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rtPA for Submacular Hemorrhage: Mechanisms, Administration Routes, and Therapeutic Strategies

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Abstract

Aims:

This review aims to evaluate the clinical utility of recombinant tissue plasminogen activator (rtPA) in submacular hemorrhage (SMH) by characterizing its mechanisms of action, comparing intravitreal versus subretinal delivery routes, assessing adjunctive strategies—including anti-VEGF and pneumatic or hybrid techniques—and summarizing safety and complication profiles.

Methods:

We performed a systematic PubMed search (up to April 2025) using "rtPA" OR "recombinant tissue plasminogen activator" AND "submacular hemorrhage" OR "subretinal hemorrhage." Publications from January 2019 onward were prioritized, except foundational mechanistic studies without a date limit. After screening titles and abstracts (n = 69) and reviewing full texts (n = 61), 29 studies met inclusion criteria (clinical adult SMH, rtPA dosing/route, and specified outcomes). Study types included one randomized controlled trial, one meta-analysis, eight retrospective cohorts (≥ 25 eyes), twelve case series (5–24 eyes), and seven case reports.

Results:

Mechanistic data confirm fibrin-selective plasminogen activation by rtPA. Intravitreal rtPA plus gas achieved clot displacement in 75–90% of eyes (mean LogMAR VA improvement from 1.2 to 0.8 at six months), while subretinal injection yielded ≥ 90% clearance and comparable or superior functional gains. Adjunctive anti-VEGF and hybrid subretinal air + rtPA + anti-VEGF approaches further improved outcomes. Overall adverse event rates ranged from 20% to 25%, including vitreous hemorrhage, retinal detachment, macular hole formation, and RPE tears.

Conclusions:

rtPA—administered intravitreally or subretinally—combined with pneumatic displacement and anti-VEGF, provides effective SMH management. Notwithstanding encouraging results, complications and reliance on retrospective data highlight the need for standardized protocols and prospective trials such as TIGER.

Keywords:

submacular hemorrhage; rtPA; intravitreal injection; subretinal injection; pneumatic displacement; anti-VEGF.

1.Introduction

Submacular hemorrhage (SMH) is a vision-threatening complication most commonly seen in neovascular age-related macular degeneration (nAMD) and retinal arterial macroaneurysm, with incidence estimates ranging up to 15 % in advanced nAMD cohorts (1). The rapid accumulation of blood beneath the fovea exerts mechanical traction on photoreceptors and creates a diffusion barrier that impairs oxygen and nutrient transport from the retinal pigment epithelium (RPE), leading to irreversible photoreceptor damage and poor visual prognosis if left untreated (2).

Traditional management strategies—observation, pneumatic displacement alone, or pars plana vitrectomy (PPV)—have delivered inconsistent outcomes. Observation risks permanent central scotoma, while gas-only pneumatic techniques often fail to fully clear dense clots, and PPV introduces surgical morbidity without directly dissolving fibrin (3,4). These limitations have driven interest in enzymatic fibrinolysis.

Recombinant tissue plasminogen activator (rtPA) selectively binds fibrin and converts plasminogen into plasmin, rapidly liquefying subretinal clots, restoring metabolic exchange, and reducing both mechanical and biochemical photoreceptor injury (2,5). However, optimal delivery—whether via intravitreal injection or direct subretinal administration—remains under investigation, as each route balances efficacy, invasiveness, and safety (6,7).

Adjunctive therapies further expand the treatment armamentarium. Pneumatic displacement with expansile gases (SF_6, C_3F_8) enhances mechanical clot clearance (1), while intravitreal or

subretinal anti-VEGF injections suppress neovascular drive and reduce recurrence risk (8,9). Emerging "hybrid" protocols—combining rtPA, gas, air tamponade, and anti-VEGF—seek to tailor intervention timing and technique to hemorrhage size and patient factors (10,11).

Despite promising results, safety considerations—such as vitreous hemorrhage, retinal detachment, macular hole formation, and RPE tears—occur in a notable minority of cases and are influenced by clot characteristics, technique, and recent anti-VEGF exposure (12,13,14).

Looking ahead, the forthcoming TIGER trial—a prospective, randomized, multicenter study comparing intravitreal versus subretinal rtPA with gas tamponade—promises to provide high-level evidence to guide optimal delivery routes and standardized protocols.

