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# Fluid-air exchange as a secondary treatment for unclosed macular hole after primary vitrectomy: a retrospective cohort study

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## Abstract

● **AIM:** To evaluate whether fluid-air exchange is an effective treatment for unclosed macular hole (MH) after primary vitrectomy.

● **METHODS:** This retrospective study included patients with an unclosed MH within 1-2wk after vitrectomy. Patients were divided into the vitrectomy, fluid-air exchange, and observation groups according to the secondary treatment. The anatomical outcomes and postoperative visual acuity were recorded.

● **RESULTS:** The analysis included 25 eyes in 25 patients (16 females) aged 37-74y (vitrectomy group, $n$=10; fluid-air exchange group, $n$=9; observation group, $n$=6). Closure rate after secondary treatment was 100% in the vitrectomy group, 88.9% in the fluid-air exchange group and 33.3% in the observation group. Optical coherence tomography images obtained at the last follow-up revealed that continuity of the external limiting membrane (ELM) was significantly more common ($P$=0.004) in the fluid-air group (8/9 eyes, 88.9%) than in the vitrectomy group (2/10 eyes, 20.0%) and that macular morphology was better in the fluid-air group than in the vitrectomy group. No serious complications were observed after secondary treatment.

● **CONCLUSION:** Fluid-air exchange is an alternative option to repeat vitrectomy for patients with an unclosed MH after initial vitrectomy with elevated macular edge.

● **KEYWORDS:** fluid-air exchange; macular hole; vitrectomy

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## INTRODUCTION

Idiopathic macular hole (IMH) is a discontinuity in the retina that most often involves the fovea[1]. The incidence of macular hole (MH) requiring surgery was recently determined to be 3.14 per 100 000 person-years in Korea[2], and the prevalence was reported to be 1.6 per 1000 people in China[3] and 2.7 per 1000 people in India[4]. IMHs are thought to arise due to vitreoretinal traction at the fovea[5]. IMH commonly presents as decreased vision, metamorphopsia and central dark spots[5]. The prognosis of untreated MH is poor, with visual acuity falling to 20/200 or worse in 74% of affected eyes after 5 or more years[6]. Thus, early detection and treatment of IMH is essential.

Management options for IMH[7] include observation (for early-stage disease), pneumatic vitreolysis, vitreopharmacolysis and vitreoretinal surgery including pars plana vitrectomy (PPV) with the inverted internal limiting membrane (ILM) flap technique, vitrectomy with double ILM insertion, PPV with complete ILM removal, vitrectomy with insertion of multiple free ILM flaps, vitrectomy with lens capsular flap transplantation[8-15]. Vitrectomy combined with peeling of the ILM and expansive gas tamponade is currently the primary treatment method and achieves MH closure rates of 79%–98%[16-19]. Unfortunately, IMH closure is not successful in a minority of patients treated with vitrectomy. It has been speculated that the non-closure or reopening of an MH may involve residual traction from an epiretinal membrane or inadequate face-down positioning after the operation[20]. The factors associated with a poor surgical outcome include lower preoperative visual acuity, longer duration of symptoms, larger hole size, higher stage, and presence of a posterior vitreous detachment[21-22]. When primary surgery fails to close an IMH, the re-intervention strategies include secondary vitrectomy with extension of the ILM peel, translocation of an ILM flap, use of an autologous neurosensory retinal free flap, transplantation of autologous neurosensory retina or transplantation of human amniotic membrane[23-29]. However, re-intervention with a complex surgical procedure increases the risk of infection and other complications and places additional psychological and financial burdens on the patient. Fluid-gas exchange with an expansive gas (such as sulfur hexafluoride or perfluoropropane) is a straightforward and cost-effective method of closing a MH after failure of primary surgery[30-34].

The use of air instead of expansive gas for tamponade has the advantages of shorter absorption time in the eye, shorter postoperative face-down time, greater patient comfort and reduced risk of raised intraocular pressure (IOP)[16]. Furthermore, most studies have indicated that air tamponade achieves comparable IMH closure rates to gas tamponade, especially for small/medium MHs (≤400 μm)[16-19,21,35]. However, it has not been established whether fluid-gas exchange with sterilized air can be used to treat an MH that persists after primary surgery.

