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Comparison of air and SF6 tamponade in idiopathic macular holes under 500 μm diameter – a randomized controlled trial

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Research Article

Keywords: idiopathic macular hole, vitrectomy, tamponade, internal limiting membrane, optical coherence tomography

Posted Date: September 16th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9495221/v1

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Additional Declarations: No competing interests reported.

Abstract

Purpose

To prospectively compare air and 10% SF6 tamponade in idiopathic macular holes (IMH) under 500 µm diameter operated with internal limiting membrane (ILM)-peeling or -inverted flaps.

Methods

Patients with IMHs under 500 µm diameter underwent vitrectomy with air or 10% SF6 tamponade after randomization. ILM peeling or -inverted flaps were performed/created according to the same criteria in both groups. IMH closure served as the main outcome measure and was evaluated by optical coherence tomography (OCT) after two weeks.

Results

Twenty-four and 21 patients were operated with air and 10% SF6, respectively. IMH closure was achieved in 19 of 24 patients (79%) operated with air and in 19 of 21 patients (90.5%) operated with SF6 ($p = 0.42$). ILM peeling was performed in 16 of 24 (66.7%, air) and 15 of 21 eyes (71.4%, SF6), whereas inverted ILM-flaps were created in 8 of 24 (33.3%, air) and 6 of 21 eyes (28.6%, SF6). Patients with ILM peeling achieved IMH closure in 11 of 16 eyes (68.8%, air) and in 13 of 15 eyes (86.7%, SF6), respectively. All patients with ILM-flaps achieved IMH closure in both groups.

Conclusion

We found no statistically significant differences between air and SF6 tamponades regarding macular hole closure. Different combinations of tamponade type/ILM management for specific patient groups should be investigated in future studies.

Introduction

Idiopathic macular holes (IMHs) constitute small breaks in the fovea, the most central part of the retina. This condition is age-related, associated with vitreomacular traction and results in significant loss of central vision. IMH grading evolved from Gass' slit-lamp based classification [1] to newer systems that are optical coherence tomography (OCT)-based [2]. State of the art treatment for IMHs consists of pars plana vitrectomy, internal limiting membrane (ILM)-peeling with or without inverted flaps [3], filling of the vitreous cavity with air/gas tamponade and subsequent face-down or non-supine positioning. Tamponade types include air or mixtures of air with sulfur hexafluoride (SF6), hexafluoroethane (C2F6) and octafluoropropane (C3F8). Air alone is usually resorbed within 10 days [4], but other tamponades act for longer periods [5]. As long as the tamponade is in the eye, the patient's vision is reduced because air

and gases have different optical properties compared to vitreous or balanced salt solution. Furthermore, patients with gas tamponades need to be discouraged from air travel due to the risk of potentially harmful gas-related elevations in intraocular pressure. For these reasons, there is a trend towards shorter acting gases. On the other hand, there is concern that the use of short acting agents may result in less satisfactory closure rates. Previous studies have yielded inconsistent results on this matter: Yu et al. reported that eyes with minimum linear diameters below a cutoff value of 677 µm are likely to achieve satisfactory outcomes with air tamponade based on a series of 135 consecutive patients [6]. Similarly, Yao et al. found no significant differences in anatomical closure rates between 20% SF6 and air in IMHs ≤ 520 µm minimum linear diameter [7]. Furthermore, Tao et al. reported 100% primary closure in eyes with IMHs ≤ 400 µm minimum linear diameter using air tamponade [8]. On the other hand, Lindtjørn et al. recently found that air showed inferior closure rates in small- and medium-sized macular holes compared to 26% SF6 tamponade in a prospective trial [9].

With this investigation, we aim to provide additional data on the comparison of air and SF6 in macular hole surgery. Previous studies have shown inconsistent results, and only one randomized controlled trial has been published until now [9]. Special attention has been given to ILM management (ILM peeling and ILM-inverted flaps) due to its impact on surgical outcomes.

