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EFFICACY AND SAFETY OF THE DEVELOPED NANOPARTICLES FOR THE TREATMENT OF RETINAL DEGENERATION

Dr. NARDEV SINGH
Department of Pharmacy, Graphic Era Hill University, Dehradun, Uttarakhand, India 248002

Abstract

The advancement of medicine has entered a new phase because to the study of nanoparticles (NPs). Nanoparticles (NPs) are tiny particles, on the scale of cells and molecules, with a size between 10 and 1,000 nm. NPs have the potential to transport pharmaceuticals to bypass barriers, drug targeting, drug sustained release, medication safety, and even gene therapy, making them an attractive alternative to conventional ophthalmic treatments. After a quick overview of NP categorization, we will propose novel approaches developed from NPs with the aim of improving the diagnosis and treatment of a variety of retinal illnesses.

Keywords: Nanomaterials, retina, gene therapy, drug delivery

INTRODUCTION

Nanoparticles (NPs) are tiny particles, on the nanometer scale, in the range of cellular and molecular structures, typically between 10 and 1000 nm in size. Liposomes, nanospheres, dendrimers, hydrogels, and nanoemulsions are all different types of NPs. Adsorption, encapsulation, capture, and covalent coupling of bioactive chemicals or drugs to NPs may modify their pharmacokinetics and pharmacodynamics. The aspect ratio and surface properties of NPs have an effect on their uptake by cells, drug delivery, and diffusion. Nanoparticles (NPs) offer several benefits, including timed release, medication targeting, and higher bioavailability. Nanotechnology's rapid advancement has allowed for exciting new possibilities in healthcare. Research on NPs is now common and is employed in the treatment of a variety of retinal illnesses. In what follows, we'll take a look at how NPs have been used to diagnose and treat retinal disorders. The average visual result seven years following anti-VEGF medication in individuals with AMD was worse than their baseline visual acuity, according to research. Avoiding intravitreal injection would decrease the likelihood of complications including infection, hemorrhage, retinal detachment, leakage, scarring, discomfort, and damage to the retinal pigment epithelium (RPE).

LITERATURE REVIEW

Scheive, M., Yazdani, S., & Hajrasouliha, A. R. (2018), It's intriguing to think of the clinical applications of nanotechnology in the fields of medicine, diagnosis, and surgery. Ocular medication and gene delivery systems targeting eye illnesses, especially retinopathies, are examples of nanotechnologies in nano-ophthalmology that are only beginning to find their way into clinical situations. The invasiveness of conventional therapies, such as intravitreal injections, makes it difficult to treat retinal illnesses. In this article, we take a look at the therapeutic applications of nanotechnology in the treatment of retinal illnesses. By penetrating the retina's protective anatomical and physiological barriers, nanotechnology may revolutionize pharmacological and surgical therapies. Nanoparticles have been shown in preclinical studies to increase the sensitivity and specificity of current diagnostic and screening methods, allowing for earlier and more straightforward illness detection as well as more precise monitoring of disease development.

Srichana, T.; Paliwal, H.; Prajapati, B.G.; Singh, S.; Patel, R.J. (2019), Factors such as aging populations, environmental changes, smoking, genetic anomalies, etc., have contributed to a rise in the number of individuals seeking treatment for ocular problems. One prevalent eye illness that may cause

blindness in advanced stages is age-related macular degeneration (AMD). Advanced age-related macular degeneration may be either dry or moist. There are a number of therapeutic approaches being studied for the treatment of AMD, but as of yet, no FDA-approved drug exists to effectively slow the progression of dry AMD into its later stages. To slow the disease's development and preserve or restore patients' eyesight, researchers have recently focused on creating more specific treatment agents. Intravitreal treatment for the administration of anti-VEGF drugs has shown promise in the management of AMD, and innovative formulation procedures have been used in a number of trials to boost their effectiveness. Hydrogel, microspheres, polymeric nanoparticles, liposomes, implants, etc. are only some of the new methods that have been proposed. Biologic and gene therapy research has also focused on subretinal, suprachoroidal, and port delivery methods. This article describes the present methods of treating AMD, the findings from recent studies, and the patent information for the new method of medication administration.