Therefore, the aim of this retrospective analysis was to evaluate whether fluid-gas exchange with sterilized air was an effective secondary treatment for patients with an unclosed MH after the initial operation.

## PARTICIPANTS AND METHODS

**Ethical Approval** This study was conducted in accordance with the tenets of the Declaration of Helsinki and is registered in the Chinese Clinical Trial Register (ChiCTR1800019620). The study was approved by the Ethics Committee of The Eye Hospital, Wenzhou Medical University (KYK[2018] No.41). The patient's informed consent was waived by the ethics committee.

**Study Design and Participants** This retrospective study included patients diagnosed with an unclosed MH within 1–2wk after vitrectomy at The Eye Hospital of Wenzhou Medical University (Wenzhou, China) from January 1, 2017 to June 30, 2022. The closure of the MHs include two situations: 1) The outer layers of macular or external limiting membrane (ELM) are continuous. 2) The edge of the MH is flat, and the macular layers are interrupted or tamponade. The enclosure of the MHs: the MH became warped and was unchanged or enlarged in size. The inclusion criteria were: a diagnosis of IMH was made based on the history and clinical examination (including slit lamp and dilated fundus examinations); the patient was treated with vitrectomy, and failure of MH closure was detected within 1–2wk after primary surgery. Patients with glaucoma or optic neuropathy were excluded from the current study. The physician selected the secondary treatment strategy according to the characteristics of the unclosed MH and the patient's wishes after the primary vitrectomy. It is advised that patients having unclosed MHs greater than 400 μm have another vitrectomy. We advised a fluid-air exchange for patients with unclosed MHs less than 400 μm, and we advise this procedure even more if the MH has an elevated edge. And a fluid-air exchange is advised for patients who are around two weeks away from their initial operation. All patients were under standard 23G vitrectomy with ILM peeling with sterilized air tamponade on first vitrectomy. The patients were divided into a vitrectomy group, fluid-air exchange group and observation group according to the secondary treatment used. During primary vitrectomy, the extent of ILM peeling during initial PPV in all patients was 3 papilla diameter (PD). Only one patient in the vitrectomy group retained 1 PD fovea-sparing during ILM peeling, while two patients in the fluid-air exchange group and two patients in the observation groups did the same. In the vitrectomy group, only one patient underwent ILM flap filling; in the fluid-air exchange group, three patients underwent ILM flap filling and in the observation groups, only one patient underwent ILM flap filling. ILM flap covering was not performed by any patients. Patients in the observation group had refused secondary surgery and requested observation instead.

**Data Collection** The patient's demographic data and clinical examination data were collected from the electronic medical records, including age, gender, surgical eye, IOP, and the results of preoperative and postoperative visual acuity, slit-lamp, spectral-domain optical coherence tomography (SD-OCT) and fundus examinations (including the size and shape of the MH). The primary outcome (MH closure rate) and secondary outcomes (visual acuity and time to secondary treatment) were also collected during the postoperative follow-up. Additionally, any complications during follow-up were collected up to the time of the last outpatient visit after the second treatment.

**Surgical Procedure**

**Secondary vitrectomy** Patients in the vitrectomy group were administered retrobulbar anesthesia in the operating theatre and placed in the supine position. Standard 23 G, three-port, PPV was carried out after irrigation of the conjunctival sac with 5% povidone iodine. An infusion tube was placed in the temporal side to lavage the vitreous cavity, and an inverted ILM flap was used to close the MH. Five of them underwent ILM flap filling and five underwent flute needle massage for the MH in our study. Fluid-air exchange was performed before the cannula was removed. The IOP was measured by finger palpation at the end of the procedure. Face-down positioning was adopted for one week after surgery.

