

Peer Review File

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Reviewer A

Response to reviewer #A:

We thank the reviewer for these valuable comments regarding our manuscript. We have carefully revised the manuscript and highlighted the modifications. Line numbers have been added in the revised manuscript for added convenience.

Some comments are concerning on the same topic, so we merged them to make the response letter more concise.

Our responses and the main corrections to the paper are as follows:

Comment 1 & 10:

In the description of the surgical procedure method, the authors state that dissection was done through the superior incision directly without pocketing the two interfaces of the lenticular edge first. This likely led to increased incidence of unintended dissection of the posterior plane. While this does not invalidate the authors' findings, it should be mentioned in the Discussion section as a possible cause for increased incidence of unintended dissection of the posterior plane. Pocketing the two interfaces of the lenticular edge first should also be mentioned in the section listing special considerations for novice surgeons.

Line 95, One major criticism has to do with the fact that most surgeons during the initial phase of learning curve are encouraged to identify the anterior and posterior interface with small creation of a small pocket for the two interfaces before the surgeon proceeds with the anterior dissection completely and then the subsequent dissection of the posterior plane. In line 95, it is mentioned that no initial pocketing of the two interfaces were attempted. One may argue that this could be a contributing factor.

Response:

We agree that most surgeons during the initial phase of learning curve are encouraged to identify the anterior and posterior interface with creation of a small pocket for the two interfaces first. However, it is not necessary. To our knowledge, after solid theoretical study and pig eye practice, doctors had the ability to finish SMILE procedure without pocket first. Moreover, we think creating a small pocket cannot guarantee the right dissection order.

Moreover, in our experience, for an expert, it is easy for him to dissect the surfaces that he intends to. In our previous study, to study the OCT outcomes with difference surface dissection, Dr. Zhou was asked to dissect the anterior surfaces first in right eyes, and

the posterior surfaces first in left eyes of the same patients. (Identification of separated lenticular planes using optical coherence tomography. European Journal of Ophthalmology. 2019) Practice makes perfect.

However, we agree that this might also lead to an increased incidence of unintended dissection of the posterior plane in this study. We added it into the Discussion section. Changes are shown on lines 219-221.

In addition, the dissection in this study was done through the superior incision directly without pocketing the two interfaces of the lenticular edge first. This might also lead to an increased incidence of unintended dissection of the posterior plane.

Comment 2 & 16:

The authors did a great job positing causes for increased rates of unintended dissection of the posterior plane, especially in left eyes. The proposed mechanisms for increased incidence in eyes with high J0 values and low SE/sphere are also well-cited. As the authors also mention long axial length as a risk factor, they should endeavor to explain this as a risk factor as well, given that it seemingly contradicts other risk factors (low SE/sphere).

Line 164, how can long axial length increase the risk of advertent posterior plane dissection? This is somewhat contradictory to your finding of lower spherical equivalents. Long axial length usually means higher myopes?

Response:

As shown in Table 3, eyes without unintended initial dissection had a longer axial length (Without 25.99 ± 1.1 mm vs With 25.34 ± 0.8 mm), which is coincident with other factors. It was a mistake in Line 164. It should be short axial length that increase the risk of advertent posterior plane dissection.

Maybe our description in Results section was misunderstanding, thus, we added T value in Results section as well as the Abstract section.

Changes are shown on lines 42-43, 137-138 and 181.

However, in this study, difficulty in plane dissection during SMILE was encountered significantly more often in eyes with low SE, low sphere, high J0 or short axial length. As shown in Table 3, significant differences were found in sphere ($T = 2.8$, $p = 0.006$), SE ($T = 2.37$, $p = 0.019$), J0 ($T = 2.05$, $p = 0.043$) and axial length ($T = -2.79$, $p = 0.006$) between eyes in which plane dissection was difficult and those in which it was not.

Comment 3&4:

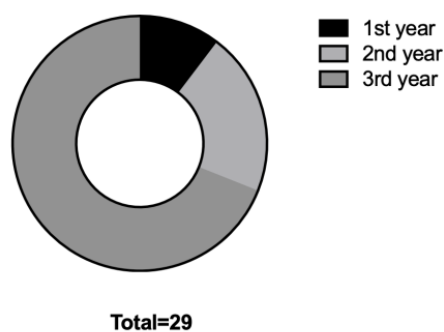
As far as learning curve for a novice surgeon is concerned, authors should have shown us the frequency of this type of complication from the 1st 20 cases to the last 20 cases for the entire sample size. Authors cannot claim that this complication is part of the learning curve.

