

Clinical outcomes of nonpenetrating subretinal tissue plasminogen activator injection through a focal internal limiting membrane window for severe submacular hemorrhage

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Abstract

Background

To evaluate the clinical outcomes and safety of nonpenetrating subretinal tissue plasminogen activator delivery through a focal internal limiting membrane window in a heterogeneous series of severe submacular hemorrhage.

Methods

This retrospective, single-surgeon case series included 13 eyes of 12 patients treated with pars plana vitrectomy, focal internal limiting membrane removal at the selected injection site, tangential subretinal tissue plasminogen activator delivery without deliberate cannula penetration, and gas tamponade. The series included five etiologies, three eyes with hemorrhagic retinal detachment, and one patient with severe acute myeloid leukemia-related pancytopenia. Best-corrected visual acuity was converted to logarithm of the minimum angle of resolution units. Twelve eyes completed 6 months of follow-up; all 13 eyes were included in the safety analysis.

Results

Mean age was 57.08 ± 20.58 years. Causes included age-related macular degeneration in 5 eyes, retinal arterial macroaneurysm in 3, trauma in 2, acute myeloid leukemia-related hemorrhage in 2, and myopic choroidal neovascularization in 1. In the 12 eyes with complete follow-up, mean visual acuity improved from 1.96 ± 0.34 logMAR at baseline to 0.88 ± 0.52 at month 6 (Friedman test, $P < 0.001$). All 12 eyes improved by at least 0.3 logMAR. No macular hole, retinal detachment, epiretinal membrane, endophthalmitis, or other procedure-related complication was observed.

Conclusions

Nonpenetrating subretinal tissue plasminogen activator delivery through a focal internal limiting membrane window was feasible in this clinically heterogeneous series. Visual and anatomical improvement was observed even in eyes with hemorrhagic retinal detachment and in a patient with severe pancytopenia. No procedure-related complication was observed, although the sample was too small to exclude uncommon adverse events. These findings extend previous technical and experimental reports by providing clinical outcomes across varied and medically challenging presentations.

Background

Submacular hemorrhage can cause rapid and irreversible photoreceptor injury through fibrin contraction, iron toxicity, and separation of the photoreceptors from the retinal pigment epithelium [1–3]. Pneumatic

displacement, intravitreal or subretinal tissue plasminogen activator (tPA), anti-vascular endothelial growth factor (anti-VEGF) therapy, and pars plana vitrectomy (PPV)-based procedures have therefore been used to move blood away from the fovea and treat the underlying disease [3–6]. For thick or extensive hemorrhage, PPV with subretinal tPA and gas tamponade provides direct fibrinolytic treatment and may achieve useful anatomical displacement [4–7].

Conventional subretinal delivery places a fine cannula through the neurosensory retina [8]. Although a 41-gauge retinal needle creates a small opening, the maneuver is not mechanically risk-free. Movement of the hand or globe can enlarge the retinal opening, withdraw the cannula during injection, or direct the fluid jet into retinal tissue. Novelli and colleagues specifically described retinotomy enlargement, hemorrhage, and cannula withdrawal as concerns during manually controlled subretinal injection [6]. Macular holes have also been reported after subretinal tPA for hemorrhage caused by retinal arterial macroaneurysm [7]. These events are uncommon, but their consequences may be substantial in an already fragile macula.

Local removal of the internal limiting membrane (ILM) as an access step for subretinal injection is not new. Okanouchi and colleagues described focal ILM removal that allowed the cannula tip to contact the exposed retinal nerve fiber layer and initiate a subretinal bleb without puncturing the retina [9]. Subsequent experimental work from the same group showed that removal of approximately one-quarter of a disc area of ILM permitted nonpenetrating injection at a pressure as low as 6 psi and that higher injection pressure caused greater outer retinal and retinal pigment epithelial injury [10]. A later 17-eye series of massive submacular hemorrhage secondary to exudative age-related macular degeneration used local ILM removal with automated subretinal prourokinase and air injection [11].

Clinical evidence for this approach nevertheless remains limited, particularly across causes other than neovascular age-related macular degeneration and in eyes with unusually severe ocular or systemic disease. We therefore evaluated 13 consecutive eyes treated with a small focal ILM window and tangential subretinal tissue plasminogen activator delivery. The aim was to assess the feasibility, visual and anatomical outcomes, and observed complications of the technique across heterogeneous submacular hemorrhage, including hemorrhagic retinal detachment and severe pancytopenia.

