

# Comment on: Amniotic membrane for covering high myopic macular hole associated with retinal detachment following failed primary surgery

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**Dear Editor,**

Qiao *et al*<sup>[1]</sup> have published “Amniotic membrane for covering high myopic macular hole associated with retinal detachment following failed primary surgery”. This prospective non-control case study presents the efficacy and the safety of amniotic membrane (AM) for covering high myopic macular hole (MH) associated with retinal detachment (RD) following failed primary surgery. They explained that they improved the technique published by Caporossi *et al*<sup>[2]</sup>, with a new technique using a covering AM rather than an AM plug. Indeed, it is interesting to discuss about surgical techniques using this adjuvant to close complex MHs. Whatever the adjuvant, the question of “to fill or not fill the MH” is still unsolved.

However, even if their paper was not a review, we were surprised they did not mention a surgical variation we developed, using a lyophilized AM (IAM) in epiretinal position (*i.e.*, covering AM), that we published before the submission of their study, in may 2021<sup>[3]</sup>. We published for the first time this adjuvant used in epiretinal position to treat different complex MHs, including persistent MHs in highly myopic eyes. We

would appreciate Qiao *et al*<sup>[1]</sup> discussed about our point of view and our rationale of the published standardized protocol, which puts into perspective all the issues in treating complex MHs.

Thus, they could have detailed three key points: the nature of AM, the position of AM, and the orientation of AM. Additional references were cited, which could deliver the readership a more precise overview of the issues, when an adjuvant (especially AM) is used to promote MH closure. Our standardized surgical technique<sup>[3]</sup> combined the advantages of the lyophilization and of the epiretinal position, with “chorion up” (*i.e.*, IAM used as a “true” overlay defined by Letko *et al*<sup>[4]</sup> for corneal applications). We used sterile devitalized trephined trypan blue-stained discs of IAM (Visio Amtrix, TBF, Mions, France) with “chorion up” to cover the MH with ample overlap for easier handling and positioning.

Regarding the nature of AM, cryopreserved AM (cAM), a widely available tissue, provided encouraging results either used first as a plug transplanted into the subretinal space<sup>[2,5-8]</sup> or put secondly in epiretinal position<sup>[9]</sup>. The team of Caporossi *et al*<sup>[2]</sup> and Rizzo *et al*<sup>[5]</sup> were pioneer to use cAM and positioned it as plug with “chorion down”, facing the retinal pigment epithelium (RPE) (*i.e.*, as an inlay<sup>[4]</sup>). By analogy with the experience in the use of AM for the cornea, we agree with this orientation “chorion down” of plug of cAM subretinally transplanted, as it may ensure proper adhesion on RPE, preventing from secondary displacement. Moharram *et al*<sup>[9]</sup> were the first and the only team who reported epiretinal use of cAM to close MH-RD in highly myopic eyes: they positioned the cAM plug with “chorion down”, facing the retina, therefore not as a “true” overlay.

Compared to cAM, the physical, biological and structural properties of IAM are similar<sup>[10]</sup>. Compared to cAM, IAM presents several advantages: indeed, immediate availability in the operating room with simpler logistics<sup>[11]</sup>; long shelf life at room temperature; thinner and more transparent<sup>[8]</sup>, which could help it to be integrated when used as an inlay (in the subretinal position), or be a smart interface with less mask effect when used as an overlay (in the epiretinal position that

we had developed<sup>[3]</sup>); easy to trephine before rehydration, roll up allowing “no touch” technique for IAM insertion thanks to a dedicated catheter.

Regarding the position of AM, we had reported our mutually non-exclusive hypotheses: 1) Covering IAM or overlay could play the same role as an inverted internal limiting membrane (ILM) flap<sup>[12]</sup>, but would be larger, easier to position, more stable. It can be compared to a biological bandage: it could act as a scaffold to promote healing and more physiologic closure mechanism versus subretinal position<sup>[13]</sup>; besides, if complete closure is impossible, it acts as a patch and prevents MH-induced RD, particularly in highly myopic eyes. We hoped to obtain excellent functional results without filling the MH, by analogy with those already obtained for ILM used as an epiretinal inverted flap versus insertion into the MH<sup>[14]</sup>: epiretinal position resulted in significantly better recovery of photoreceptor layers, therefore better visual recovery; 2) The overlay better respects the organization of all retinal layers, preventing induction of foveal gliosis by interposition of exogenous tissue (cAM or IAM) transplanted into the subretinal space between the MH edges; 3) It seemed safer not to manipulate the MH edges, so as not to worsen the RPE and neuroretina injuries, particularly during graft insertion<sup>[15]</sup>; 4) The overlay could prevent the parafoveal atrophy described after retraction of cAM or IAM used as inlays<sup>[16]</sup>; 5) Even considering the time taken to fully unfold the trephined IAM for overlay, operating time can be shortened versus inlay, thus reducing light toxicity<sup>[17]</sup>; 6) If an adverse event occurs, the technique is reversible and the IAM can be removed.