Min Ding, Jinshun Zhaoa, Yafei Wanga, Yuanliang Gua, Linda Bowmanb, and Hong Su (2018), Potential uses of nanoparticles in medicine have been the subject of much study in recent years, thanks to the fast growth of nanotechnology. Human biosafety of nanomaterials for clinical usage is of increasing importance as their composition, form, chemical characteristics, implant locations, and possible uses grow more complicated. The accumulation of nanoparticles in the body or their interaction with molecules or chemical components of the body might possibly pose hazards to human health. This research thus examines the specific chemical and physical characteristics, possible medicinal uses, and human biosafety throughout clinical trials. This article concludes by offering some recommendations for further study in the field of nanomedicine.

Tawfik, M., Chen, F., Goldberg, J.L. et al. (2016), Drug transport to the retina remains difficult owing to anatomic and physiological limitations, despite its accessibility through the ocular surface. Improved drug bioavailability and regulated, prolonged release may be achieved by designing an appropriate delivery platform to circumvent these obstacles. Intravitreal implants and subretinal viral gene transfer are two examples of recent innovations in posterior segment therapy that meet these requirements. There has been an uptick in research into gene delivery through siRNA, mRNA, or aptamers, and there are a number of innovative drug delivery methods being researched for use in the posterior segment. Future therapeutic possibilities are highlighted, and the present status of retinal drug/gene delivery is discussed.

Yang B., et al. (2018) Among those aged 50 and over, age-related macular degeneration (AMD) is the major cause of permanent visual loss. Anti-vascular endothelial growth factor (VEGF) medicines are often administered intravitreally to treat age-related macular degeneration. Existing, high-priced treatments fail to cure the condition and have undesirable side effects. The cumulative risk of problems like endophthalmitis also rises with each additional injection. Intravitreal (eye) injections of gene therapy products have made treatment simpler and more improved visual results. Moreover, modern nano-therapy is the most promising new avenue for delivering therapeutic agents to patients with AMD. In this overview, we look at how gene therapy and nano-drug delivery methods have progressed in recent years to treat AMD. We also go through some cutting-edge targeting tactics and how these delivery modalities may be used to treat AMD. Finally, we propose a unique non-viral delivery mechanism combined with CRISPR/Cas9 technology as a therapeutic approach for the treatment of AMD.

NPs for Treatment of Retinal Diseases

Retinal Neovascularization Diseases. Choroidal neovascularization (CNV), diabetic retinopathy (DR), and exudative age-related macular degeneration (AMD) are all forms of retinal neovascularization. The abnormal angiogenesis that causes retinal or subretinal hemorrhage and exudation is characteristic of these diseases [39]. When discussing neovascular illnesses, vascular

endothelial growth factor (VEGF) often comes up. VEGF, a kind of endothelial mitogen, is essential for endothelial cell proliferation and vascular permeability. Both RPE cells and endothelial cells produce VEGF. The most cutting-edge medications used to treat neovascular disorders nowadays are anti-VEGF pharmaceuticals like aflibercept and ranibizumab.

Topical Drug Delivery. Injections of anti-VEGF medications intravitreally (IVT) have replaced laser surgery as the standard of care for treating neovascular disorders, although they are both painful and invasive, may cause bleeding and retinal detachment, and can lead to cataracts and intraocular infections. However, topical medicine has only a 5% bioavailability when placed to the back of the eye, making it challenging to transport drugs to this location. Ocular drug delivery devices in the nanoscale range enable targeted drug administration, protect the medication from external degradation, and boost bioavailability in the eye. Aptinibc (Apa)-loaded hyaluronic acid (HA) NPs were developed for topical application for the treatment of diabetic retinopathy. Apa, a novel, specific inhibitor of vascular endothelial growth factor (VEGF) receptor 2, has been shown to have anticancer effects via its ability to inhibit VEGF signaling. Retinal cell surface differentiation (CD44) receptor clusters may interact with HA [50], a biodegradable, nonimmunogenic biopolymer. Direct delivery to the retina and RPE cells, where medication efficacy may be highest, is a common use of this technique. Their research suggests that HA-BSA-NPs may be a safe and effective alternative to invasive vitreous cavity treatment, since they may be administered locally with few side effects and excellent patient compliance, all while targeting the back of the eye. Another study found that the decline in retinal function, as evaluated by electroretinograms (ERGs), in rats was attenuated by NPs containing disulfiram. Many NPs, Drugs may be delivered topically to the retina via a variety of different methods, including poly(lactic-co-glycolic acid) and peptide (PENE) NPs. Some NPs may be able to address problems in both the front and back of the eye.