**Fluid-air exchange** Patients in the fluid-air exchange group were treated in the outpatient department. The patient was placed in the supine position after the administration of topical anesthesia. The conjunctival sac was irrigated with 5%

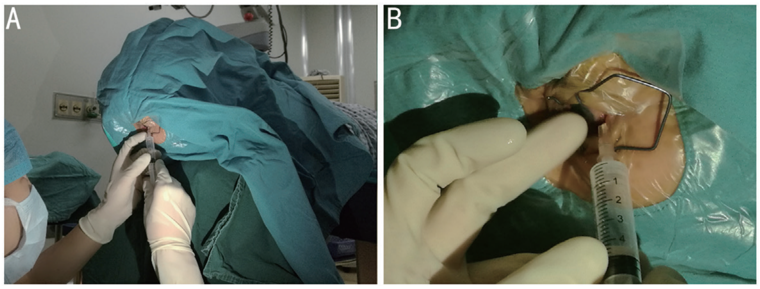


**Figure 1 Intraoperative photographs showing the fluid-air exchange technique** A: The patient adopted the prone position, and the needle was inserted obliquely at a point 3.5 mm from the inferior temporal limbus; B: Measurement of intraocular pressure during the injection of sterile air. The clinician in Figure 1 is one of the co-authors, and the patient provided informed consent for inclusion in this figure.

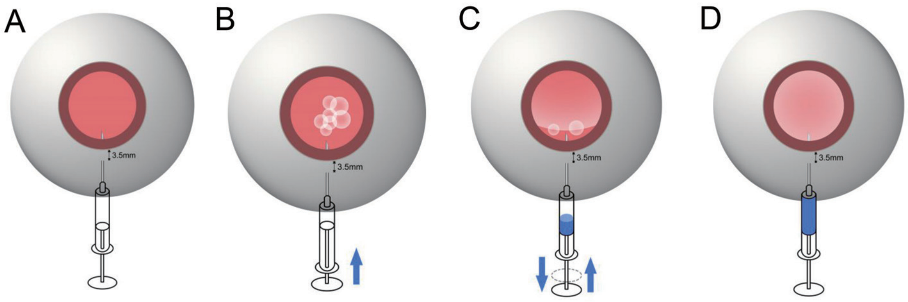


**Figure 2 The fluid-air exchange procedure performed using a single syringe** A: The needle was inserted obliquely at a point 3.5 mm from the inferior temporal limbus and advanced 7 mm towards the spherical center; B: A small amount of sterilized air was injected, a small amount of liquid in the vitreous cavity was extracted, and the needle was slowly withdrawn; C: The above procedures were repeated until gas was visible through the intraocular lens in the pupil; D: The absence of fluid flow in the pupil was taken to indicate the end of the operation (figure drawn by Lin K).

povidone iodine, and anterior chamber puncture was performed until the IOP had fallen to Tn-1. The operating bed was raised to the highest position, and the patient was asked to adopt the prone position and look superomedially with the surgical eye. A 28G air injection needle was inserted obliquely 3.5 mm from the inferior temporal limbus and advanced 7 mm towards the center of the eye (Figures 1A, 2A). A small amount of sterilized air was injected, and a small amount of the liquid in the vitreous cavity was extracted. Then, the needle was slowly withdrawn, and the intraocular pressure was measured to confirm that it was within the normal range (Figures 1B, 2B). The above procedures were repeated until visible sterilized air (Figure 2C) and no fluid (Figure 2D) was observed through the intraocular lens (IOL) and no extravasation from the vitreous cavity was evident after most of the needle had been withdrawn. By the end of the procedure (the point at which the vitreous cavity was filled with sterilized air and no more fluid could be extracted), about 4–5 mL of fluid had been extracted, and the IOP was Tn+1. The puncture site was pressed with a cotton swab for 3–5min after removal of the needle. Then, the patient was asked to adopt the supine position, the conjunctival sac was rinsed with povidone iodine, and light perception and IOP were assessed. Anterior chamber puncture was performed if the IOP exceeded Tn+1. All patients were requested to adopt a prone position for one week postoperatively. All the patients underwent 23G PPV combined with ILM peeling and sterilized air injection (with/without phacoemulsification and IOL implantation) for IMH, and the operations were performed by the same experienced senior chief physician.

**Statistical Analysis** SPSS 22.0 (IBM Corp, Armonk, NY, USA) was used for the statistical analysis. The Kolmogorov-Smirnov test was used to test whether the data conformed to a normal distribution. Continuous data with a normal distribution are presented as mean±standard deviation and were compared between groups using Student's *t*-test (two groups) or one-way analysis of variance (three groups). Continuous data with a non-normal distribution are described as median (range) and were compared between groups using the Mann-Whitney *U* test (two groups) or Kruskal-Wallis *H* test (three or more groups). Enumeration data are shown as *n* (%) and were compared using $\chi^2$ test or Fisher's exact test. $P<0.05$ was considered statistically significant.

