Commentary: Learning curve of a trained vitreo-retinal surgeon in sub-retinal injections in a rat model: Implications for future clinical trials

Drug delivery to the posterior segment of eye is always challenging due to presence of blood-retinal barrier formed by retinal pigment epithelium (RPE) and retinal vascular endothelium. The subretinal route is emerging as an alternative to the traditional intravitreal route. It offers certain advantages such as precise localization of the drug near RPE/photoreceptors, reduction of the required dose of drug and lack of immune response, as it is an immune privileged site. There can be three approaches for subretinal injections: a) transcorneal through pupillary plane, b) trans scleral through pars plana or limbal area, c) trans scleral through choroid without penetration of retina.[1] These are equally efficacious and have their own disadvantages.

The scope of subretinal route of drug delivery is immense. It has proven its effectiveness in the management of submacular hemorrhage due to various causes like neovascular age related macular degeneration (AMD). Various authors have proposed limited vitrectomy followed by injecting a cocktail of tissue plasminogen activator, anti-VEGF and air subretinally through self-sealing retinotomies using 41G needle.[2] This technique effectively causes pneumatic displacement of thick hemorrhage and allows simultaneous treatment of the underlying pathology resulting in favorable outcomes.

Nowadays, subretinal drug delivery has been extensively used as part of both gene therapy and cell therapy, in clinical as well as experimental settings for the treatment of retinal degenerative diseases like Retinitis Pigmentosa (RP), Leber's Congenital Amaurosis (LCA), Stargardt's disease and AMD.[1] In gene therapy, normal functional target gene is delivered to its desired action site like RPE with the help of vectors. Recently, FDA approved LUXTURNA, a subretinal gene therapy for inherited retinal disorders caused by biallelic RPE65 gene mutations like RP, LCA using AAV2 viral vector.[3] More drugs and therapies are in pipeline. Stem cell therapy has shown initial fruitful outcomes in AMD (especially in geographic atrophy cases) and other inherited retinal disorders.[4,5]

There are several potential challenges in using the subretinal route of drug delivery in animal or human studies. Proficiency of the surgeon is a must. As highlighted in the present study by Dave *et al*., there is a considerable learning curve which can lead to potential complications like retinal detachment, choroidal hemorrhage or cataract.[6] Various animal studies support the use of 30G needle for subretinal injections for better outcomes.[7] In humans, we use 41G instruments to make self-sealing retinotomies. Vitreous loss could be minimized by suturing MVR wounds. There is a likely benefit of using an assistant in such cases to push the plunger while the surgeon stabilizes the needle resulting in reduction of various intraoperative complications. Other issues that must be kept in mind while recommending these therapies are cost-effectiveness, toxicity profile and limited study data about their safety and efficacy.[1,3]

In conclusion, subretinal route of drug delivery is emerging as a great therapeutic modality. The learning curve of the surgeon should be given due importance while designing the research methodology and interpretation of results involving novel drug targets.

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