Objectives:

This review aims to (I) elucidate the mechanisms of rtPA action in SMH, (II) compare administration routes, (III) evaluate combined therapeutic strategies and adjunct treatments, and (IV) summarize safety profiles and complications. By integrating current evidence, we seek to provide a comprehensive framework for optimizing rtPA-based management of submacular hemorrhage.

2. Methods

2.1 Search Strategy

We conducted a systematic literature search of the PubMed database in April 2025, using the following terms: "rtPA" OR "recombinant tissue plasminogen activator" AND "submacular hemorrhage" OR "subretinal hemorrhage." No language restrictions were applied. To capture foundational mechanistic studies, no lower date limit was imposed for Section 4.1; for all other sections, we prioritized clinical publications from January 2019 through April 2025.

2.2 Eligibility Criteria

Studies were eligible if they met all of the following criteria:

- **Population:** adults with submacular hemorrhage of any etiology.
- **Intervention:** treatment with rtPA via any ocular route (intravitreal or subretinal).
- **Outcomes:** reported rtPA dosing, administration route, and at least one of the following—anatomic displacement, visual acuity change, or safety/adverse events.

We excluded preclinical or in vitro studies, narrative reviews without original clinical data, reports lacking clear rtPA dose or route information, and studies combining multiple hemorrhage locations without separate SMH outcomes.

2.3 Study Selection

All 69 unique records retrieved were screened by title and abstract. Articles meeting preliminary criteria (n = 61) underwent full-text review. Two investigators independently applied the eligibility criteria; disagreements were resolved by consensus. Thirty-two manuscripts were excluded at full-text review, resulting in 29 studies included for qualitative synthesis in Section 4.

2.4 Data Extraction and Synthesis

From each included study, we extracted: study design, sample size, rtPA dose and formulation, administration route (intravitreal vs. subretinal), adjunctive treatments (gas tamponade, anti-VEGF, air, or silicone oil), primary outcomes (clot displacement rate, change in best-corrected visual acuity), follow-up duration, and reported safety outcomes. Data were tabulated according to the thematic structure of the review (mechanisms, administration routes, therapeutic strategies, and safety/complications).

2.5 Quality Assessment

We assessed the methodological quality of included studies using a modified Newcastle–Ottawa Scale for retrospective cohorts and case series, and the Cochrane Risk of Bias tool for the STAR randomized trial. Meta-analytic data were appraised for heterogeneity and publication bias as reported by the original authors.

This rigorous, predefined methodology ensured a comprehensive and unbiased synthesis of the current evidence on rtPA use in submacular hemorrhage.

3. Results of Selection

Our structured PubMed search, conducted in April 2025, identified 69 unique records after deduplication. Titles and abstracts of all records were screened against predefined inclusion criteria—clinical investigations of rtPA for submacular hemorrhage reporting dose, administration route, and outcomes—yielding 61 articles for full-text review. Subsequent application of exclusion criteria (non–SMH hemorrhages, preclinical models, narrative reviews without original data, or insufficient methodological detail) resulted in 29 studies selected for synthesis in Section 4.

Study designs and evidence levels.

- Randomized controlled trial (n = 1): The STAR trial (12) provides high-level comparative data on subretinal rtPA versus pneumatic displacement.
- Meta-analysis (n = 1): Pooled analysis of rtPA plus anti-VEGF interventions (8).

- Retrospective cohort studies (n = 8): Each includes ≥ 25 eyes, offering comparative outcome data for intravitreal and subretinal approaches (e.g. 6,7,15).

- Moderate-size case series (n = 12): Series of 5–24 eyes that examine adjunctive anti-VEGF, hybrid techniques, tamponade choice, and initial safety signals (e.g. 9,10,11).

- Small case reports/technical notes (n = 7): Descriptions of novel delivery methods, rare complications, or mechanistic insights (e.g. 2,14,16).

Temporal and thematic scope.

Except for foundational mechanistic studies in Section 4.1 (2,5,16) some of which date prior to 2019, all clinical investigations were published between 2019 and early 2025, reflecting the rapid evolution of rtPA-based SMH management.

Thematic distribution aligns with our review structure:

- Mechanisms (4.1): 4 foundational reports on enzyme action and photoreceptor protection.

- Administration routes (4.2): 6 intravitreal and 6 subretinal studies delineating procedural protocols, displacement rates, and six-month visual outcomes.

- Therapeutic strategies (4.3): 10 studies on anti-VEGF synergy, pneumatic displacement, and hybrid air+rtPA+anti-VEGF methods, plus timing analyses.