Subconjunctival Drug Delivery. Subconjunctival (SC) injections use a delivery mechanism that has been shown to increase bioavailability in the retina. This delivery approach may also be used to target posterior ocular structures. For prolonged and effective distribution to the back of the eye, researchers created and optimized chitosan (CS)-coated PLGA NPs containing bevacizumab. It was shown that the optimized CS-coated NPs could maintain their controlled drug release profile in vitro for more than 72 hours. The researchers also discovered that intravitreal (IVT) and topical (OT) administration of CS-PLGA NPs in the retinopathy model did not lower VEGF levels as effectively as SC injection [60]. Tsai et al. examined the effectiveness of injecting hyaluronic acid-coated NPs into the back of the eye by topical application vs SC injection. Topical administration (eye drops) was shown to be less effective than SC injections for delivering NPs to the posterior ocular area (choroid/retina), In order to prevent retinal cell death and alleviate alterations to the retina's microstructure, researchers researching DR developed NPs to convey insulin to the retina through SC injection, which is more effective than topical treatments.

Intravitreal Injections. The use of polymeric NPs for drug delivery has the potential to lessen medication cytotoxicity and expedite the introduction of additional medicines for clinical use. Leukemia, breast, and ovarian malignancies have all been treated with the HIF-1a inhibitor adriamycin (DOX) in the past. Iwase et al discovered that choroidal neovascularization was enhanced in mice when DOX was injected intravitreally. Nevertheless, nonspecific cytotoxicity has been shown to make DOX therapy dangerous. Researchers found that polymeric NPs encapsulating DOX might both lessen its cytotoxicity and release the medication steadily over time. The findings suggest that nanoparticles (NPs) manufactured using nanoprecipitation (NPC) may be the most efficient NP agents for DOX nano-delivery. Drug release regulation, or prolonged half-life, fewer doses, and less hazards are all possible with NP-associated sustained-release anti-VEGF delivery methods. While itraconazole (ITZ) was first developed as an antifungal medicine, it has now been shown to be a potent antiangiogenic agent. In order to provide additional treatment options for neovascular AMD, Scientists developed PLGA NPs conjugated to R5K peptide and loaded with ITZ. These R5KITZ-NPs are ITZ-controlled

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release nanoparticles with antiangiogenic properties.

It has also been reported that restoring retinal thickness and decreasing neovascularization in DR mice using PLGA NPs loaded with IL12, a chemokine with potent antiangiogenic properties. To cure retinal ischemia, researchers loaded Cx43 mimetic peptide onto HA NPs. This peptide is a sequence of a gap junction protein found in the retina. Retinal ganglion cell degeneration is slowed or prevented, and vision is restored after RVO treatment, thanks in large part to the efficacy of polydopamine (PDA) NPs in neutralizing reactive oxygen species (ROS).

Cerium oxide, gold, and silica NPs have all been shown to prevent neovascularization and increase disease improvement after being injected intravenously (IVT). It is hypothesized that cerium oxide NPs may restrict VEGF and ROS production by acting as a surrogate for superoxide dismutase (ROS). Lipofuscin deposits in the retina caused by AMD may also be reduced by targeted therapy with cerium oxide NPs. Retinal inflammation is reduced and VEGF-2 expression is downregulated in response to Au NPs through transrepression of nuclear factor kappa B (NF-B). It has been found that CNV may be blocked even when Au NPs are injected intravenously. Inhibition of VEGF-induced neovascularization by silica NPs has also been shown.