Methods

Study design and patients

We performed a retrospective review of consecutive eyes with submacular hemorrhage treated at China Medical University Hospital, a tertiary medical center in central Taiwan, by one vitreoretinal surgeon (M.C.H.). Eyes were included when the hemorrhage involved the fovea and the treating surgeon selected vitrectomy with subretinal tPA because of hemorrhage thickness, extent, associated hemorrhagic retinal detachment, or inadequate suitability for a less invasive displacement procedure. Etiology was not restricted to neovascular age-related macular degeneration. The study period was from December 1,

2021, to December 1, 2024. The Institutional Review Board of China Medical University Hospital approved the study (CMUH 114-REC1-105) and waived the requirement for informed consent because of its retrospective design and use of anonymized clinical data. The study was conducted in accordance with the Declaration of Helsinki.

The available record contained 13 treated eyes. Twelve eyes had 6 month follow up. One patient with acute myeloid leukemia died from the systemic disease during month 3 after reaching a decimal visual acuity of 0.2 at month 2; this eye remained in the safety analysis and in analyses at available time points.

Surgical technique

All procedures were performed by one surgeon (M.C.H.). Standard PPV and posterior hyaloid separation were performed. The ILM was stained with Brilliant Blue G or indocyanine green according to the operative plan. Rather than peeling the ILM across the macula, the surgeon created a small focal ILM window only at the intended injection site. The site was selected outside the foveal center, at a location that allowed the injected fluid to extend beneath the hemorrhage while avoiding major retinal vessels and visibly atrophic retina.

A 41-gauge subretinal cannula connected to tPA at a concentration of 33 µg/mL was lowered until its distal segment lay tangential to the retinal surface. The cannula tip was placed flat on the retina within the focal ILM window. It was not pushed through or inserted into the neurosensory retina. tPA was delivered slowly, either by an assistant or with the viscous fluid injection function of the surgical system, while the surgeon maintained tangential contact. Formation and extension of the subretinal bleb were observed directly and, when available, with intraoperative optical coherence tomography. The injected volume was adjusted to the extent of hemorrhage; a uniform volume was not documented in the source data and is therefore not specified.

Fluid-gas exchange was then performed using either 8% perfluoropropane (C3F8) or 24% sulfur hexafluoride (SF6) according to the operative plan. Patients were instructed to maintain prone positioning for 3 days. Anti-VEGF treatment was given when indicated by the underlying choroidal neovascular disease. The operation did not require deliberate retinal elevation with an instrument, enlargement of a retinotomy, or direct evacuation of the clot. The same approach was used in eyes with hemorrhagic retinal detachment.

Outcome measures

Outcome measures

Best-corrected visual acuity (BCVA) and central macular thickness (CMT) were obtained from the medical record. Decimal acuity was converted to logMAR. Counting fingers, hand motions, and light perception were assigned values of 1.9, 2.3, and 2.7 logMAR, respectively, for statistical analysis, consistent with published methods for quantifying very low vision [12]. The principal functional analysis

used the 12 eyes with complete baseline, 1-month, 3-month, and 6-month measurements. CMT was compared between baseline and month 1 when both numeric measurements were available. Safety outcomes included macular hole, retinal detachment, epiretinal membrane, endophthalmitis, recurrent hemorrhage, and other intraoperative or postoperative adverse events.

Statistical analysis

Continuous variables are reported as mean $\pm$ standard deviation and range, where appropriate. Change in logMAR visual acuity across four visits was tested with the Friedman test. Baseline-to-postoperative comparisons were examined with Wilcoxon signed-rank tests; Holm adjustment was applied to the three visual acuity comparisons. Paired t tests were calculated as sensitivity measures. Exact binomial confidence intervals were used for proportions. Spearman correlation tested the association between time from symptom onset to surgery and 6-month visual acuity or visual improvement. Etiologic subgroup comparisons were exploratory and used the Kruskal–Wallis test. Because one patient contributed both eyes, a sensitivity analysis repeated the longitudinal visual acuity analysis after excluding either eye from that patient. Analyses used available observations, and no value was imputed after the death of the patient with acute myeloid leukemia. A two-sided P value below 0.05 was considered statistically significant.