I suggest Authors to show us the change in this complication overtime in the form of a timetable.

Response:

We compared the frequency with the 1st 20 cases and the last 20 cases for the entire sample size as suggested. There were 3 cases with unintended initial dissection in the 1st 20 cases, and 1 with the last 20 case.

We also did a statistics analyses over the influence of time on the incidence rate of unintended initial dissection. The results were not correlated with time. The cases with unintended initial dissection were showed with the surgery year in the figure below.



The reasons are as follows. Firstly, there was a surgical peak for patients to have the surgery, which was usually summer and winter holiday. The frequency of surgery opportunity was not evenly distributed in the timeline. In some months, even there was no surgery. Secondly, we found out that the eyes with low SE or high J0 values were more likely to be difficult in plane dissection in this study. We cannot decide when did those patients with low SE or high J0 values came to our clinic. It may be in the first or third year. However, With the increase of experience, the surgeon is more and more confident to complete the operation successfully even under the condition of wrongful plane separation.

We agreed that this complication maybe is not part of the learning curve for all the surgeons. We changed the mode of expression.

Changes are shown on line 210.

Change “unintended dissection of the posterior plane is inevitable during the learning curve of SMILE” into “unintended dissection of the posterior plane is a common complication”

Comment 5&15:

What if a left handed surgeon was performing the procedures? Can we draw the conclusion that the complications would be more prevalent in the right eye?

In your discussion section, I suggest authors to mention that the result may potentially be different for a left-handed surgeon.

Response:

It was a very interesting and practical question. All the surgeons in our hospital were right-hand, we thought the results that unintended dissection of the posterior plane was significantly more likely to occur in the left eye was limited to the right-hand doctors. The result may potentially be different for a left-handed surgeon, that unintended dissection of the posterior plane was significantly more likely to occur in the right eye. Changes are shown on lines 48, 173 and 229.

The result may potentially be different for a left-handed surgeon.

In conclusion, in the present study, difficulty in plane dissection during SMILE was encountered significantly more often in left eyes for a right-hand doctor, and in eyes with low SE or high J0 values.

Comment 6 & 17:

It is somewhat contradictory to see that there is a correlation between the level of spherical equivalent and the frequency of this complication but no correlation with the thickness of the lenticule.

Line 172-176 Is there any way for the authors to analyze their data by stratifying pure spherical SMILE from those that had astigmatic SMILE in order to see if this complication is more prevalent among the toric treatments based on the statement in this paragraph.

Response:

Central Lenticular thickness was not a significant factor in the present study. The reason is that peripheral lenticular thickness besides the small incision is the key point rather than central lenticule thickness. The peripheral lenticule thickness of eyes with low SE or high J0 values is thin, thus plane dissection is challenging.

In addition, to make a clear influence of the mixed factor of sphere and astigmatism, we used a linear mixed model was used to analyze factors associated with unintended dissection of the posterior plane, the parameters that we found out should have an independent influence on the incidence, and vice versa.

We changed the explanation into a new paragraph to make it more conspicuous.

Changes are shown on lines 189-192.

Central Lenticular thickness was not a significant factor in the present study. The reason is that peripheral lenticular thickness besides the small incision is the key point rather than central lenticule thickness. The peripheral lenticule thickness of eyes with low SE or high J0 values is thin, thus plane dissection is challenging.

Comment 7:

Can author provide us a short statement concerning management of this type of

complication once it occurs? It would be useful for the novice surgeons.

Response:

We added the management into the manuscript.

Changes are shown on lines 216-227.

Learning to use both hands, and intra-operative optical coherence tomography can be helpful in preventing unintended dissection of the posterior plane.

Comment 8:

I am not sure that the objective of this paper is to reflect the learning curve of this procedure in avoidance of this type of complication. If that is the purpose, I'm afraid the objective is not achieved. It would be better to simply report the incidence of this complication and compare it to the existing literature.