Materials and Methods

Patients requiring vitrectomy for IMHs were prospectively recruited between August 2020 and October 2022 at a tertiary center. Inclusion criteria were idiopathic, unilateral macular holes < 600 µm minimum linear diameter and the willingness to sign informed consent forms after an introductory patient briefing. Exclusion criteria were patient age under 18 years, unwillingness to give written informed consent, systemic pathologies making examinations difficult for the patient, epiretinal membranes, idiopathic/primary macular holes ≥ 600 µm minimum linear diameter, any secondary macular holes, chronic macular holes, previous eye trauma, a history of glaucoma or diabetes, anisometropia > 2 diopters, high myopia (spherical equivalent > 6 diopters and/or axial length > 26.5 mm), complicated cataract surgery (previous or intraoperative), any other ophthalmic pathology except moderate cataract, and any significant media opacity interfering with optical coherence tomography (OCT). Stage 1b occult macular holes according to Gass, characterized by breaks in the continuity of the receptor cell layer at the umbo, while the internal limiting membrane of the foveolar retina and a thin layer of horizontally oriented Müller cell processes remain uninvolved in the central retinal break, were included. By definition, their minimum linear diameter was zero. In contrast, stage 1a impending macular holes and stage 1b impending macular holes were excluded [1]. Notably, stage 1a and 1b impending macular holes as well as stage 1b occult macular holes are subsumed under “vitreomacular traction” in the classification proposed by Duker et al. [2]. After recruitment, patients were electronically randomized (https://www.randomizer.at, Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz) to one of two groups (simple randomization [10]). Patients in the first group received air following vitrectomy, whereas those in the second group received 10% sulfur hexafluoride (SF6), in accordance with our clinic’s standard protocol. The surgeon and patient were not blinded regarding the

used tamponade. ILM peeling was performed or inverted ILM-flaps were created according to specific criteria in both groups: Flaps were generally utilized in macular holes with minimum linear diameters greater than 300 µm. For macular holes smaller than 300 µm, the surgeon could choose an ILM-flap if preoperative OCT suggested that the available foveal tissue might be insufficient for complete anatomical closure with ILM peeling alone, indicating risk of type 2 closure. Type 2 closure (also referred to as flat-open closure) is characterized by postoperative flattening of the hole edges with a persistent foveal defect, indicating insufficient foveal tissue for complete anatomical closure [11, 12].

ILM peeling was generally performed for macular holes with minimum linear diameters smaller than 300 µm, as recent findings have indicated that ILM-flaps may hinder postoperative restoration of the external retinal layers and therefore recommend ILM peeling alone for smaller holes [13]. In macular holes larger than 300 µm, ILM peeling alone (without flap creation) could be performed if preoperative OCT suggested that the available foveal tissue was sufficient for complete anatomical closure despite the larger size (indicating a likely type 1 closure) and when ILM-flap creation was not feasible due to intrinsic properties of the ILM (e.g., uncontrollable tearing of the flap) or patient-related factors (e.g., poor intraoperative visibility or patient agitation/sudden head movements that hindered precise flap creation). Type 1 closure (also referred to as flat-closure) is characterized by postoperative flattening of the hole edges without a persistent foveal defect and is typically associated with favorable functional outcomes [11, 12]. All analyses are regarded exploratory in nature, the study adhered to the tenets of the Declaration of Helsinki including its later amendments and was approved by the Ethics committee of the Medical University Graz, Austria (registration number: EK-32-465 ex 19/20), and registered at ClinicalTrials.gov (ID: NCT05223205).