Gene Therapy

Retinal neovascularization illnesses may potentially be treated with the use of gene therapy and nanotechnology. Small interfering RNAs (siRNAs) are a family of tiny RNA molecules that have been proven to "silencing" certain mRNAs dependent on their sequence. Naked RNAs, however, may be easily broken down by nucleases. In order to limit retinal neovascularization and reduce VEGF mRNA and protein expression, Wang et al. encapsulated VEGF siRNA in lipid-like NPs, which the body may potentially break down. MicroRNAs (miRNAs) are a kind of small non-coding RNA that occur naturally in the body. MiRNAs have a crucial role in controlling cell proliferation, death, and differentiation, and are responsible for the regulation of more than 60% of human proteins. By reducing levels of vascular endothelial growth factor (VEGF), the powerful antiangiogenic factor miR200-b suppresses angiogenesis. Three months after intravitreal (IVT) injection, Mitra et al. discovered that in type 1 diabetes, miR200-b dosage had a negative effect on VEGFR-2 expression. In addition, They found that the retina was protected against neovascularization when VEGFR-2 expression was downregulated through NP-mediated mir200-b injection. As a result, VEGF-mediated neovascularization may have a new gene treatment option thanks to advances in nanotechnology (Figure 1).

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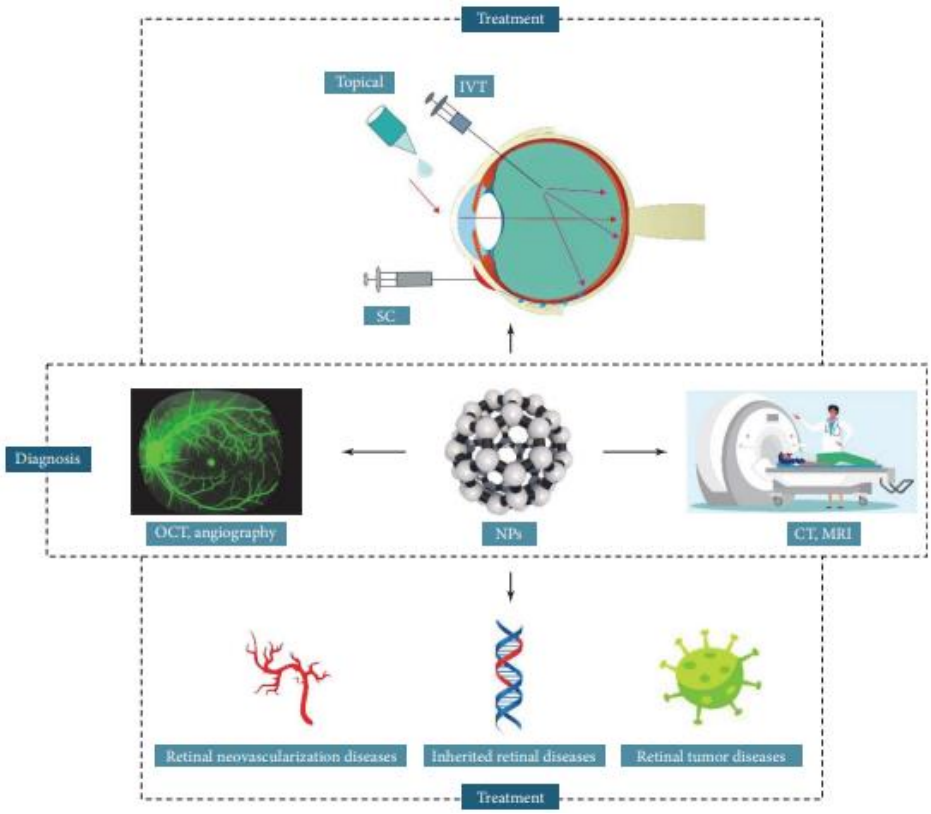

FIGURE 1: Schematic diagram of NPs for diagnosis and treatment of retinal diseases.