## RESULTS

**Characteristics of the Study Participants** A total of 25 eyes in 25 patients (16 females, 64.0%) aged 37–74y were included in this study. The secondary management strategy used after failure of primary surgery was vitrectomy with the inverted ILM flap technique in 10 patients (40.0%), fluid-air exchange in 9 patients (36.0%) and observation in 6 patients (24.0%). The clinical characteristics of the patients before and 1–2wk

**Table 1 Clinical characteristics of the study participants**

| Characteristic | Observation group (*n*=6) | Vitrectomy group (*n*=10) | Fluid-air exchange group (*n*=9) | *P* |
|---|---|---|---|---|
| Age (y) | 57.8±12.2 | 59.7±10.6 | 63.8±6.5 | 0.482 |
| Gender | | | | 0.944 |
| Male | 2 (33.3%) | 4 (40.0%) | 3 (33.3%) | |
| Female | 4 (66.7%) | 6 (60.0%) | 6 (66.7%) | |
| Surgical eye | | | | 0.421 |
| Right | 4 (66.7%) | 4 (40.0%) | 6 (66.7%) | |
| Left | 2 (33.3%) | 6 (60.0%) | 3 (33.3%) | |
| Management during first vitrectomy | | | | |
| Retained 1 PD fovea-sparing during ILM peeling | 2 (33.3%) | 1 (10.0%) | 2 (22.2%) | 0.517 |
| No fovea-sparing retained during ILM peeling | 4 (66.7%) | 9 (90.0%) | 7 (77.8%) | |
| ILM flap filling | 1 (16.7%) | 1 (10.0%) | 3 (33.3%) | 0.435 |
| No ILM flap filling | 5 (83.3%) | 9 (90.0%) | 6 (66.7%) | |
| MH size before first vitrectomy (μm) | 553.8±236.3 | 414.0±123.4 | 494.4±157.1 | 0.269 |
| MH size within 1–2wk after first vitrectomy (μm) | 338.3±192.0 | 390.2±130.6 | 354.8±148.9 | 0.783 |
| MH morphology 1–2wk after first vitrectomy | | | | |
| Elevated MH edge | 2 (33.3%) | 9 (90.0%) | 8 (88.9%) | 0.019 |
| Flatten MH edge | 4 (66.7%) | 1 (10.0%) | 1 (11.1%) | |
| MH edema 1–2wk after first vitrectomy | 5 (83.3%) | 9 (90.0%) | 6 (66.7%) | 0.435 |
| Acuity before first vitrectomy (logMAR) | 1.49±0.46 | 1.00±0.18 | 1.45±0.57 | 0.043 |
| Acuity 1–2wk after vitrectomy (logMAR) | 1.59±0.83 | 1.36±0.54 | 1.64±0.56 | 0.617 |

MH: Macular hole; PD: Papilla diameter; ILM: Internal limiting membrane.

after the primary vitrectomy are compared between groups in Table 1. There were no significant differences between groups in age, gender, surgical eye (left *vs* right), visual acuity, MH size or MH morphology before the primary vitrectomy (Table 1). Whether 1 PD fovea-sparing was maintained during peeling during the primary vitrectomy did not differ significantly between the three groups (Table 1). Meanwhile, with or without ILM flap filling during the primary vitrectomy did not differ significantly between the three groups (Table 1). OCT performed 1wk after the initial vitrectomy demonstrated that most of the unclosed MHs presented with an elevated edge and edema (17/25 cases, 68.0%), but the morphological characteristics of the unclosed MHs were comparable between groups (Table 1). Furthermore, the sizes of the unclosed MHs did not differ significantly between the three groups, although the diameter of the unclosed MH was numerically higher in the vitrectomy group (390.2±130.6 μm) than in the fluid-air exchange group (354.8±148.9 μm) or observation group (338.3±192.0 μm). Visual acuity within 1–2wk after the primary vitrectomy did not differ significantly between the three groups (Table 1).