Study visits

Patients were enrolled one day before surgery (study visit 1) after collection of full medical and ophthalmologic patient data. Primary macular hole closure was evaluated two weeks after surgery (study visit 2) using OCT. Another follow-up visit was scheduled three months after surgery (study visit 3). Axial eye length (IOL Master 700, Carl Zeiss Meditec AG, Germany) and arterial blood pressure were measured preoperatively (study visit 1). Best-corrected visual acuity (BCVA), slit-lamp examination including funduscopy, applanation tonometry, and structural OCT (Heidelberg Spectralis, Heidelberg Engineering, Heidelberg, Germany) were performed at study visits 1, 2 and 3. Preoperatively, IMHs were staged according to Duker et al. [2]. The minimum linear diameter was used to measure macular hole size [14]. IMH closure/non-closure was evaluated at study visits 2 and 3. Postoperative integrity of the external limiting membrane (ELM) and ellipsoid zone (EZ) was assessed using OCT at 3 months. Following a previous publication, eyes were categorized into three subgroups [15]: (1) ELM continuous and EZ continuous, (2) ELM discontinuous and EZ discontinuous, and (3) ELM continuous and EZ discontinuous. BCVA was performed using a Snellen chart positioned 6 m away with subsequent conversion to logMAR to enable statistical calculation.

Surgery

Vitrectomy was performed using DORC's Eva 25 or 27-gauge vitrectomy platform (DORC, Zuidland, the Nederlands). Patients were anesthetized locally using a retrobulbar block and sclerotomies were subsequently inserted superonasally, superotemporally and inferotemporally (infusion line) at a distance of 3.5 mm to the limbus. Patients with cataracts generally received combined phacovitrectomy, whereas pseudophakic patients received vitrectomy alone. In select cases, vitrectomy alone could be performed in phakic patients according to the surgeon's preference (e.g., clear crystalline lens with expected postoperative anisometropia). Phacoemulsification was performed using 2.2 mm self-sealing corneal incisions. Posterior vitreous detachment was induced after core vitrectomy, if necessary. The internal limiting membrane (ILM) was stained with a combination of 0.025% Brilliant Blue G and 0.15% Trypan Blue (Membrane Blue-Dual, DORC, Zuidland, the Nederlands) and then peeled using a 25- ("Microforceps: ILM", DORC, Zuidland, the Nederlands) or 27-gauge ("Disposable Microforceps: Extended reach – Wide grip", DORC, Zuidland, the Nederlands) microforceps. Alternatively, an inverted 360° ILM-flap was created.

ILM peeling was started in proximity to the superior or inferior arcades, resulting in an ILM peeling size of approximately two disc diameters centered on the foveola. The presence of epiretinal hemorrhages in the peeled area and the inability to re-stain the ILM were defined as criteria for successful ILM peeling and evaluated by the surgeon intraoperatively. Similarly, for ILM-flap creation, the ILM was grasped in proximity to the superior or inferior arcades and peeled in a circular fashion for approximately two disc diameters around the macular hole, leaving it attached at the edges. Peripheral segments were trimmed using the vitreous cutter, and the central ILM was gently inverted over the hole so that the surface normally facing the vitreous body now faced the retinal pigment epithelium [16]. All surgeons (A.H., G.S., C.M., D.I.) are high-volume vitreoretinal surgeons with extensive experience with both techniques. Standard postoperative therapy consisted of topical Neomycinesulfate and Betamethasonedinatrium-phosphate and all patients were advised to follow a postoperative prone positioning regimen for three days.

Outcome measures

The IMH closure rate after two weeks served as the main outcome measure and was compared between both study groups. Mean changes (preoperative to three-month postoperative) in best-corrected visual acuity (BCVA, logMAR) and postoperative ELM/EZ integrity served as secondary outcome measures. Again, all parameters were compared between both study groups.

Statistical analysis

Metric parameters were descriptively summarized using mean, standard deviation and range (minimum - maximum). Categorical parameters were given as absolute and relative frequencies. Microsoft Excel (Microsoft Corporation, Redmond, USA) was used for data management. Calculations were performed

using IBM SPSS Statistics (Version 26, 2018, International Business Machines Corporation, Armonk, NY, USA). The Shapiro-Wilk test was used to assess if continuous variables followed a normal distribution. The Chi-squared/Fisher's exact test and the independent/unpaired Student's t-test were used for intergroup comparison depending on data characteristics. Because this study followed a hypothesis-generating approach, no power calculations were performed, and all analyses are therefore considered exploratory. A p-value of < 0.05 was deemed statistically significant.