Response:

As written in the abstract, the purpose of this study was to investigate potential risk factors for unintended initial dissection of the posterior plane during small incision lenticule extraction (SMILE). We would like to doctors to pay attention to the eyes with the potential risk factors.

Changes are shown on lines 79-80. We emphasized the purpose of the study.

Comment 9 & 12 & 13:

I think authors' claim concerning the angle and direction of astigmatism along the vertical meridian affecting more difficult dissection with an inadvertent dissection of the posterior plane is a valid one that is worthy of publication.

It is not transparent from your result how many of the eyes in your study had a toric SMILE treatment. This may reflect weather the transition zone that is added to the astigmatic SMILE increases the diameter of the lenticule and makes it such that the side-cut is closer to the SMILE incision at the 90 degrees.

What is the transition zone for your astigmatic treatments?

Response:

Thanks.

244 of 263 eyes had a toric SMILE treatment. As for the reason, we think high J0 may influence the peripheral lenticular thickness beside the small incision. Thin peripheral lenticular thicknesses increase the difficulty encountered during plane dissection.

The transition zone for the astigmatic treatments was 0.1 mm. We added it into the Methods section.

Changes are shown on line 104.

The transition zone for the astigmatic treatments was 0.1 mm.

Comment 11:

Please reflect some of the limitations that are mentioned in this commentary in your discussion. This would make your discussion more balanced and comprehensive.

Response:

We revised the limitation section.

Changes are shown on lines 207-211.

Comment 14:

Line 130, you need a reference to support your statement in this sentence.

Response:

We added the reference. Changes are shown on line 146.

Interface dissection difficulty is one of the most common intraoperative complications during SMILE procedures, especially when performed by relatively inexperienced surgeons. (Reinstein DZ, Carp GI, Archer TJ. 2018. The Surgeon's Guide to SMILE: Small Incision Lenticule Extraction. SLACK, Incorporated)

Comment 18:

Line 179-181, Do you have data to support this statement? In another word authors result showed that the diameter of the lenticule did not have any impact on this complication but in this paragraph, they claim if the edge of the corneal cap and a lenticular side-cut are close to one another then this complication may potentially occur. Please provide evidence in your results section. I was under the impression that the diameter of the lenticule did not have an impact based on your results.

Response:

Thank you for your remind. We did not have data to support the hypothesis. We agreed to delete the confusing paragraph.

Changes are shown on line 204. We deleted related sentences.

Comment 19:

I congratulate the authors for their fine manuscript. I believe authors have provided us some insightful information but the results need better transparency and further stratified analysis. I also recommend authors to revise their discussion section to reflect some of the shortcomings and limitations of their paper.

Response:

Thank you for your comments. We changed the limitation section and some details in the manuscript.

Changes are shown on lines 207-211.

Reviewer B

Response to reviewer #B:

We thank the reviewer for these valuable comments regarding our manuscript. We have carefully revised the manuscript and highlighted the modifications. Line numbers have been added in the revised manuscript for added convenience. Our responses and the main corrections to the paper are as follows:

Comment 1:

Background sentence of the abstract as well as the last sentence should stress/clarify that the study deals with risk factors relevant in the initial learning curve of SMILE

Response:

We added it into the sentences.

Changes are shown on lines 32 and 79.

Comment 2:

Informed consent statement is unclear: was IC given orally or written

Response:

Written informed consent was obtained from all the patients.

Changes are shown on line 95.

Written informed consent was obtained from all the patients.

Comment 3, 9 & 10:

Side cut length: why only 2mm? Discuss!

In the European Union, the manufacturer of the Visumax platform (Carl Zeiss Meditec AG) demands a novice surgeon to start with 20 cases of the Relex-FLEX procedure (an all femtosecond-laser predecessor technique of SMILE, similar to LASIK) before transferring to SMILE, which would also be the reviewer's recommendation to novice surgeons.

Furthermore, a broader incision of up to 4.00mm fostering easier identification of the lenticule border can be used without compromising safety or efficacy.

Response:

The comments are concerning on the same topic, so we merged them to make the response letter more concise.

We quite agree with the European guide. However, small incision brings smaller wound healing reaction. For the benefit of patients, and in combination with our hospital's own conditions that many experienced doctors in SMILE surgery in our hospital, who can provide help in time, the surgeon in this study, also many Chinese doctors did not do FLEx surgery in the beginning, but directly used 2-mm small incision to complete the surgery. In addition, very solid theoretical study has been learnt and more than 50 pig eyes has been practiced before the operation on human beings.

