Human amniotic membrane graft for refractory macular hole: a single-arm meta analysis and systematic review

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Review question / Objective: Currently, pars plana vitrectomy (PPV) with ILM peeling is the gold standard treatment for full thickness macular hole (FTMH). Despite of the high macular hole closure rate, a refractory FTMH may occur. The next step for a recurrent or persistent MH is usually repeat PPV with extended ILM peeling. This is not always an option especially with high myopia patients or those who had already undergone an aggressive ILM peeling at initial surgery. A variety of novel techniques have been developed to address this issue, among which human amniotic membrane seems to be a promising adjuvant. However, there are still uncertainties regarding the integration and the long-term effects of of the graft.


INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 February 2022 and was last updated on 23 February 2022 (registration number INPLASY202220098).
However, there are still uncertainties regarding the integration and the long-term effects of the graft.

**Condition being studied:** A full-thickness macular hole (MH) is defined as a full-thickness break within the fovea that can cause a significant decrease in vision. The annual incidence has been reported to be between 4.05 and 8.69 eyes per 100,000 population per year. The primary closure rate for macular holes is greater than 90% with current methods, which consist of a pars plana vitrectomy with or without internal limiting membrane (ILM) peeling, and gas tamponade. Macular holes may reopen in approximately 3.3–9.2% of cases, and larger holes are more likely to fail primary surgery. The management of recurrent and persistent MHs remains challenging for vitreoretinal surgeons.

**METHODS**

**Search strategy:** Studies published in PubMed, Embase, Web of science, Cochrane library, Wanfang Data Knowledge Service Platform, China National Knowledge Infrastructure databases, sinomed(CBM), VIP database, Clinical Trials.gov and Chinese Clinical Trial Registry. The search keywords were “Retinal Perforations” OR “Perforation, Retinal” OR “Perforations, Retinal” OR “Retinal Perforation” OR “Retinal Holes” OR “Hole, Retinal” OR “Holes, Retinal” OR “Retinal Hole” OR “Retinal Dialyses” OR “Dialyses, Retinal” OR “Retinal Dialyse” OR “Retinal Tears” OR “Retinal Tear” OR “Tear, Retinal” OR “Tears, Retinal” OR “Retinal Breaks” OR “Break, Retinal” OR “Breaks, Retinal” OR “Retinal Break” OR “Macular Holes” OR “Hole, Macular” OR “Holes, Macular” OR “Macular Hole” AND “amnion” OR “Amnions” OR “Amniotic Membrane” “Amniotic Membranes” OR “Membrane, Amniotic” OR “Membranes, Amniotic” OR “Amniotic membrane plug” OR “hAM” OR “amnion membrane graft” OR “amnion membrane grafts”. The search terms “Retinal Perforations” OR “macular hole” OR “retinal breaks” OR “retinal hole” OR “macular perforations” AND “amnion” OR “amnion plug” OR “amnion transplantation” OR “amnion patch” were searched in Chinese databases such as China National Knowledge Infrastructure (CNKI), Wanfang database, Sinomed(CBM) and VIP database. Clinicaltrials.gov and Chinese clinical trial registry were searched for any unpublished clinical trial.

**Participant or population:** Refractory macular hole, reopened macular hole, refractory full thickness macular hole, unclosed macular hole, failed macular hole.

**Intervention:** Human amniotic membrane transplantation.

**Comparator:** Untreated refractory macular holes

**Study designs to be included:** Prospective and retrospective studies, case series, randomised controlled studies, and non-randomized controlled studies.

**Eligibility criteria:** The inclusion criteria were as follows: (1) prospective studies and retrospective studies (including clinical studies in which hAM graft were performed following a failed vitrectomy and ILM peeling) (2) Outcome: at least one outcome parameter (pre and postoperative logarithm of the minimum angle of resolution best-corrected visual acuity (LogMAR BCVA) or visual acuity improvement rate, macular hole closure rate, hAM dislocation/contracture rate) . The exclusion criteria were as follows: (1) incomplete data for the targeted outcomes; (2) lack of information of previous surgery (exclude studies that did not clarify whether the ILM peeling were performed during the previous operations); (3) reporting overlapping data or reports with no outcomes of interest;(4) conference abstracts, reviews, comments, case reports of fewer than 3 subjects, cases that reported incomplete information, and cellular or animal studies.