Optical coherence tomography (OCT), angiography, computed tomography (CT), and magnetic resonance imaging (MRI) are the major imaging modalities used by NPs in the diagnosis of retinal disorders. NPs are often administered topically, subconjunctivally (SC), or intravitreally (IVT) to treat retinal disorders. Different drug-delivery systems and their respective drug-delivery pathways are shown in the picture.

New Technologies Derived from NPs Development

Retinal degeneration and irreparable damage may now potentially be treated thanks to the creation and improvement of artificial retina. Nanomaterials, because to their unique biological properties, are being progressively included into the many structures and linkages involved in the conversion of retinal light signals in the pursuit of creating a more sensitive, durable, and stable artificial retina. In the synthetic retina, NPs may serve as artificial photoreceptors. Recent studies have shown that bacteriorhodopsin's (bR) photoconversion capabilities and remarkable chemical/thermal stability make it a promising candidate for application in the development of a wide range of optoelectronic devices, including artificial retinas. Accelerating the bR photocycle to create stable photocurrents, Npconversion NPs (UCNPs) mostly made of lanthanides may combine with bR to form photoreceptors. It is also being looked at whether or not Au NPs have a role in the make-up of synthetic photoreceptors.

When drugs are injected into the vitreous cavity, they encounter significant resistance at the inner limiting membrane (ILM) on their way to the retina. Clerck et al. aimed to increase drug uptake by the retina by puncturing the ILM with NPs laden with ICG. High-intensity laser pulses were directed at the bovine retina after ICG NPs were injected; this produced vapor nanobubbles (VNBs), the collapse of which may cause mechanical disruption of the inner nuclear layer (ILM). This method led to improved delivery of model NPs in the retina with a size of 120 nm, and it has the potential to increase NP effectiveness in the retina by a factor of 5. Vitreous opacity may also be safely dissolved in vivo by

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VNBs when induced by laser.

TABLE 1: Some NPs for the treatment of retinal diseases

Disease classification	Treatment mode/disease name	NPs
Retinal neovascularization diseases	Topical drug delivery	HA-BSA-NPs
		PLGA-NPs
		PENE-NPs
	Subconjunctival drug delivery (SC)	CS-PLGA-NPs
		HA-EGCG-NPs
		PLGA-PEG-NPs
	Intravitreal injections (IVT)	DXR-PSA-PEG-NPs
		NPC-NPs
		R5K-ITZ-NPs
		PLGA-NPs
		HA-Cx43 MP-NPs
		PDA-NPs
		Cerium oxide NPs
		Au NPs
		Silica NPs
	Gene therapy	VEGF-siRNA-NPs
		miRNA-NPs
Inherited retinal diseases (IRDs)	Retinitis pigmentosa (RP)	PEGPOD-DNA-NPs
		GCS-DNA-NPs
		DNA-Au NPs
		PEG-PLGA-PLL-siRNA-NPs
	Leber congenital amaurosis (LCA)	S/Mar DNA-NPs
		Mrna-NPs
	Stargardt disease	ABCA4 DNA-NPs
		ECO/pRHO-ABCA4-NPs
	Best vitelliform macular dystrophy (BVMD)	Cur-PLGA-NPs
Retinal tumor diseases	Retinoblastoma (Rb)	TPH-TCs-NPs
		CMD-TCs-NPs
		PDLLA-NPs
		ICG-NPs
Endophthalmitis		PLA-CHI NPs
		PS-Ag-NPs

Dose Response and Efficacy of RGD.Flt23k.NP on the Regression of Laser-Induced CNV in Mice