Results

Patient characteristics

Thirteen eyes of 12 patients were treated. Mean age was 57.08 ± 20.58 years (range, 23–86 years). The causes were age-related macular degeneration in 5 eyes (38.5%), retinal arterial macroaneurysm in 3 (23.1%), trauma in 2 (15.4%), acute myeloid leukemia-related hemorrhage in 2 (15.4%), and myopic choroidal neovascularization in 1 (7.7%). Three eyes had hemorrhagic retinal detachment. Time from symptom onset to surgery ranged from 0 to 30 days. Twelve eyes completed 6 months of follow-up. Patient-level clinical data are summarized in Table 1.

Table 1
Patient level clinical data

Case	Cause	Age	Eye	Time to surgery days	Baseline VA	Month 1 VA	Month 3 VA	Month 6 VA
1	Trauma	28	OS	14	CF at 20 cm	0.1	0.1	0.1
2	Trauma	23	OD	12	CF at 20 cm	0.4	0.6	0.7
3	AMD with hemorrhagic RD	84	OD	5	CF at 10 cm	CF at 30 cm	0.04	0.04
4	AML with hemorrhagic RD	50	OS	13	CF at 15 cm	0.04	0.04	0.04
5	RAM	69	OS	1	0.02	0.1	0.3	0.3
6	AMD	75	OS	1	LP	CF at 10 cm	CF at 10 cm	CF at 10 cm
7	RAM	86	OS	3	CF at 10 cm	0.2	0.3	0.3
8	AMD	69	OS	1	0.02	0.02	0.1	0.1
9	AMD	60	OD	30	0.04	0.04	0.1	0.1
10	RAM	86	OD	7	HM	0.2	0.5	0.5
11	Myopic CNV	43	OD	30	CF	0.1	0.1	0.1
12	AML related hemorrhage	42	OD	3	CF	0.1	0.2 at month 2	NA
13	AMD with hemorrhagic RD	56	OD	0	HM	0.02	0.1	0.4
<i>AMD, age-related macular degeneration; AML, acute myeloid leukemia; CF, counting fingers; CNV, choroidal neovascularization; HM, hand motions; LP, light perception; NA, not available; RAM, retinal arterial macroaneurysm; RD, retinal detachment; VA, visual acuity. Case 12 died from acute myeloid leukemia during month 3.</i>								

Visual and anatomical outcomes

Among the 12 eyes with complete longitudinal data, mean visual acuity improved from 1.96 ± 0.34 logMAR at baseline to 1.23 ± 0.51 at month 1, 0.94 ± 0.49 at month 3, and 0.88 ± 0.52 at month 6 (Friedman $\chi^2 = 30.73$, $P < 0.001$). Mean improvement from baseline was 0.73 logMAR at month 1, 1.02

logMAR at month 3, and 1.08 logMAR at month 6. Each comparison remained significant after Holm adjustment (adjusted $P = 0.0039$, 0.0015 , and 0.0015 , respectively). At month 6, all 12 eyes had improved by at least 0.3 logMAR, 11 eyes (91.7%) by at least 0.5 logMAR, and 5 eyes (41.7%) by at least 1.0 logMAR. Nine eyes (75.0%; exact 95% confidence interval, 42.8%–94.5%) achieved decimal visual acuity of at least 0.1. In the sensitivity analysis accounting for the patient who contributed both eyes, the longitudinal change remained significant after either eye was excluded (Friedman $\chi^2 = 27.77$, $P < 0.001$ for each analysis). Functional outcomes are summarized in Table 2.

Table 2
Functional anatomical and safety outcomes

Outcome	Baseline	Month 1	Month 3	Month 6	Statistical result
VA in complete cases, mean $\pm$ SD logMAR	1.96 $\pm$ 0.34 n = 12	1.23 $\pm$ 0.51 n = 12	0.94 $\pm$ 0.49 n = 12	0.88 $\pm$ 0.52 n = 12	Friedman $\chi^2 = 30.73$; $P < 0.001$
Improvement from baseline, mean $\pm$ SD logMAR	—	0.73 $\pm$ 0.55	1.02 $\pm$ 0.50	1.08 $\pm$ 0.56	Holm adjusted Wilcoxon $P = 0.0039$, 0.0015 , 0.0015
Central macular thickness, mean $\pm$ SD μm	572.3 $\pm$ 275.0 n = 10	293.0 $\pm$ 87.3 n = 10	—	—	Wilcoxon $P = 0.014$
Decimal VA at least 0.1	—	—	—	9 of 12, 75.0%	Exact 95% CI 42.8% to 94.5%
Procedure related complication	—	—	—	0 of 13	Exact 95% CI 0% to 24.7%
Recurrent hemorrhage	—	—	—	1 of 13, 7.7%	Macroaneurysm rerupture
<i>CI, confidence interval; SD, standard deviation; VA, visual acuity. Counting fingers, hand motions, and light perception were assigned 1.9, 2.3, and 2.7 logMAR, respectively.</i>					

