Recombinant Tissue Plasminogen Activator (rtPA) in the Treatment of Macular Hemorrhages

Ativador Recombinante do Plasminogénio Tecidual no Tratamento de Hemorragia Macular

Sara Alves Pereira[1], Rui Carvalho[1], Pedro Coelho[1], Tiago Maio[1], Renato Barbosa[1]

[1] Department of Ophthalmology, Unidade Local de Saúde de Matosinhos, Matosinhos, Portugal

Received/Recebido: 14-03-2021
Accepted/Aceite: 14-04-2021
Published/Publicado: 30-06-2021

ABSTRACT

Macular hemorrhage is a frequent complication of retinal macroaneurysms and rep-resents a threat to central vision. We report the surgical use of recombinant tissue plasminogen activator (rtPA) in the treatment of macular hemorrhage.

Two eyes of 2 female patients with macular hemorrhage from ruptured retinal macroaneurysms were treated with subretinal rtPA injection. Visual acuities on admission were of counting fingers (<20/400) in the 2 eyes treated. Best corrected visual acuity improved to 20/100. No major intraoperative complications were reported.

Macular hemorrhage presents a low rate of spontaneous resolution and, left untreated, portends a poor prognosis. Subretinal injection of rtPA is a challenging, yet effective surgical technique, with rates of hemorrhage displacement reported between 50%-90%.

KEYWORDS: Intravitreal Injections; Retinal Hemorrhage/tratamento; Recombinant Proteins; Tissue Plasminogen Activator

RESUMO

A hemorragia macular é uma complicação frequente em casos de macroaneurisma retiniano e representa uma ameaça significativa à visão central. Neste estudo, os autores reportam o uso cirúrgico de ativador recombinante do plasminogénio tecidual no tratamento de hemorragia macular.

Dois olhos, de duas pacientes do sexo feminino, com hemorragia macular por rutura de macroaneurisma retiniano foram tratados com injeção subretiniana de ativador recombinante do plasminogénio tecidual. As acuidades visuais à admissão eram de conta dedos (<20/400) nos 2 olhos tratados. As melhores acuidades visuais corrigidas melhoraram para 20/100 em cada olho tratado. Não se registaram complicações operatórias.

A hemorragia macular apresenta uma baixa taxa de resolução espontânea e, na ausência de tratamento, acarreta um mau prognóstico. A injeção subretiniana de ativador recombinante do plasminogénio tecidal é uma técnica cirúrgica desafiante e eficaz, com taxas reportadas de deslocamento da hemorragia entre os 50%-90%.

PALAVRAS-CHAVE: Ativador de Plasminogénio Tecidual; Hemorragia Retiniana/tratamento; Injeções Intravítreas; Proteínas Recombinantes

INTRODUCTION

Macular hemorrhages represent a significant threat to central vision. Its main causes are neovascular age-related macular degeneration (AMD) and rupture of retinal arterial macroaneurysms (RAM).[1]

Retinal arterial macroaneurysms (RAM) are characterized by an acquired focal dilation of a retinal arteriole (usually fusiform or saccular). Although uncommon, RAM are more frequently found in elderly women, and are highly associated with systemic hypertension and arteriosclerosis. Visual prognosis in eyes with RAM can be favorable, unlike neovascular AMD, where macular hemorrhages portend a poor prognosis.[2]

Untreated, macular hemorrhages can cause irreversible damage to the retina, photo-receptores and the retinal pigment epithelium (RPE), from direct toxic effect of the iron in the haemoglobin and from blood clot formation.[3] Early intervention is paramount in preserving visual acuity and retinal function.

Recombinant tissue plasminogen activator (rtPA) converts plasminogen into plasmin and was introduced in the 1990s to promote clot liquefaction and accelerate the hemorrhage clearance. In 1996, Heriot first described the use of intravitreal injection of rtPA and gas for the treatment of macular hemorrhage.[4] Surgical options have evolved, with injection of rtPA, subretinal or intravitreal, combined with gas/air tamponade, being frequently used nowadays. The rationale of these methods involves the displacement of submacular blood to an extrafoveal location, preventing damage to the photoreceptors.[4,5]

CASE REPORT

Two female pseudophakic patients, aged 76 and 81 years old, presented to the Emergency Department complaining of sudden unilateral vision loss. On ophthalmological examination, patient 1 presented best corrected visual acuities of 20/20 on the right eye and counting fingers at 20 cm (<20/400) on the left eye, with a relative afferent pupillary defect of the left eye. Slit-lamp examination showed bilateral pseudophakia and mydriatic fundoscopy was normal on the right eye and revealed an extensive macular hemorrhage on the left eye.

Patient number 2 presented with a history of sudden left eye vision loss with 8 days of evolution. Best corrected visual acuities were 20/25 on the right eye and counting fingers at 50 cm (<20/400) on the left eye. Slit-lamp examination showed bilateral pseudophakia and dilated fundus examination revealed hemorrhage of the inferior macular area. Right eye fundus was normal, with absence of drusen or pigmentary changes, making the diagnosis of age-related macular degeneration unlikely.