In our series of complex MH cases with no alternative<sup>[3]</sup> (minimum and maximum diameters, respectively 945±330 and 1507±717 µm; axial length 26.58±3.38 mm; number of prior surgeries 1.4±0.96), the overlaid epiretinal large disc of ILM blue-stained IAM with “chorion up” seemed to promote anatomic success (80% of MH closed, 20% had reduced diameter, all MH-associated rhegmatogenous RD were reattached without recurrence) and functional recovery (mean logMAR BCVA improved from 1.92±0.58 to 1.17±0.57,  $P<0.001$ , with 90% of eyes achieving  $\geq 0.3$  logMAR improvement) with 1-year follow-up. Thus, our technique using IAM as overlay should be considered as valuable encouraging minimally invasive surgery, among the options to close recurrent or persistent MHs. We have followed the same rationale regarding the position, using another adjuvant in epiretinal position: femtosecond laser-cut autologous anterior lens capsule can help safely close refractory MH and provide satisfactory functional results<sup>[18]</sup>.

Indeed, from now randomized multicentric studies should compare these techniques to one another.

## ACKNOWLEDGEMENTS

**Conflicts of Interest:** Garcin T, None.

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### Authors Reply to the Editor

#### Dear Editor,

We appreciate the attention and comments by Professor Thibaud Garcin about our article<sup>[1]</sup> “Amniotic membrane for covering high myopic macular hole associated with retinal detachment following failed primary surgery”. We are pleased to have more ophthalmologists to understand and approve of the meaning of this technique. This also strengthens our determination to continue the exploration of the clinical application of this new technique.

Actually, our research and literature search had focused on treating recurrent and refractory high myopic macular holes (MHs) in the past few years. Since March 2019, our team had started to research a new technique for treating MH which we called amniotic membrane (AM) covering, and also started the collection of the research data. The first manuscript of the Chinese version was completed at the end of 2020. The sample data which could be included in this research such as visual acuity (VA), clinical parameters, and typical optical coherence tomography (OCT) images had also been presented in the article. After completing the collation and statistic of the data and the English translation and revision of the manuscript, this article was submitted to the magazine in June 2021. However, the article<sup>[2]</sup> of Professor Thibaud Garcin published online in May 2021. Before this time, we had completed the writing of the English paper, remaining only the final data statistics, picture checking, and the final revision of the English paper, so we did not continue to pay attention to the publication of the latest literature of relevant research. After the reminder of Professor Thibaud Garcin, we have searched and read several articles<sup>[1,3]</sup> by them. We admire and agree with the ideas and technological innovations of Professor Thibaud Garcin, and we

find a highly consistency in understanding of the mechanism of MH healing between our view and Professor Thibaud Garcin’s view. However, there are also many differences about the specific surgical method, the use purpose and method of the auxiliary material between our research and Professor Thibaud Garcin’s research. And the specific discussion is as follows.

First, we strongly agree with the importance of covering the auxiliary material on the hole surface in the MH healing mechanism. Whether it is the internal limiting membrane (ILM) or AM or other materials, as long as the auxiliary material provides tight coverage of the MH will help the MH healing. Even the MH in pathological myopia combined with choroidal atrophy or other refractory giant MH could be healed. This phenomenon is similar to that a large area corneal epithelial defect can be repaired more quickly after wearing a corneal bandage lens. We speculate that this healing mechanism is due to that the auxiliary material provides a bridge for retinal glial cells to crawl, thus accelerating the healing of MH.

Therefore, the second point to be explained from the above mechanism is that it does not matter what the auxiliary material itself is, as long as we provide such a covered environment, the similar effect can be achieved. But due to the importance and particularity of the macular location, the requirements of the material are actually very demanding. The material needs to be transparent, have no toxic and side effect, have no repulsive reaction, and should be obtained easily. And the operation of implanting this material needs to be as simple as possible, the surgical incision needs to be as small as possible. The ILM in macular area should be the best material at present, so we recommend the method of inverting ILM flap<sup>[4-6]</sup> at the initial surgery. But in many complex cases, we could not obtain enough ILM for surgery. In the absence of ILM, we can choose lens capsule, peripheral retina and AM to replace it. Currently, after a comprehensively evaluate that the AM has the advantages of easy to obtain, simple operation, and no increasing iatrogenic damage, we preferentially choose AM to treat recurrent and refractory MHs.