Paired central macular thickness measurements were available in 10 eyes. Mean thickness decreased from $572.3 \pm 275.0 \mu\text{m}$ before surgery to $293.0 \pm 87.3 \mu\text{m}$ at month 1. The mean paired reduction was $279.3 \mu\text{m}$ (95% confidence interval, 55.0 to $503.6 \mu\text{m}$; Wilcoxon signed rank $P = 0.014$; paired t test $P = 0.020$). Anatomical outcomes are also summarized in Table 2.

Representative severe cases

Case 1

A 42-year-old woman with acute myeloid leukemia presented with sudden visual loss to counting fingers in her only functionally useful eye; the fellow eye was amblyopic with visual acuity below 0.1. Despite platelet transfusion for 3 consecutive days, laboratory testing on the morning of surgery showed a white blood cell count of 1,000/ μ L, hemoglobin of 6.2 g/dL, and platelet count of 34,000/ μ L. The focal-window technique avoided a deliberate retinal puncture and direct clot manipulation. Visual acuity improved to 0.1 at month 1 and 0.2 at month 2 without an ocular complication. She died from acute myeloid leukemia during month 3.

Case 2

A 56-year-old woman with age-related macular degeneration had a massive submacular hemorrhage with hemorrhagic retinal detachment. Baseline vision was hand motions and CMT was 602 μ m. Surgery was performed on the day of presentation using the same focal ILM window and tangential injection technique, without lifting the retina or evacuating the clot. The operative steps are shown in Additional file 1. Gas tamponade with 8% perfluoropropane was used, and she was asked to maintain prone positioning for 3 days. Anti-VEGF treatment was given on the day of surgery and monthly thereafter; five injections had been administered at the latest review. CMT was 350 μ m at month 1. Decimal visual acuity improved to 0.02 at month 1, 0.1 at month 3, and 0.4 at month 6, without a procedure-related complication.

Safety and exploratory analyses

No macular hole, retinal detachment, epiretinal membrane, endophthalmitis, or other procedure related complication was observed in 13 eyes. The exact 95% confidence interval around an observed complication rate of 0% was 0% to 24.7%. One 86 year old patient had recurrent hemorrhage after rerupture of a retinal arterial macroaneurysm; vision subsequently reached 0.4. This event was considered recurrence of the underlying vascular lesion rather than a complication of the injection technique. Safety outcomes are summarized in Table 2.

No statistically significant association was detected between time to surgery and 6 month visual acuity (Spearman ρ = 0.13, P = 0.696) or visual improvement (ρ = -0.34, P = 0.288). These analyses were underpowered and should not be interpreted as evidence that delay is safe or that surgical timing is unimportant. Six month visual outcome and improvement did not differ significantly among etiologic groups in exploratory analyses (Kruskal Wallis P = 0.273 and P = 0.258, respectively).

Discussion

The present series does not introduce focal ILM removal as a new access concept. Okanouchi and colleagues previously described local ILM removal followed by subretinal injection with the cannula tip resting on the exposed retinal surface rather than penetrating the neurosensory retina [9]. Their subsequent monkey study supported the mechanical rationale: local ILM removal reduced the pressure required to initiate a bleb, while higher injection pressure produced greater transient injury to the photoreceptor outer segments and retinal pigment epithelium [10]. The contribution of the present study

is clinical. It reports outcomes in 13 consecutive eyes across five etiologies, with standardized longitudinal visual analysis and explicit surveillance for macular hole, retinal detachment, epiretinal membrane, and other procedure-related complications.

The technique limits two potential sources of trauma. Tangential placement avoids the uncontrolled deep movement that can occur when a fine cannula is deliberately advanced into diseased retina. Restricting ILM removal to the access site also avoids unnecessary forceps manipulation and preserves the ILM over most of the macula. The second point remains a mechanical rationale rather than proof of superiority. This uncontrolled series cannot establish that focal peeling is safer than conventional cannula insertion or broader ILM peeling, but no macular hole, retinal detachment, epiretinal membrane, endophthalmitis, or other procedure related complication was observed in 13 eyes.

