliation patients in our study.

4. Any explanation for those who had decrease in their diurnal IOP?

The same mechanism as the answer of number 2 could be applied to explain the problem.(line 150 ~ 154)

Temporary imbalance of aqueous flow may have an effect on these patients. Also dilation can affect greater anterior chamber depth and the wider contact region between trabecular meshwork and aqueous. There may be small amount of flare before the dilation and only few flare may also occur due to small rubbing between iris and lens when the pupil begin dilation. Thus IOP may not increase after dilation. Further evaluation with large population based study may be needed.

*We have made the suggested revision. We hope that the Editors and reviewers will now find this revised manuscript suitable for publication.*