Results

Allocation process and demographic data

Figure 1 (flowchart) illustrates the randomization process. In total, 47 patients were recruited and randomized. Two patients in the group operated with air were lost to follow-up (both refused to participate postoperatively because they were uncomfortable with the long journey to our clinic), whereas all patients in the SF6 group completed the study, resulting in 45 patients (28 women; 62%) that were evaluated. Of these, 24 patients were operated with air and 21 patients with SF6. Baseline patient characteristics are summarized in table 1. Mean (mm) ± SD (range) macular hole size (minimum linear diameter) in the air and SF6 group was 244 ± 137 (0 – 499) and 213 ± 139 (0 – 452), respectively. Although our protocol allowed inclusion of macular hole sizes up until 600 mm, no patients with macular holes ³ 500 mm were eligible for study inclusion during the recruitment process. Both groups were comparable in size, age, gender, laterality, lens status, best-corrected visual acuity, and IMH staging, although patients operated with SF6 had marginally longer eyes (mean axial length in mm ± SD: air 23.48 ± 1.18, SF6 24.31 ± 1.25) and were therefore more myopic (mean spherical equivalent in diopters ± SD: air 0.8 ± 2.1, SF6 -0.35 ± 1.8).

Table 1. Baseline characteristics of both study groups.

	Air		10% SF6	
	(n = 24)		(n = 21)	
Mean age ± SD (range), years	69 ± 8 (57 – 84)		65 ± 8 (52 – 86)	
Gender (male/female), n	7/17		7/14	
Laterality (right/left), n	14/10		11/10	
Preop lens status (phakic/pseudophakic), n	19/5		18/3	
Postop lens status (phakic/pseudophakic), n	3/21		1/20	
Mean BCVA ± SD (range), logMAR	0,59 ± 0,17 (0.2 – 1)		0,61 ± 0,24 (0.2 – 1.3)	
Mean spherical equivalent ± SD, dpt	0,8 ± 2,1 (-3.5 – 7)		-0,35 ± 1,8 (-4.5 – 2.5)	
Mean axial length ± SD, mm	23,48 ± 1,18 (21.35 – 26.49)		24,31 ± 1,24 (22.66 – 26.5)	
Preoperative minimum linear diameter, mm	244 ± 137 (0 – 499)		213 ± 139 (0 – 452)	
Preoperative IMH stage*, n	VMA	0	VMA	0
	VMT	3	VMT	3
	sFTMH	7	sFTMH	10
	mFTMH	13	mFTMH	6

	lFTMH 1	lFTMH 2

SF6, sulfur hexafluoride; SD, standard deviation; Preop, preoperative; Postop, postoperative; BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; IMH, idiopathic macular hole; VMA, vitreomacular adhesion; VMT, vitreomacular traction; sFTMH, small full-thickness macular hole; mFTMH, medium full-thickness macular hole; lFTMH, large full-thickness macular hole.

*Duker et al.[2]: sFTMH £ 250 mm; mFTMH > 250 mm but £ 400 mm; lFTMH > 400 mm.