The main strength of this series is the severity and heterogeneity of the treated eyes. All 12 eyes with complete 6-month data improved by at least 0.3 logMAR, and 9 reached decimal visual acuity of at least 0.1. The cohort included traumatic hemorrhage, retinal arterial macroaneurysm, acute myeloid leukemia related hemorrhage, myopic choroidal neovascularization, and age related macular degeneration. Three eyes had hemorrhagic retinal detachment. In the most severe AMD case, vision improved from hand motions to 0.4 without retinal lifting or direct clot evacuation. The patient with acute myeloid leukemia underwent surgery despite a white blood cell count of 1,000/ μ L, hemoglobin of 6.2 g/dL, and a platelet count of 34,000/ μ L after 3 days of transfusion; vision improved from counting fingers to 0.2 before death from the systemic disease. These cases show that the same limited access method can remain technically feasible when both the macula and the patient are unusually fragile.

Subretinal fibrinolytic injection with gas displacement is well established for large submacular hemorrhage. Previous series have reported useful displacement and visual outcomes after vitrectomy-based subretinal tissue plasminogen activator for age-related macular degeneration and other exudative hemorrhage [4, 5, 13, 14]. Ovchinnikova and colleagues reported 17 eyes with exudative age-related macular degeneration treated using local ILM removal, automated subretinal prourokinase and air injection, and gas tamponade [11]. The present cohort is smaller than that disease-specific series but includes a broader spectrum of causes and severity, detailed 6-month functional outcomes, and explicit reporting of complications relevant to nonpenetrating access. Inoue and colleagues reported macular hole formation in 4 of 22 eyes treated for hemorrhage from ruptured retinal arterial macroaneurysm [7]. Differences in disease, hemorrhage configuration, injection pressure, and operative technique prevent direct safety comparisons.

The lack of association between surgical timing and outcome must be read cautiously. The sample was small, timing ranged widely, and the causes of hemorrhage were heterogeneous. The data do not justify postponing surgery. Likewise, the exploratory etiologic comparison did not reproduce the apparent difference between macroaneurysm and age related macular degeneration reported in the earlier draft analysis. With only one to five eyes per subgroup, disease specific conclusions would be unreliable.

The study has several limitations. It is retrospective, uncontrolled, and limited to a single surgeon. The cohort is clinically heterogeneous, which supports feasibility across difficult presentations but prevents reliable disease-specific efficacy estimates. Injection volume and delivery pressure were not recorded uniformly, gas selection was not standardized, and follow up beyond 6 months was incomplete. Very low visual acuity required numeric assignment for analysis. The absence of observed complications in 13 eyes does not exclude uncommon events, as shown by the wide exact confidence interval around a complication rate of zero. A prospective comparison should standardize injection pressure and volume, record the size and location of the focal ILM window, and compare focal nonpenetrating delivery with conventional transretinal cannula insertion.

Conclusions

Nonpenetrating subretinal tissue plasminogen activator delivery through a focal ILM window was feasible in 13 eyes with severe submacular hemorrhage of varied causes. The series included hemorrhagic retinal detachment and profound systemic illness, and visual and anatomical improvement was observed without a procedure-related complication. These findings provide clinical support for an access method described previously in technical and experimental reports and justify comparative evaluation in a larger, standardized cohort.

Abbreviations

AMD

age-related macular degeneration

AML

acute myeloid leukemia

anti-VEGF

anti-vascular endothelial growth factor

BCVA

best-corrected visual acuity

CMT

central macular thickness

ILM

internal limiting membrane

logMAR

logarithm of the minimum angle of resolution

PPV

pars plana vitrectomy

RAM

retinal arterial macroaneurysm

tPA

tissue plasminogen activator.

Declarations

Ethics approval and consent to participate

The Institutional Review Board of China Medical University Hospital approved this study (CMUH 114-REC1-105) and waived the requirement for informed consent because of its retrospective design and use of anonymized clinical data. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

The IRB (CMUH 114-REC1-105) waiver also covers publication of these deidentified materials.

Availability of data and materials

The deidentified patient-level data supporting the findings are included in this article. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MCH performed all surgeries. YJC and MCH analyzed and interpreted the patent data. YJC and MCH wrote the manuscript. HYL, CCC, YWC, Jennifer HCH, and YYT revised the manuscript. All authors read and approved the manuscript.

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