**Effectiveness of the Secondary Management Strategy** The interval between first vitrectomy and secondary intervention was longer (*P*=0.054) in the vitrectomy group (82.8±14.0d; range, 12–300d) than in the fluid-air exchange group (14.0±6.6d; range, 6–28d), indicating that treatment of the unclosed MH was performed far more quickly in the fluid-air exchange group. Overall, the MH closure rate after secondary treatment was 80.0% (20/25 eyes) in all patients. MH closure rate after the secondary intervention was numerically higher in the vitrectomy group (10/10 eyes, 100%) than in the fluid-air exchange group (8/9 eyes, 88.9%), although the difference was not significant (Table 2 and Figure 3). Since the MH closure rate was very low in the observation group (2/6 eyes, 33.3%), further analysis of the data for this group was not performed.

**Table 2 Outcomes following the secondary intervention**

| Characteristic | Vitrectomy group (*n*=10) | Fluid-air exchange group (*n*=9) | *P* |
|---|---|---|---|
| Time to secondary treatment (d) | 82.8±14.0 | 14.0±6.6 | 0.054 |
| MH closure rate | 10 (100%) | 8 (88.9%) | 0.474 |
| MH morphology | | | |
| IS-OS continuity | 1 (10.0%) | 2 (25.0%) | 0.412 |
| U/V-shaped closure | 2/3[a] | 5/3 | 0.413 |
| ELM continuity | 2 (20.0%) | 8 (88.9%) | 0.004 |
| Follow-up (mo) | 16.8±16.3 | 10.2±12.7 | 0.344 |
| Visual acuity (logMAR) | 0.87±0.36 | 0.96±0.28 | 0.577 |

ELM: External limiting membrane; IS-OS: Inner segment-outer segment; MH: Macular hole. [a]Data available for only 5 patients who did not undergo inner boundary membrane of an internal limiting membrane flap.

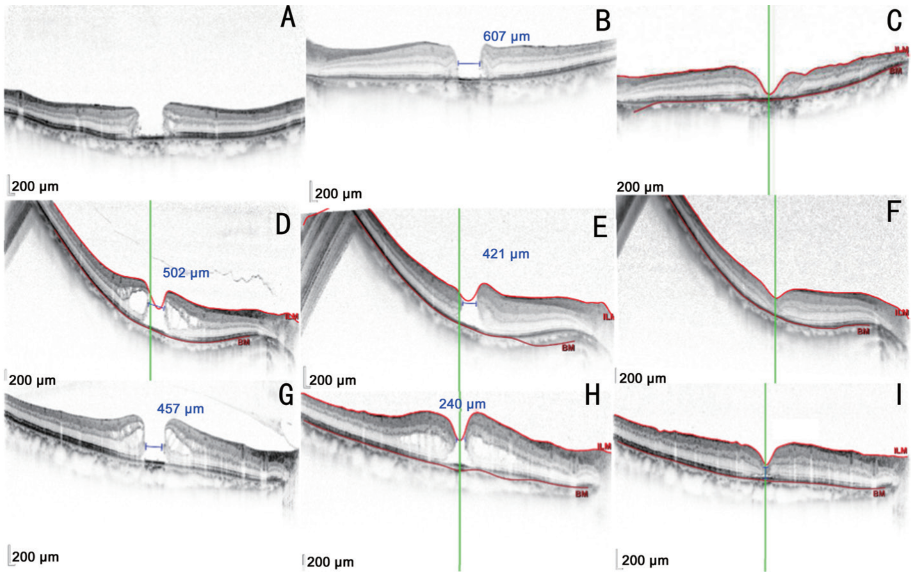


**Figure 3 The sizes of the MHs in three patients before and after intervention** The MH in a patient from the vitrectomy group before the initial vitrectomy (A), after the initial vitrectomy (B) and 8mo after repeat vitrectomy (C). The MH in a patient from the fluid-air exchange group before the initial vitrectomy (D), after the initial vitrectomy (E) and 6mo after secondary treatment with fluid-air exchange (F). The MHs of pre-, 7d post-, 3mo post-1st vitrectomy (G–I) in a patient from the observation group, with V-shaped closure and ELM discontinuity of a patient. MH: Macular hole; ELM: External limiting membrane.