We added the related discussion into the limitation section.

Changes are shown on lines 207-209.

A limitation of the present study is that the surgery and practice experience of a single surgeon may differ from that of others. Moreover, for the benefit of patients, the surgeon started SMILE with a 2-mm incision.

Comment 4:

Line 93: Surgical procedure: why were the lenticule planes not “pocketed” before separation (which is commonly employed surgical approach to SMILE)?

Response:

We agree that most surgeons during the initial phase of learning curve are encouraged to identify the anterior and posterior interface with small creation of a small pocket for the two interfaces first. However, it is not necessary. As we known, many doctors in China did not do the pocket first. After solid theoretical study and pig eye practice, we had the ability to finish SMILE procedure without pocket first. Moreover, we think creating a small pocket can not guarantee the right dissection order.

Moreover, in our experience, for an expert, it is easy for him to dissect the surfaces that he intends to. In our previous study, to study the OCT outcomes with difference surface dissection, Dr. Zhou was asked to dissect the anterior surfaces first in right eyes, and the posterior surfaces first in left eyes of the same patients. (Identification of separated lenticular planes using optical coherence tomography. *European Journal of Ophthalmology*. 2019) Practice makes perfect.

However, we agree that this might also lead to an increased incidence of unintended dissection of the posterior plane in this study. We added it into the Discussion section. Changes are shown on lines 204-206.

In addition, the dissection in this study was done through the superior incision directly without pocketing the two interfaces of the lenticular edge first. This might also lead to an increased incidence of unintended dissection of the posterior plane.

Comment 5:

Which surgical instrumentation was used with the right hand to initially enter the plane to be dissected? Which instrument was used for dissection itself?

Response:

As our previous study, a spatula (model No.52435T; 66 Vision-tech Corp., Suzhou, China) separated the cap–lenticule interface through the 2-mm incision at the 12-o’clock position without pocketing the two interfaces of the lenticule edge first. (Development of the Continuous Curvilinear Lenticulerrhexis Technique for Small Incision Lenticule Extraction. *Journal of Refractive Surgery*. 2015.10.3928 /1081597x-20141218-02)

We added the surgical instrumentation mode into the Methods. Changes are shown on

lines 106-108.

During the dissection, the surgeon used the left hand to control the eye with forceps and used the right hand to dissect the anterior interface with a spatula (model No.52435T; 66 Vision-tech Corp., Suzhou, China) followed by the posterior interface through the superior incision directly.

Comment 6:

A wrongful plane separation of 11% is exceptionally high, even considering the initial learning curve was included. Did the results get better during the course of the first 263 eyes operated?

Response:

Yes. However, it could not be shown in the analysis. Since there was a surgical peak for patients to have the surgery, which was usually summer and winter holiday, the frequency of surgery opportunity was not evenly distributed in the timeline. In addition, operated eye condition is diverse. There was no statistical relationship between the probability of complications and the operation time. However, With the increase of experience, the surgeon is more and more confident to complete the operation successfully even under the condition of wrongful plane separation.

The authors concluded and added some of their experience. Changes are shown on lines 216-227.

Comment 7:

Authors should state the overall experience level of the corneal surgeon (e.g. how much experience with LASIK or keratoplasty?)

Response:

Thank for your advice.

The surgeon in the present study have finished more than 100 LASIK, LASEK and PRK.

We added it into the manuscript. Changes are shown on lines 98-99.

Comment 8:

Tables 2 and 3 are missing and apparently not part of the submission despite being referred to in the manuscript body and, hence, unfortunately cannot be considered in the review process.

Response:

Sorry, you didn't see the forms due to our uploading errors. We separated them carefully to confirm the stable uploading this time.

Changes are shown on Table 2 and 3.

Comment 11:

Moreover, minimum lenticule thickness may be increased for easier identification of lenticule planes and better refractive outcome in very thin lenticules (Siedlecki, Luft et al. JRS 2018: Variation of Lenticule Thickness for SMILE in Low Myopia).

Response:

Thank you for your suggestion. We added it into our manuscript.

Changes are shown on lines 227-227.