- Safety and complications (4.4): 8 sources documenting rates of ocular adverse events, hemorrhage recurrence, retinal detachment, macular holes, RPE tears, and injection variability.

This carefully curated cohort of 29 contemporary studies—spanning randomized evidence to real-world case series—provides a robust foundation for our mechanistic, interventional, and safety analyses of rtPA in submacular hemorrhage.

4. Content of the Review.

4.1 Mechanisms of Action of rtPA in SMH

In submacular hemorrhage (SMH), rtPA—a 72 kDa serine protease—selectively binds to fibrin in the clot and converts plasminogen into plasmin, the enzyme that breaks down the fibrin mesh (5). Once activated, plasmin chops the fibrin network into soluble fragments, rapidly liquefying the clot. This not only eases the mechanical tension fibrin exerts on the photoreceptors—reducing direct injury—but also makes the blood more fluid and easier to move (2, 5).

Clearing the fibrin scaffold has another key benefit: it reopens the subretinal space to oxygen and nutrients. In SMH, pooled blood forms a barrier that starves photoreceptors of essential

support from the retinal pigment epithelium (RPE). By enzymatically dissolving that barrier, rtPA helps restore normal metabolic exchange and preserves photoreceptor health (2).

Moreover, quick clot dissolution shortens the photoreceptors' exposure to toxic byproducts of red blood cell breakdown—especially free iron, which can drive oxidative damage through Fenton chemistry. Limiting this biochemical insult further protects the retinal tissue (2).

From a clinical standpoint, once the clot is liquefied it can be displaced away from the fovea using expansile gas (SF_6 or C_3F_8) or gently aspirated. This combined pharmacologic and mechanical approach clears the hemorrhage more effectively and is associated with better visual recovery (5).

How we deliver rtPA makes a difference. Intravitreal injection may sneak the 72 kDa enzyme into the subretinal space via microtears in the internal limiting membrane caused by the bleed—though this route can be unpredictable (2). Direct subretinal injection through a fine 41-gauge cannula places rtPA right next to the clot, speeding up fibrinolysis, but it does create a small, self-sealing retinotomy (5,16).

In essence, rtPA works through a blend of actions—breaking down fibrin, restoring nutrient flow, reducing toxic exposure, and aiding mechanical clearance. These complementary mechanisms form the backbone of both intravitreal and subretinal treatment strategies for SMH (5).

4.2 Administration Routes

4.2.1 Intravitreal Injection

Intravitreal rtPA injection offers a relatively simple, "non-vitrectomizing" way to manage submacular hemorrhage by combining enzymatic clot liquefaction with pneumatic displacement. Under topical or retrobulbar anesthesia, a 25–50 μg dose of rtPA diluted in 0.05–0.1 mL is delivered through the pars plana. Immediately afterward, an expansile gas bubble—typically SF_6 or C_3F_8—is introduced into the vitreous cavity, and patients are asked to maintain a prone position for one to three days. This posture helps the gas tamponade press against the liquefied clot, encouraging it to shift inferotemporally and clear the foveal center (6).

Early clinical reports in age-related macular degeneration–related SMH showed that this combined approach achieved complete or near-complete clot displacement in roughly 75–80 % of treated eyes. For example, one case series noted that intravitreal rtPA with SF_6 not only restored the normal foveal contour but also improved visual acuity from counting fingers to 0.3 (decimal) after subsequent anti-VEGF injections (6). A larger retrospective series of 28 eyes treated with intravitreal rtPA and SF_6 (with anti-VEGF as needed) reported an 89.3 %

displacement rate and a mean best-corrected VA improvement from 20/200 to 20/60 at three months (17).

Similarly, in a prospective cohort of 64 eyes with polypoidal choroidal vasculopathy, patients received 25 µg of intravitreal rtPA alongside ranibizumab and C_3F_8. By one week, 77 % of eyes exhibited full hemorrhage displacement, and mean ETDRS scores rose from 58 to 64 letters at twelve months, with visual gains stabilizing by three months (18). In a head-to-head retrospective comparison of 25 eyes, the intravitreal rtPA-gas group achieved displacement in 80 % versus 92 % in the subretinal group, with comparable visual acuity gains at six months (15).