Outcome measures

Descriptive analysis of all outcome measures is summarized in table 2. Macular hole closure was achieved in 19 of 24 patients (79%) operated with air and in 19 of 21 patients (90.5%) operated with SF6. Primary non-closure was therefore observed in 5 of 24 patients (21%) operated with air and in 2 of 21 patients (9.5%) operated with SF6. These differences were not statistically significant (p = 0.42, Fisher's exact test). Mean ± SD (logMAR) BCVA change in the air and SF6 group was -0.35 ± 0.32 and -0.37 ± 0.3, respectively (p = 0.84). All five eyes in the air group that failed to close had diameters above 250 mm. Eyes in the SF6 group that failed to close had preoperative diameters of zero (stage 1b occult hole, axial length 26.4 mm) and 160 (axial length 25.51 mm), respectively. All seven eyes that failed to achieve primary closure were eventually closed following a second procedure that included the re-instillation of 10% SF6. ILM peeling was performed in 16 of 24 patients (66.7%) operated with air, whereas ILM-flaps were created in the remaining 8 of 24 patients (33.3%). In patients operated with SF6, ILM peeling was performed in 15 of 21 eyes (71.4%), whereas inverted ILM-flaps were created in the remaining 6 of 21 eyes (28.6%). Patients with ILM peeling showed macular hole closure in 11 of 16 eyes (68.8%, air group) and in 13 of 15 eyes (86.7%, SF6 group), respectively. Patients with ILM-flaps showed macular hole closure in 8 of 8 eyes (100%, air group) and in 6 of 6 eyes (100%, SF6 group), respectively. The totality of eyes receiving ILM peeling achieved macular hole closure in 24 of 31 cases (77.4%), whereas all 14 eyes receiving ILM-flaps closed. While suggestive of higher success with ILM-flaps, this difference was not statistically significant (p = 0.081, Fisher's exact test) due to low power. There were no statistically significant differences between both groups in mean BCVA change (p = 0.84; independent Student's t-test). At the 3-month follow-up, ELM/EZ restoration patterns did not differ significantly between eyes operated with air versus 10% SF6 (chi-squared test, p = 0.74) or between those treated with ILM-peeling versus ILM-flaps (chi-squared test, p = 0.38). Continuous ELM and EZ restoration was the most frequent pattern across all subgroups.

Table 2. Results.

	Air	10% SF6	p-value
	(n = 24)	(n = 21)	
ILM peeling, n (%)	16 (66.7)	15 (71.4)	
ILM flap, n (%)	8 (33.3)	6 (28.6)	
Closure, n (%)	19 (79)	19 (90.5)	0.42*
Primary non-closure, n (%)	5 (21)	2 (9.5)	
ILM peeling closure, n (%)	11 (68.8)	13 (86.7)	
ILM flap closure, n (%)	8 (100)	6 (100)	
Mean preoperative BCVA** ± SD (range), logMAR	0.59 ± 0.17 (0.2 – 1)	0.61 ± 0.24 (0.2 – 1.3)	
Mean postoperative BCVA** ± SD (range), logMAR	0.25 ± 0.31 (0 – 1.5)	0.24 ± 0.23 (0 – 0.8)	
Mean BCVA change** ± SD (range), logMAR	-0.35 ± 0.32 (-0.8 – 0.9)	-0.37 ± 0.30 (-1 – 0.3)	0.84***

SF6, sulfur hexafluoride; ILM, internal limiting membrane; BCVA, best-corrected visual acuity.

*Fisher’s exact test

**Preoperative to three months after vitrectomy

***Independent t-test

Discussion

We compared air and 10% SF6 for the treatment of idiopathic macular holes under 500 µm minimum linear diameter and found no significant differences between both tamponades (closure rate air: 19/24, closure rate SF6: 19/21; p = 0.42). Investigators have previously analyzed the feasibility of ILM peeling

and air tamponade in macular hole surgery with inconsistent results: Usui et al. retrospectively compared air and 20% SF6 in 22 macular holes < 500 µm minimum linear diameter and found no differences in closure rates (100% in both groups) and postoperative visual acuity [17]. Forsaa et al. reported a closure rate of 95% in 20 macular holes ≤ 400 µm, but only 57% in 14 macular holes > 400 µm using air tamponade [4]. Yu et al. reported that eyes with minimum linear diameters below a 677 µm cutoff are likely to achieve satisfactory outcomes with air tamponade based on a series of 135 consecutive patients [6]. Yao et al. found no significant differences in closure rates between 20% SF6 and air in IMHs ≤ 520 µm minimum linear diameter [7] and Tao et al. reported 100% primary closure in eyes with IMHs ≤ 400 µm minimum linear diameter using air [8].