Patients in the vitrectomy and fluid-air exchange groups were followed-up for 16.8±16.3 and 10.2±12.7mo, respectively ($P$=0.344). OCT images obtained at the last follow-up revealed that, among the patients with successful MH closure, continuity of the ELM was significantly more common ($P$=0.004) in the fluid-air group (8/9 eyes, 88.9%) than in the vitrectomy group (2/10 eyes, 20.0%). The proportion of patients with inner segment-outer segment (IS-OS) continuity was not significantly different between the fluid-air group (2/9 eyes, 29.0%) and vitrectomy group (1/10 eyes, 10.0%). U-shaped closure and V-shaped closure were observed in 2 and 3 cases, respectively, in the vitrectomy group (data available for only 5 patients) and 5 and 3 cases, respectively, in the fluid-air group (Table 2).

Visual acuity improved in 68.4% (13/19) of the patients who received secondary treatment. Notably, the 4 patients who showed no improvement in visual acuity after the second intervention were shown by OCT to have a discontinuous ELM at the last follow-up. The visual acuity of the vitrectomy group increased from 1.36±0.54 logarithm of the minimum angle of resolution (logMAR) before secondary therapy to 0.87±0.36 logMAR at the last follow-up, and 6 of the patients in this group (60.0%) exhibited differing degrees of improvement. In the fluid-air exchange group, visual acuity improved from 1.64±0.56 logMAR before secondary treatment to 0.96±0.28 logMAR at the last follow-up, and all patients showed some improvement (Table 2).

**Safety** Three eyes (12.0%) developed a high IOP (>21 mm Hg) one week after the primary vitrectomy, but IOP normalized after the administration of IOP-lowering drugs. IOP remained within the normal range after the secondary treatment in all patients. There were no complaints of dark shadows, metamorphopsia or discomfort after the secondary intervention. One patient in the vitrectomy group developed cataract 3mo after the second treatment and received Yttrium Aluminum Garnet (YAG) laser posterior capsulotomy. No complications such as retinal detachment or choroidal hemorrhage were observed.

## DISCUSSION

The objective of this retrospective study was to investigate whether fluid-gas exchange with sterilized air could be used as a secondary treatment for unclosed MH after primary vitrectomy. Numerous studies have verified the relationship between the parameters of the pre-operative MH and the prognosis of primary surgery to repair the MH[21-22]. In our study, all eyes had already undergone PPV and ILM peeling. Therefore, it is likely that the eyes were less affected by tangential traction and more affected by edge mobility and the size of the unhealed MH. However, there were no significant differences in MH size or MH edge type among the three groups, and our results indicated that better macular reconstruction was achieved for MHs<400 μm in size with an elevated edge. We speculate that an elevated macular edge around a relatively small-sized MH indicates a higher degree of macular activity and mobility and thus an increased likelihood of the edges reattaching to each other, particularly as traction factors had been removed previously.

Secondary vitrectomy with translocation of an ILM flap or extension of the ILM peel followed by tamponade with gas or silicone oil is widely used to treat unclosed MH after primary vitrectomy[23-25]. In the present study, secondary vitrectomy with the ILM flap technique achieved a closure rate of 92.9%, and visual acuity at last follow-up (16.5±15.1mo) was significantly improved when compared to that before secondary treatment (0.88±0.31 *vs* 1.39±0.53 logMAR). Our findings are broadly consistent with those of other published studies. For example, previous investigations of secondary vitrectomy for unclosed MH have reported success rates of 46.7%[23], 76.5%[36], 84.9%[37], 85.0%[38], 88.8%[24], 92.3%[39] and 100%[40] as well as significant improvements in visual acuity. Thus, our results and those of others demonstrate that secondary vitrectomy is an effective intervention for unclosed MH after primary vitrectomy.