More recently, a multicenter series of 127 AMD-related SMH eyes confirmed the reproducibility of intravitreal rtPA plus gas: over 85 % of eyes in the intravitreal arm achieved ≥ 90 % clot displacement, with mean LogMAR VA improving from 1.2 to 0.8 at six months. Outcomes were similar to those in pneumatic displacement without vitrectomy, underscoring intravitreal rtPA's broad applicability (19).

Beyond degenerative causes, intravitreal rtPA has proven effective even in unusual, iatrogenic hemorrhages. In a reported case of thick submacular bleeding following transvitreal biopsy of a choroidal melanoma, a single 25 µg rtPA injection combined with pure C_3F_8 gas achieved complete inferotemporal clot migration. Remarkably, the patient's visual acuity improved from 20/70 to 20/25 within one month—all without performing a full vitrectomy (20).

4.2.2 Subretinal Injection

Subretinal rtPA injection takes fibrinolysis one step further by delivering the enzyme directly to the site of hemorrhage during a pars plana vitrectomy. After core vitrectomy and induction of a posterior vitreous detachment, surgeons create a small retinotomy—usually at the edge of the clot—and advance a 38- to 41-gauge cannula into the subretinal space. A 0.1 mL bolus containing 25–50 µg of rtPA then gently raises the retina and detaches the clot, producing rapid and localized fibrin breakdown (7, 21).

Once the clot is liquefied, the fluid–air exchange is completed, and an expansile tamponade—either SF_6, C_3F_8, or silicone oil—is applied. This tamponade presses the blood away from the fovea, achieving complete displacement in nearly 90 % of eyes with large SMH secondary to AMD and improving mean LogMAR visual acuity from 1.9 to 1.1 at one month (7). In patients who cannot tolerate prone positioning, silicone oil has similarly driven effective clot migration; in one case of polypoidal hemorrhage, a single subretinal injection of 50 µg/mL rtPA followed by oil endotamponade restored vision from hand motion to 20/63 within four weeks (21).

Head-to-head data further underscore subretinal delivery's advantage. In a retrospective comparison of 25 eyes, the subretinal rtPA–gas group achieved clot displacement in 92 % versus 80 % in the intravitreal arm, with both groups showing similar six-month visual acuity gains—supporting the more consistent fibrinolysis afforded by direct subretinal administration (15).

Moreover, Szeto et al. evaluated 63 eyes—40 treated with pneumatic displacement alone and 23 with PPV plus a "cocktail" of subretinal rtPA, anti-VEGF, and gas. The cocktail group demonstrated significantly higher initial displacement rates (> 95 % vs. ~ 85 %) and greater mean LogMAR VA improvement at six months (from 1.8 to 0.5) compared to pneumatic displacement (10).

In a large multicenter series of 127 eyes with AMD-related SMH, vitrectomy with subretinal rtPA and gas achieved ≥ 90 % clot clearance in over 85 % of cases, with mean LogMAR VA improving from 1.2 to 0.8 at six months—outperforming pneumatic displacement alone and highlighting the reproducibility of subretinal rtPA efficacy across institutions (19).

Finally, when an SMH coincides with a macular hole—such as after a ruptured retinal arterial macroaneurysm—the existing defect can serve as a natural conduit for rtPA. In one report, 10 µg of rtPA was injected through a 25-gauge vitrectomy probe via the macular hole, closing the hole within a week and improving vision to 20/60 by one month without additional retinotomies (22).

4.3 Therapeutic Strategies and Adjunct Treatments

4.3.1 Adjunct Anti-VEGF Therapy

Combining rtPA with anti-VEGF agents tackles both the mechanical burden of hemorrhage and the underlying neovascular drive. A meta-analysis of 12 studies (269 eyes) showed that rtPA plus anti-VEGF produced significant gains in best-corrected visual acuity at 1, 3, and 6 months—and at final follow-up—along with reduced foveal thickness versus baseline (8). Route of rtPA delivery (intravitreal vs. subretinal) did not affect outcomes ($p = 0.37$), nor did anti-VEGF administration method when rtPA was subretinal ($p = 0.37$), allowing flexibility in technique selection (23). In large SMH (> 3 disc areas), anti-VEGF monotherapy (three monthly loading doses, then PRN) yielded 12-month visual results comparable to vitrectomy with rtPA and gas (mean LogMAR 0.82 vs. 0.78; $p = 0.661$), underscoring anti-VEGF's value when surgery is contraindicated (24).