While these studies reported good performance of air in macular holes, Lindtjørn et al. recently published a randomized controlled trial and reported inferior closure rates after air tamponade compared to 26% SF6 for IMHs ≤ 400 µm minimum linear diameter. Although no significant differences were observed between our groups ($p = 0.42$), statistical significance might have been achieved with a larger sample size and sufficient statistical power. In Lindtjørn's intention-to-treat analysis, 65 of 75 patients (87%) operated with air and all 75 patients (100%) operated with SF6 achieved primary hole closure [9]. These results differ from ours because the closure rate in our SF6 group was 90.5% (and only 86.7% in ILM-peeled eyes compared to 100% in Lindtjørn's study) and mean macular hole diameter (213 µm ± 139 SD) was smaller in our series compared to Lindtjørn et al. (mean diameter 300 µm, range 107–395). However, there were in fact only two SF6 patients with primary non-closure in our study and although both had preoperative hole diameters well below 400 µm, their axial lengths (26.4 mm and 25.51 mm, respectively) were only marginally within our inclusion criteria (spherical equivalent ≤ 6 diopters and/or axial length ≤ 26.5 mm). Because Lindtjørn and colleagues did not disclose inclusion/exclusion criteria concerning axial length/myopia in their study, we can only speculate if our patients with macular hole non-closure (axial lengths of 26.4 mm and 25.51 mm) would have been included in their study. There were no differences in closure rates between air and SF6 for small macular holes (≤ 250 µm) in the investigation by Lindtjørn et al., although their study was not powered to prove non-inferiority in this subgroup. These findings are in good agreement with our results, because all patients with a hole size ≤ 250 µm showed primary closure in our air group. Last, it is noteworthy that SF6 concentration was different in our study compared to Lindtjørn et al. (10% in our study, 26% in Lindtjørn et al. [9]), although we can only speculate about the importance of this distinction and the optimal SF6 concentration at this point. In our clinic, 10% SF6 represents the standard of care, primarily to minimize the risk of postoperative intraocular pressure elevation when patients return home (generally immediately after surgery, otherwise on the first postoperative day), as some must travel across mountainous regions where changes in altitude could lead to gas expansion. However, patient noncompliance with postoperative positioning may have an even greater negative impact on anatomical outcomes when lower SF6 concentrations are employed. Gas-foveal contact time and gas-fluid interface slippage are two further concepts that require reflection in the context of our results. Poor gas fill and insufficient adherence to postoperative positioning may reduce the gas-foveal contact time and cause the gas-fluid interface to "slosh" the fovea in the early postoperative period ("slippage"). Gas fill is particularly relevant

in the context of our study because previous data show that gas fill has a significant relation to gas-foveal contact and, therefore, a significant impact on anatomical outcomes [18]. Compared with air, SF6 likely provides longer gas-foveal contact time and less slippage due to its longer acting period.

The main strength of our study is its prospective/randomized design evaluating air and SF6 tamponades in the context of ILM peeling and -flaps. Limitations include the hypothesis-generating nature of our study, the absence of a power calculation, the variability of surgeons, and the non-randomized approach to ILM management, which depended on the surgeon's subjective preoperative assessment. Because surgeons were not blinded to the tamponade, the choice of intraoperative ILM management might have been influenced. Although ILM peeling was generally targeted at two disc diameters centered on the foveola, its actual size may have varied between surgeons and surgeries, potentially affecting anatomical outcomes. Furthermore, our study was not designed to prove our hypotheses regarding tamponade selection and ILM management and secondary outcome analyses should generally be interpreted with caution in series with low sample size. On the other hand, our data indicate that ILM management and tamponade selection are aspects that may require coordination because both significantly influence macular hole closure rates in specific settings. Our study may serve as a starting point for future investigations addressing this issue. In conclusion, we found no statistically significant differences between air and SF6 tamponades in our study groups. Different combinations of ILM management and tamponades for specific patient groups should be investigated in future studies because both aspects influence macular hole closure together.