To evaluate the impact of Flt23k.NP on the resolution of laser-induced CNV in mice, we used fluorescein angiography (FA) to detect CNV leakage and optical coherence tomography (OCT) to determine lesion volume. According to FA results, pFlt23k loaded in RGD at dosages between 0 and 3 mg. At every time point examined, Flt23k.NP did not prevent CNV leaking. Nevertheless, between 1- and 3-weeks post-treatment, dosages of 10 to 60 mg faintly prevented CNV leakage, and CNV lesions were dramatically decreased. CNV volume did not decrease with dosages of pFlt23k loaded in RGD ranging from 0 to 3 mg, as measured by OCT. Flt23k.NP, however it went into remission when given pFlt23k loaded with RGD at a dosage of 10-60 mg. Flt23k.NP. RGD's effectiveness and dose-response curves. About 30 mg pFlt23k loaded in RGD, the Flt23k.NP began to level off. Two weeks after therapy, the amount of CNVs in Flt23k.NP had decreased by 30%. CNV volume regression was not different between 30 and 60 mg pFlt23k loaded in RGD, according to an analysis of variance. Two weeks after therapy, Flt23k.NP (Figure 2B).

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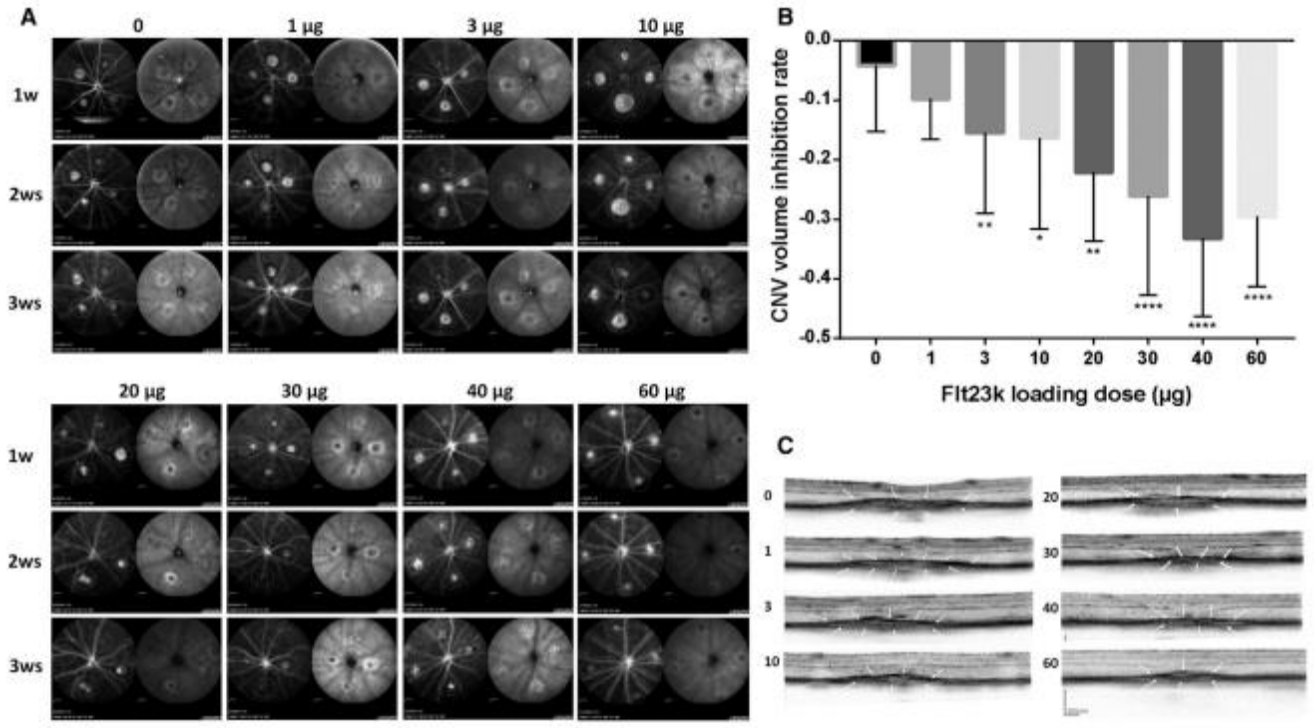