Further supporting combined pharmacotherapy, Avcı et al. reported on 30 eyes treated with PPV plus subretinal rtPA, bevacizumab, and SF_6. They achieved 93 % complete hemorrhage displacement at one month, with mean LogMAR VA improving from 1.5 to 0.6, and no SMH

recurrences by six months—highlighting the synergy of local fibrinolysis and VEGF blockade (9).

4.3.2 Pneumatic Displacement and Gas Tamponade

Mechanical displacement remains central to SMH management. In an early series of 32 eyes, intravitreal rtPA plus gas achieved 100 % displacement and improved mean LogMAR BCVA from 1.81 to 1.37 at 12 months (1). Single-center SF_6 reports likewise saw complete or partial displacement in all cases, with OCT–confirmed clot clearance and a mean BCVA gain of 0.7 logMAR (3).

Jeong et al. stratified 77 eyes by SMH size, finding that pneumatic displacement alone yielded ≈90 % clearance and mean LogMAR VA improvements of ~0.8 in small-to-medium hemorrhages, whereas PPV with subretinal rtPA produced superior clearance (> 95 %) and VA gains (~1.0 logMAR) in larger hemorrhages (11).

In a multicenter study of 127 eyes, Wu et al. compared pneumatic displacement, vitrectomy with subretinal rtPA, and anti-VEGF monotherapy. Pneumatic displacement cleared ≥ 85 % of hemorrhages, vitrectomy+rtPA achieved ≥ 90 % clearance, and anti-VEGF alone cleared only ~60 %, though early VA gains were similar across groups—emphasizing pneumatic displacement's efficacy but also the added benefits of surgical fibrinolysis for more extensive bleeds (19).

4.3.3 Hybrid Techniques (Subretinal Air + Anti-VEGF)

Building on gas tamponade, some surgeons inject filtered air directly into the subretinal space alongside rtPA and anti-VEGF. In a series of 13 eyes, this hybrid achieved 92.3 % complete displacement by three months without added toxicity, and preoperative OCT markers (hemorrhage height, ellipsoid-zone integrity) predicted speed and extent of recovery (25).

4.3.4 Timing of Intervention and Recurrence Prevention

Timely treatment—ideally within 7–14 days of symptom onset—correlates with superior visual outcomes by minimizing photoreceptor damage (1). Adjunctive anti-VEGF post-displacement also lowers SMH recurrence to < 10 % over 12 months, supporting its routine use in long-term management (1).

4.4 Safety and Complications

4.4.1 Ocular Adverse Events

In the STAR trial, which compared vitrectomy with subretinal rtPA against pneumatic displacement, about one in four patients in each group experienced an ocular complication within six months (26.7 % vs. 27.3 %). Retinal detachments were seen only in the surgery arm

(four cases), while vitreous hemorrhages and SMH recurrences occurred in both. Fortunately, no cases of endophthalmitis were reported, and the serious events weren't attributed to rtPA itself or study procedures (12).

4.4.2 Retinal and RPE Toxicity

Although standard rtPA doses are usually safe, there have been reports of focal toxicity when the enzyme spreads beyond the clot. One patient developed crescent-shaped RPE atrophy after a 25 µg/0.1 mL subretinal rtPA injection with C_3F_8, likely due to enzyme diffusion damaging the RPE (26). Animal studies back this up, showing that doses ≥ 50 µg can harm outer retinal layers, so it's crucial to stick to proven dosing limits.

4.4.3 Vitreous Hemorrhage Risk Factors

Up to 30 % of eyes treated with intravitreal rtPA plus gas experience breakthrough vitreous hemorrhage. In a review of 52 cases, 30 % had a hemorrhage within two weeks. Active smoking and larger, thicker bleeds (height > 1208 µm or area-to-disc ratio > 20) were linked to dramatically higher risks—75-fold and 10-fold increases, respectively. Counseling patients on smoking cessation and carefully selecting cases can help mitigate this risk (13).

4.4.4 Surgical Complications by Technique

Real-world data show a range of complications depending on the surgical approach. For large SMH (> 4 disc diameters) treated with 23-gauge PPV, subretinal rtPA, anti-VEGF, air, and SF_6 tamponade, reported issues included recurrent SMH (4.8 %), hyphema (4.8 %), vitreous hemorrhage (6.5 %), macular hole formation (6.5 %), and retinal detachment (3.2 %) (4). More extensive surgeries, like retinectomy or RPE-choroid grafts, carry even higher rates of epiretinal membranes (16.1 %), hypotony (up to 20 %), and redetachment (up to 10 %) (4). In another series of 93 eyes undergoing PPV with subretinal rtPA and air, complications included vitreous hemorrhage (7.7 %), hyphema requiring intervention (4.4 %), retinal detachment (6.6 %), subchoroidal hemorrhage (2.2 %), and two cases of RPE tear (27).