Declarations

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Maximilian Gabriel, Daniel Djavid and Felix Innauer. The first draft of the manuscript was written by Maximilian Gabriel and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Medical University Graz (registration number: EK-32-465 ex 19/20), and

registered at ClinicalTrials.gov (ID: NCT05223205).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

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Figures

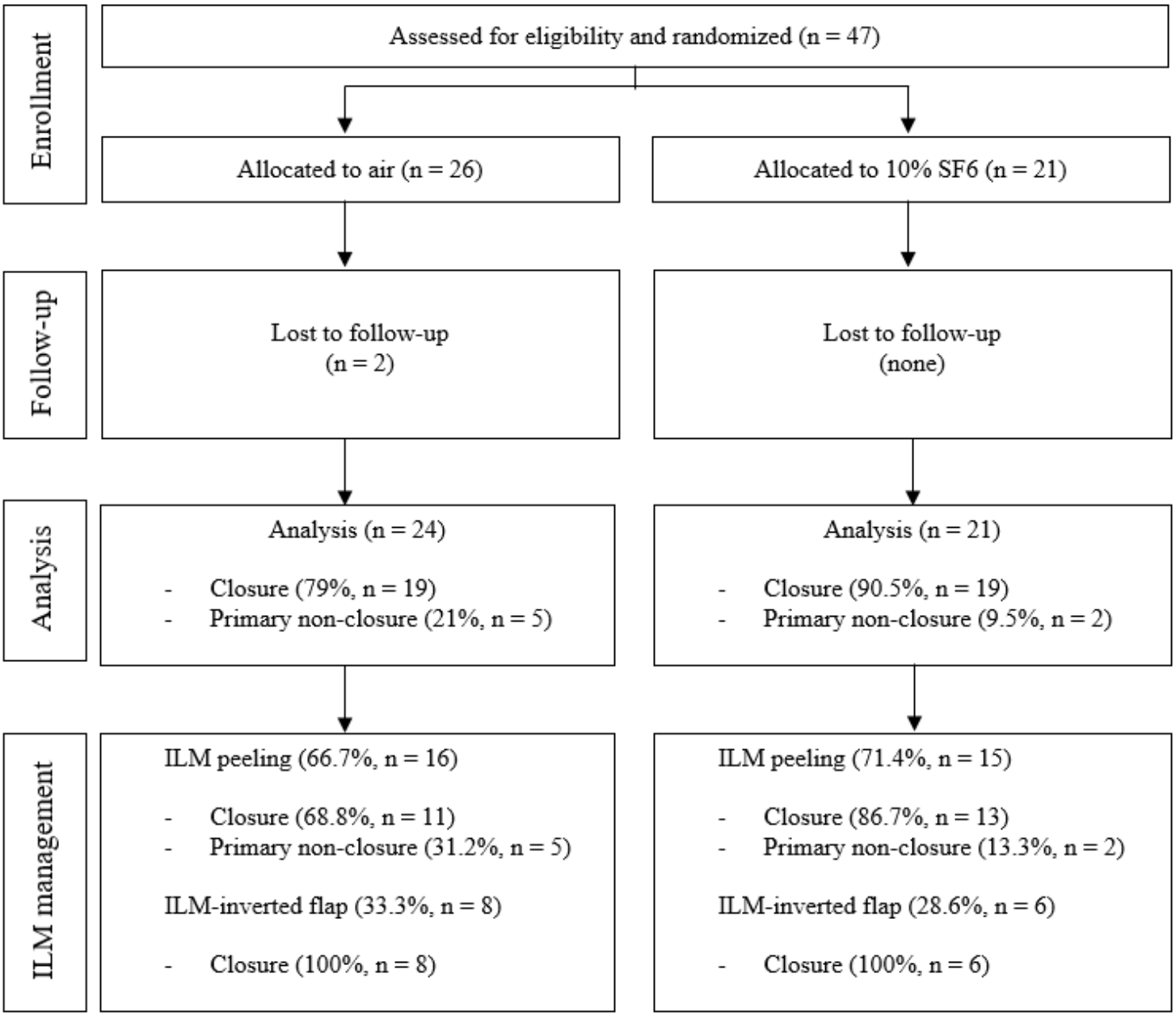


Figure 1

Diagram illustrating the allocation process.