Third, although we treated MH by biological AM (bAM, Ruiji Bio-Engineering Technology Co., Ltd., Jiangxi Province, China), similar to the lyophilized AM (IAM) of Professor Thibaud Garcin, the fresh AM and cryopreserved AM also could be used after disinfection. And some scholars had already applied the latter two AM in clinical treatment<sup>[7-8]</sup>. In the published article<sup>[2]</sup>, we made the basal layer of bAM face down to the retina. The aim was to use the active factors of bAM to promote the healing of MH. But considering that the bAM had been inactivated, we only need the bAM acted as a bridge in the healing of MH. And Professor Thibaud Garcin likened this role of IAM to a biological bandage<sup>[1]</sup>. We speculated that

whether the epithelial layer or basal layer contacts the retina, the healing effect of MH after surgery may be no difference. Before covering the bAM, we stained ILM by indocyanine green to observe whether there was any residual ILM around MH and whether the peeling range of ILM was sufficient in the previous operation. There is no way to buy trypan blue in China now, so we can only choose indocyanine green to stain ILM. In the literature<sup>[9]</sup> provided by Professor Thibaud Garcin, it stained the retina for 20min during the experiment. However, our staining time of the ILM did not exceed 30s, and most of the staining time was controlled in 10s, so the risk of toxic reactions to the retina was extremely low. In addition, although the bAM we purchased was translucent, it could still be easily identified and operated after implantation in the eyes, so the staining of bAM was not required. This both simplified the surgical steps and reduced the potential toxic effects of staining material to the retina.

Fourth, our approaches of surgical operation details were also different from Professor Thibaud Garcin's approaches. The raw material of bAM we purchased was a 10×10 mm<sup>2</sup> square membrane, and the manufacturer had distinguished the epithelial layer and basal layer with the concave and convex surface design. We did not use the biopsy punch to cut the bAM into circles, but trimmed it in a simpler and faster way: we directly used the ophthalmic microscissors to trim the bAM into a square, about 2 to 3 mm long. If the hole was larger, the bAM could be trimmed a little larger to ensure that the edge of AM could exceed and cover the edge of the hole. We drained the subretinal fluid through the MH itself during gas-fluid exchange and covered the trimmed bAM directly on the surface on the MH. The residual fluid around the transplanted bAM was drained repeatedly with a flute needle to ensure the transplant attaching retina closely and no longer moved. The key to the success of the surgery was to avoid the displacement of bAM. If the bAM displaced, the surgery failed. In our study, two patients were underwent a secondary operation to adjusted the displaced bAM and supplemented gas to vitreous cavity.

Fifth, the AM is not completely transparent after all, and it cannot be absorbed for a long time. We followed up our patients for more than two years and observed no signs of AM absorption. Therefore, our view is that since the translucent AM itself may lead to a decrease in VA within its covered area, the transplant should not be too large, and it is enough to just cover the edge of the hole. And our research results also confirm the feasibility of this method. Professor Thibaud Garcin had also studied the use of autologous anterior lens capsule (ALC) transplantation to treat refractory MHs<sup>[3]</sup>, solved the problem of the opacity of auxiliary material and achieved a satisfactory curative effect. However, this method requires combining cataract surgery with fundus surgery, which

increases the surgical steps and surgical difficulties. Moreover, the ALC is very thin in thickness and it could increase the possibility of displacement of transplant during or after surgery. This procedure is also more technically demanding for the operator. And this surgical method is not suitable for patients with intraocular lens eyes.

Sixth, we all agree that the technique of covering AM is better than plugging AM. This new technique can reduce the damage to the retinal pigment epithelium (RPE) below the MH during tamponade. During the healing of MH, the each layer of retina can also be healed into their corresponding structures with a clearer stratification rather than a disturbed scar healing<sup>[7-8]</sup>.

In summary, we agree more with the technique of covering AM. The AM as a cover material is only a relatively good choice at present. In consideration of the defective of AM, this technique is mainly used for the patients who have low VA and recurrent, refractory MH, especially for the high myopic MH combined with ultra-long ocular axis and choroid atrophy. We have also researched on new transparent auxiliary material and the research findings will be submitted soon. We look forward to having better auxiliary materials that can meet the above requirements to apply into the clinical treatments in the future. We appreciate Professor Thibaud Garcin and other colleagues once again for their attention to this technique. With your peers, the road of medical exploration will be more interesting and wonderful.

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