OCT was performed on admission and the OCT findings are compatible with massive macular multilevel hemorrhages (Fig.s 1 and 2).

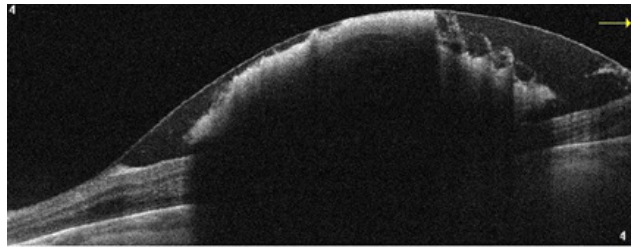

Figure 1 OCT on admission from patient 1. There is distension of the posterior hyaloid and ILM with a large posterior cystic space, hyperreflective on the surface and with shadowing effect, limiting the view of the retina

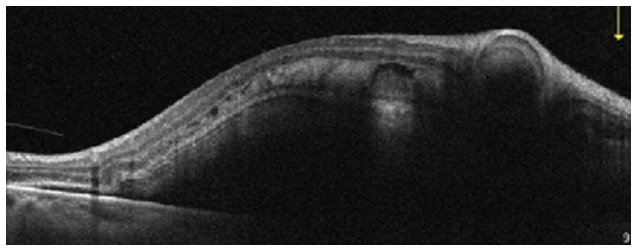

Figure 2 OCT on admission from patient 2. A considerable retinal thickening with accumulation of hyporeflective material, mainly on the subretinal space, is evident. On the internal layers of the temporal retina, a round formation is visible, compatible with a macroaneurysm

The eyes were submitted to PPV with subretinal injection of rtPA. The surgical technique involved performing a standard three-port 23-gauge PPV with core vitrectomy and posterior hyaloid detachment (using triamcinolone acetonide). After complete posterior vitreous detachment, the internal limiting membrane (ILM) was peeled and preretinal blood aspired. Then, a 41-gauge flexible cannula (attached to a 20-g cannula) was inserted via sclerotomy. The 41-g cannula was inserted into the subretinal space and rtPA injected, in a maximum quantity of 50 µg (dissolved in balanced salt solution – the total amount of the solution de-pends on hemorrhage size), creating a local retinal detachment, and promoting inferior displacement of the hemorrhage. After fluid-air exchange, tamponade with sulfur hexafluoride (SF6) was completed.

On the first patient, after the aspiration of a large component of preretinal blood, a smaller component of subretinal blood was noticed and was mobilized after the subretinal rtPA injection. On the second patient, the blood was mainly in the intraretinal and subretinal spaces.

In the immediate postoperative period, patient number 1 suffered from nausea and vomiting, which resulted in hyphema and required surgical intervention with anterior chamber washout. No other complications were reported, intra or postoperatively.

Visual acuities improved to 20/100 in the 2 eyes submitted to treatment, one month postoperatively. OCT was repeated (Fig.s 3 and 4) and showed absence of macular hemorrhage, with normalization of retinal architecture and foveal depression. Different degrees of outer retinal atrophy were also evident on OCT.

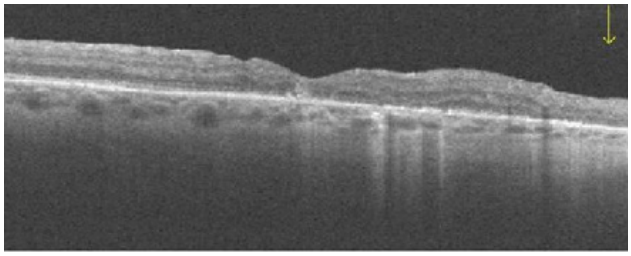

Figure 3 OCT from patient 1, two months postoperative. Outer retinal atrophy and absence of macular hemorrhage are noticed

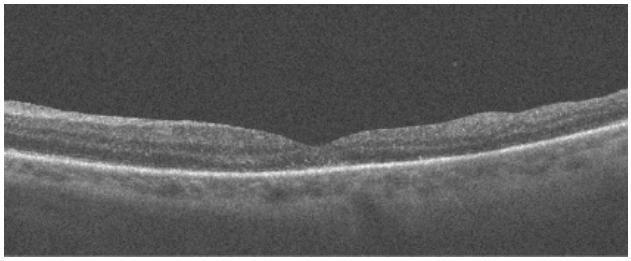

Figure 4 OCT from patient 2, two months postoperative. There is temporal retinal thinning and disorganization of internal layers, as well as outer retinal atrophy with disruption of the ellipsoid. No intraretinal or subretinal blood is visible

DISCUSSION

Submacular hemorrhage has a low rate of spontaneous resolution and, left untreated, visual prognosis is poor.[1] Surgical intervention should be performed as soon as possible, ideally in first 14 days of the hemorrhage, because longer time of hemorrhage is associated with worse functional outcomes.[6] Functional outcome is also associated with hemorrhage size, with bigger diameter of the hemorrhage associated with worse final visual acuity.[7]

The ideal candidate for vitrectomy combined with subretinal rtPA and tamponade is a patient with a recent-onset and large/medium-sized hemorrhage from a ruptured RAM, with blood located mainly in the subretinal space. Patients with a large component of sub-RPE blood or with massive hemorrhages extending beyond the vascular arcades present a very poor prognosis, even with treatment.