Figure 2: RGD Functionalized Nanoparticles Reached the Highest Effective Dose above 30 mg RGD.Flt23k.NPs

No Systemic or Hemolysis Was Detected after RGD.Flt23k.NP

The purpose of this study is to evaluate the safety of Flt23k nanoparticles prior to submitting an Investigational New Drug application to the FDA, mice were given single and repeated intravenous injections of 30 mg pFlt23k. The body and organ weights of the single-dose-treated mice and the control group were not significantly different before and after treatment. Mice in all groups developed normally after one month of therapy, as shown by a significant rise in body weight. At no point were there statistically significant differences in weight gain or loss between the control and treatment groups during the repeat-dosing phase. At 2 months post-treatment, the body weights of repeat-dose-treated mice followed the predicted growth curve identical to those of normal control mice.

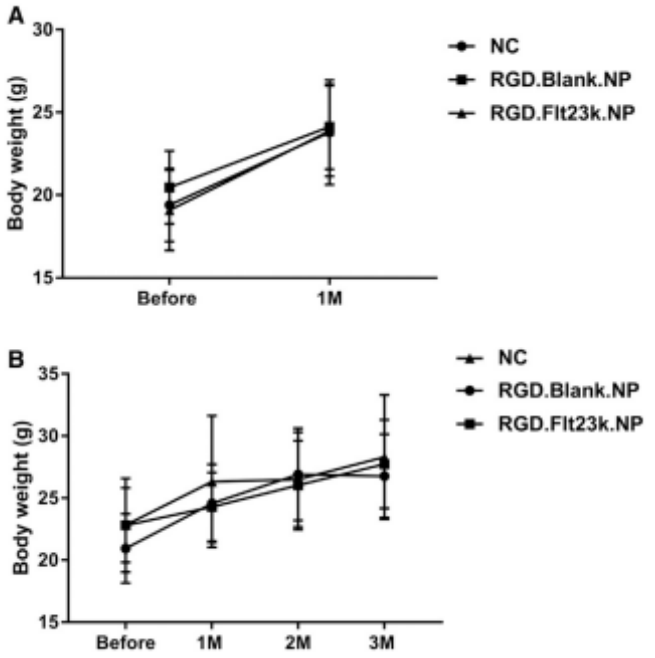

Figure 3: No Systemic Toxicity Was Detected after Treatment with RGD Functionalized Nanoparticles

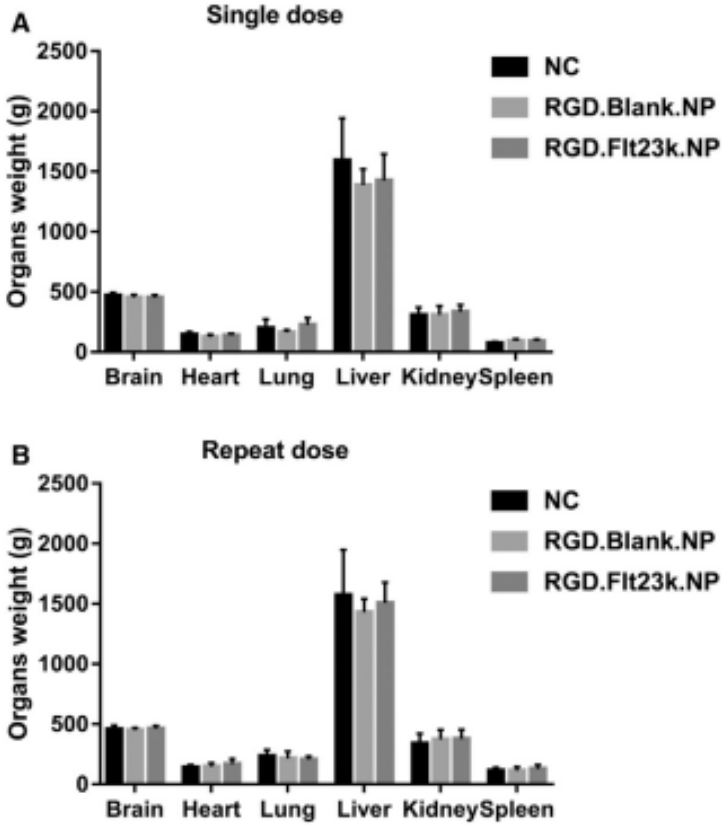

Figure 4: No Systemic Toxicity Was Detected with RGD Functionalized Nanoparticles

DISCUSSION

Safety and efficacy of intravenous administration of Flt23k intraceptor gene therapy were evaluated.