Since repeat vitrectomy is a complex and expensive procedure that is not without potential complications, several investigations have evaluated whether fluid-gas exchange might be a viable alternative for patients with unclosed MH after initial vitrectomy. The fluid-gas exchange technique has been used in the outpatient setting for more than 30y[41-42]. Gas tamponade is thought to seal the hole and restrict the flow of vitreous humor to the macular area as well as promote the proliferation and migration of glial cells[43]. Imai *et al*[30] reported that fluid-gas exchange with 15% octafluoropropane achieved MH closure in all 5 eyes treated (*i.e.*, 100% closure rate) as well as an improvement in visual acuity. Similarly, Iwase and Sugiyama[31] described a 100% closure rate and enhanced visual acuity in 7 eyes that underwent fluid-gas exchange using 20% sulfur hexafluoride. Johnson *et al*[32] found that fluid-gas exchange achieved MH closure and visual acuity improvement in 17 of 23 eyes (73.9%). Rao *et al*[33] successfully treated 32 of 36 eyes (88.9%) using fluid-gas exchange with two expansive gases and achieved MH closure in 32 cases, with 22 eyes (61.1%) achieving type 1 closure and 10 eyes (27.8%) achieving type 2 closure (flattened MH edge, reduced size and neurosensory defect). However, none of the above investigations evaluated the use of sterilized air for fluid-gas exchange. To our knowledge, the present study is the first to report that an unclosed MH can be treated by fluid-gas exchange with sterilized air, which would avoid the potential complications of using an expansive gas. Notably, the MH closure rate using this technique was 87.5%, and visual acuity improved from 1.64±0.56 logMAR before secondary treatment to 0.81±0.29 logMAR at the last follow-up. Furthermore, ELM continuity after the intervention was 100.0% in the fluid-air group and only 23.1% in the vitrectomy group. This latter finding is interesting because ELM discontinuity may be associated with poorer visual acuity during long-term follow-up[44]. It is possible that ELM discontinuity in the vitrectomy group occurred because the inner boundary membrane or other tissues were packed during the operation to promote healing, but this led to disruption of the ELM. By contrast, packing with filler/tissue was not used in the fluid-air exchange group, and this may have allowed ELM continuity to be maintained during healing. Most of the ELM recovery occurred within the first 3mo of follow-up, hence ELM continuity at 3mo potentially could be used as a biomarker for macular reconstruction. Additionally, fluid-air exchange was not associated with any serious complications.

There are some limitations to this study. Since this analysis was retrospective, it may be prone to information bias or selection bias. This was a single-center study, so the generalizability of the results remains to be determined. The sample size was quite small, so the analysis may have been underpowered to detect some real differences between groups. But this cannot be avoided, given the high success rate of MH surgery these days meaning that less number of eyes will require repeat intervention. The grouping of the patients was determined by the patient's clinical condition and patient preference, which likely introduced some bias. Indeed, MH morphology differed between groups at 1–2wk after the first vitrectomy, with the vitrectomy group having more patients with an elevated MH edge than the fluid-air exchange group (90.0% *vs* 88.9%; Table 1). And our results indicated that better macular reconstruction was achieved for MHs<400 μm in size with an elevated edge, but how about MHs>400 μm, we do not know. Furthermore, the time to secondary treatment was numerically much shorter for the fluid-air exchange group than for the vitrectomy group (14.0±6.6d *vs* 82.8±14.0d). Additionally, it remains possible that benign cases were more likely to be assigned to the observation group, intermediate cases were more likely to be assigned to the fluid-air exchange group, and the most challenging cases were more likely to be assigned to the vitrectomy group. Therefore, despite most of the baseline characteristics being similar between groups, we recommend that the results are interpreted with a degree of caution. Future prospective randomized controlled studies are needed to further analyze the effectiveness of liquid-air exchange as a secondary treatment for unclosed MH after primary vitrectomy.

In conclusion, the findings of this study suggest that liquid-air exchange may be an effective management strategy for patients with an unclosed IMH after initial vitrectomy. Our technique is straightforward (requiring only a single syringe), inexpensive and associated with a low risk of infection, and can be performed in an outpatient clinic under topical anesthesia. Prospective randomized controlled trials are needed to further compare this technique with other methods (such as repeat vitrectomy) and establish which subset of patients will best benefit from this management strategy.

## ACKNOWLEDGEMENTS

**Data Availability Statement:** Data associated with our study has not been deposited into any publicly available repository. Data associated with our study will be made available on request.

**Conflicts of Interest: Lin B,** None; **Ye LY,** None; **Lin K,** None; **Wu RH,** None; **Hu ZX,** None.

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