Treatment of macular hemorrhages with combined subretinal rtPA and air or gas tamponade is quite effective, with studies reporting rates of hemorrhage displacement from 50%-90%.[8-10] Subretinal rtPA seems to be more effective than intravitreal rtPA, although it may be associated with higher complication rates.[10] Complications of subretinal rtPA include rebleeding and vitreous hemorrhage, retinal detachment or macular hole formation.[6]

Subretinal injection of rtPA is a challenging, yet effective, option for the management of macular hemorrhages. Displacement of the hemorrhage from the macular area can improve the prognosis in these eyes.

ETHICAL DISCLOSURES

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of Human and Animal Subjects: The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association.

Provenance and Peer Review: Not commissioned; externally peer reviewed.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia de 2013 da Associação Médica Mundial.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

REFERENCES

1. Araujo J, Sousa C, Faria PA, Carneiro A, Rocha-Sousa A, Falcao-Reis F. Intravitreal in-jection of recombinant tissue plasminogen activator in submacular hemorrhage: case series. Eur J Ophthalmol. 2016;26:e49-51. doi: 10.5301/ejo.5000682.
2. Inoue M, Shiraga F, Shirakata Y, Morizane Y, Kimura S, Hirakata A. Subretinal injection of recombinant tissue plasminogen activator for submacular hemorrhage associated with ruptured retinal arterial macroaneurysm. Graefes Arch Clin Exp Ophthalmol. 2015;253:1663-9. doi: 10.1007/s00417-014-2861-6.
3. Gonzalez-Lopez JJ, McGowan G, Chapman E, Yorston D. Vitrectomy with subretinal tissue plasminogen activator and ranibizumab for submacular haemorrhages secondary to age-related macular degeneration: retrospective case series of 45 consecutive cases. Eye. 2016;30:929-35. doi: 10.1038/eye.2016.65.
4. van Zeeburg EJ, van Meurs JC. Literature review of recombinant tissue plasminogen activator used for recent-onset submacular hemorrhage displacement in age-related macular degeneration. Ophthalmologica.

2013;229:1-14. doi: 10.1159/000343066.
5. van Zeeburg EJ, Cereda MG, van Meurs JC. Recombinant tissue plasminogen activa-tor, vitrectomy, and gas for recent submacular hemorrhage displacement due to retinal macroaneurysm. Graefes Arch Clin Exp Ophthalmol. 2013;251:733-40. doi: 10.1007/s00417-012-2116-3.
6. Sonmez K, Ozturk F, Ozcan PY. Treatment of multilevel macular hemorrhage second-ary to retinal arterial macroaneurysm with submacular tissue plasminogen activator. Eur J Ophthalmol. 2012;22:1026-31. doi: 10.5301/ejo.5000140.
7. Boiche M, Angioi-Duprez K, Conart JB, Berrod JP. Traitement des hématomes de la dégénérescence maculaire liée à l'âge par vitrectomie et injection sous-rétinienne de rt-PA : résultats préliminaires. J Fr Ophtalmol. 2019;42:e391-e7. doi: 10.1016/j.jfo.2019.02.016.
8. Chang W, Garg SJ, Maturi R, Hsu J, Sivalingam A, Gupta SA, et al. Management of thick submacular hemorrhage with subretinal tissue plasminogen activator and pneumatic dis-placement for age-related macular degeneration. Am J Ophthalmol. 2014;157:1250-7. doi: 10.1016/j.ajo.2014.02.007.
9. Waizel M, Todorova MG, Rickmann A, Blanke BR, Szurman P. Efficacy of Vitrectomy Combined with Subretinal rtPA Injection with Gas or Air Tamponade. Klin Monbl Augen-heilkd. 2017;234:487-92. doi: 10.1055/s-0042-121575.
10. Hillenkamp J, Surguch V, Framme C, Gabel VP, Sachs HG. Management of submacular hemorrhage with intravitreal versus subretinal injection of recombinant tissue plasminogen activator. Graefes Arch Clin Exp Ophthalmol. 2010;248:5-11. doi: 10.1007/s00417-009-1158-7.

Corresponding Author/
Autor Correspondente:

Sara Alves Pereira
Ponte do Mouro – Barbeita
4950-052 Monção
Portugal
salves_gp@hotmail.com

ORCID: 0000-0001-8924-4359