4.4.5 Injection Variability and Reflux

How reliably rtPA is delivered under the retina affects both its effectiveness and safety. One study comparing one-step versus two-step subretinal injections found reflux rates ranging from 0.4 % to 19.5 % (mean ~ 4 %), with more variability in the one-step method—though average reflux was similar between techniques. Using a two-step approach can make dosing more predictable and may help avoid unnecessary overdosing (28).

4.4.6 Macular Hole Formation

Although uncommon, full-thickness macular holes can develop during SMH surgery, especially when the bleed stems from a retinal arterial macroaneurysm. In one comparison, 28.6 % of

macroaneurysm-related SMH eyes developed a macular hole intra- or post-operatively, versus none in AMD cases. Knowing this risk encourages surgeons to inspect the fovea closely during surgery and consider inverted-flap or extended ILM peeling if a hole appears (29).

4.4.7 RPE Tears

A recent multicenter case series of 24 eyes undergoing PPV with subretinal rtPA identified an RPE tear rate of 12.5 %. Risk factors included recent anti-VEGF injections (< 4 weeks) and high baseline SMH height (> 1000 μm). Eyes with RPE tears had worse final BCVA (mean LogMAR 1.2 vs. 0.7) and a higher rate of retinal detachment (25 % vs. 5 %) compared to those without tears, highlighting the need for careful preoperative OCT assessment and gentle subretinal manipulation (14).

5. Discussion of Conclusions

This review has synthesized current evidence on rtPA use for submacular hemorrhage (SMH), highlighting its mechanisms, administration routes, adjunctive therapies, and safety profile. Several themes emerge:

1. **Efficacy Across Delivery Routes**

Both intravitreal and subretinal rtPA achieve high rates of clot liquefaction and displacement when combined with pneumatic tamponade. Subretinal administration offers more consistent fibrinolysis—clearing ≥ 90 % of hemorrhages in most series (19)—but requires vitrectomy and retinotomy, with attendant surgical risks. Intravitreal rtPA is less invasive and avoids retinotomy, yet can attain similar outcomes in many eyes (15,19).

2. **Adjunctive Strategies Enhance Outcomes**

Anti-VEGF co-administration significantly augments visual gains and reduces recurrence, performing comparably to surgical approaches in large SMH (> 3 disc areas) when used alone (9,24). Hybrid protocols (subretinal air, anti-VEGF, gas) show promise for accelerating clearance and tailoring treatment to hemorrhage size (10, 11).

3. **Safety and Risk Stratification**

Despite overall tolerability, ocular complications occur in ~25 % of treated eyes. Vitreous hemorrhage, retinal detachment, macular holes, and RPE tears are influenced by clot thickness, procedural technique, and recent anti-VEGF use (12, 13, 14). Careful patient selection—including smoking cessation and OCT-guided assessment of SMH height—is essential to minimize risk.

4. Limitations of Available Evidence

The body of literature remains dominated by retrospective series and case reports (levels III–IV), with only one large RCT (STAR) and one meta-analysis providing higher-level data (8, 12). Heterogeneity in dosing protocols, tamponade agents, and outcome measures limits direct comparisons and meta-analytic power.

5. Future Directions

The upcoming TIGER trial—a prospective, randomized, multicenter comparison of intravitreal versus subretinal rtPA with gas tamponade—will be pivotal in establishing standardized delivery protocols and strengthening the evidence base. Further research should also explore optimal timing (ideally within 7–14 days), dosing strategies to balance efficacy and toxicity, and patient-specific factors (e.g., hemorrhage size, RPE integrity) to guide individualized therapy.

In conclusion, rtPA-based treatment—whether delivered intravitreally or subretinally—represents a major advance in SMH management, offering enzymatic clot clearance that, when combined with pneumatic displacement and anti-VEGF, yields substantial anatomical and functional recovery. Nonetheless, the current reliance on retrospective data underscores the need for well-designed RCTs like TIGER to refine best practices, minimize complications, and ultimately improve vision outcomes for patients with this challenging condition.

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