**Information sources:** PubMed, Embase, Web of science, Cochrane library, Wanfang Data Knowledge Service Platform, China National Knowledge Infrastructure databases, sinomed(CBM), VIP database,
Clinical Trials.gov and Chinese Clinical Trail Registry.

Main outcome(s): The following data are collected: author's names, journal, publication's year, number of patients and eyes, gender (male/female), age (years), lens status (pseudophakic or phakic), preoperative maximum diameter of refractory full thickness macular hole (FTMH size, measured in microns), preoperative best corrected visual acuity (BCVA) converted to logarithm of minimum angle of resolution (logMAR), previous surgical technique used, interval from the previous treatment of primary FTMH to treatment of refractory FTMH (surgical interval, months), tamponade agent used, rate of refractory FTMH closure (%), morphology of FTMH closure, postoperative BCVA (logMAR), BCVA gain (postoperative BCVA-preoperative BCVA), complications, follow-up (months). The articles are divided into subgroups according to the primary diagnosis, hAM type used in treating the refractory MH. For the articles reporting a series of patients in which one or more of them presented characteristics not meeting inclusion criteria of the current study, if available, a selection of the only eligible patients from the table of published data in the analysed article is made and summary statistics are calculated. Pre and postoperative logarithm of the minimum angle of resolution best-corrected visual acuity (LogMAR BCVA) or visual acuity improvement rate, macular hole closure rate, hAM dislocation/contracture rate.

Additional outcome(s): None.

Quality assessment / Risk of bias analysis: We assessed the quality of included studies using JBI Critical Appraisal Checklist for Case Series. The JBI critical appraisal checklist for case series contains 10 questions. Four answers represent the extent to which the article meets the criteria (yes, no, unclear, and not applicable). Two reviewers (Zhang, Li) independently assessed the quality of all the studies included in the systematic review. We resolved any discrepancy in the assessment through discussion until we reached consensus.

Strategy of data synthesis: All data analyses were performed using the STATA SE16.0 (StataCorp, College Station, TX, USA). The effect size of all combined results is represented by the 95% CI (with upper and lower limits). Statistically heterogeneous heterogeneity between studies was assessed using the I2 and chi-squared test. I2 > 50% indicates statistical heterogeneity, random effect model was used and sensitivity analysis was performed for the calculation. Otherwise, the fixed-effects model was used for analysis sensitivity analysis was not performed. Moreover, potential publication bias of included studies was examined using the Begg's and Egger's tests. The articles are grouped according to the surgical techniques used for treating refractory full thickness macular hole (FTMH).

Subgroup analysis: Through the study design, the VA improvement rate was analyzed in subgroups according to preoperative diagnosis. We define the HM-MH subgroup as cases with axial length over 26mm or been directly described as HM-MH in the studies but without retinal detachment, the MH-RD subgroup as cases of MH coexisted with retinal detachment before surgery, the IMH subgroup as macular hole without obvious etiology (axial length < 26mm, exclude traumatic macular hole). All data analyses were performed using the STATA SE16.0 (StataCorp, College Station, TX, USA). Forest plots and funnel plots are also drawn by STATA SE16.0 (StataCorp, College Station, TX, USA).

Sensitivity analysis: For the subgroup analysis whose pooled effects are of great heterogeneity (I2 > 50%, P > 0.1), we performed the sensitivity analysis to determine the robustness of the overall treatment effects because of the great heterogeneity and small sample size in the included studies. Sensitivity analysis was performed by removing individual studies one by one from the pooled results. To see
if the pooled analysis in subgroups changes significantly when studies were omitted.

**Language:** The search was not restricted by region, race, age, language or payment method.

**Country(ies) involved:** China.

**Keywords:** Human amniotic membrane, refractory macular hole, vitrectomy, single-arm meta-analysis.

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