This technique makes use of PLGA nanoparticles to block VEGF signaling. With increased Flt23k concentrations, we found that CNV regression was more dramatic and leakage was decreased. RGD.Flt23k.NP showed no systemic or ocular harm in either the single-dose (30 mg Flt23k) or repeat-dose (30 mg Flt23k for 3 months) groups. Similar to the results shown with the control nanoparticles, After receiving the experimental treatment through intravenous injection, there were no changes in hematological and inflammatory markers or impairments in visual function.

Our findings indicate that RGD.Flt23k.NP significantly reduces CNV volume at 2 weeks post-treatment, but not at 1 week. Another explanation for delayed CNV regression is sluggish Flt23k nanoparticle release at the CNV lesion. Our previous study also found that Flt23k.NP stayed put at the site of the CNV lesion for around 2 weeks following treatment, thus these results are in line with our expectations. In addition, we showed that larger dosages of Flt23k were able to more effectively prevent CNV leaking and promote CNV regression. A 22% decrease in CNV volume at a dose of 10 mg Flt23k demonstrates the constancy of the RGD.Flt23k.NP delivery system across experiments. At 30 mg pFlt23k-loaded RGD, CNV lesions shrank the most. CNV volume in Flt23k.NP decreased by 30%. (Figure 2). RGD loaded with pFlt23k at doses greater than 30 mg. This metric was not noticeably better with Flt23k.NP. We postulate that the optimal dose of RGD-loaded pFlt23k is 30 mg. Flt23k.NP is equivalent to an RGD binding capacity that is maximal in terms of pharmacokinetics. Receptors on the body's own Flt23k.NP. The goal is to evaluate RGD's safety. We evaluated 30 mg of pFlt23k loaded in RGD as the maximal effective dosage of Flt23k.NP. Flt23k.NP given once or twice to a mouse. Analysis of plasma complement C3 levels and microscopic examination of key organs revealed no evidence of regional or generalized inflammation. These findings point to RGD's potential as a therapy for neovascular AMD. Flt23k.NP. Newer treatments for neovascular AMD are being tested in ongoing clinical studies. clinical experiments using viral vectors to deliver soluble Flt-1 (sFLT1) for the treatment of CNV lesions have shown encouraging results in lowering CNV lesion size. Nevertheless, a more severe inflammatory reaction was seen compared to conventional anti-VEGF therapy, which may have resulted from the body's immunological response to the viral particles. In this work, we showed that doses of RGD up to 60 mg/kg were non-toxic in a mouse model. Flt23k.NP.

Current anti-VEGF treatments and the AAV2-sFLT01 therapy in clinical trials both involve injecting medications into the eye's posterior region, but in different ways: intravitreally and subretinally, respectively. Patients' vision may be jeopardized if they need many injections of these medications intraocularly due to consequences such endophthalmitis, fibrosis, and retinal detachment. Nevertheless, RGD.Flt23k.NP intravenous administration did not reveal any of these side effects. Due to the systemic administration of RGD.Flt23k.NP, we analyzed its toxicity in the liver, brain, kidney, lungs, and adrenal glands, where the nanoparticles were found to be at their maximum concentration after intravenous administration. No systemic, ocular, or hematological harm was found after systemic distribution of Our careful evaluation of the safety profile in eyes and blood led us to conclude that the nanoparticle delivery technique for the Flt23k plasmid was safe to use.

CONCLUSION

In conclusion, NPs have the potential to expand our diagnostic and therapeutic options, modify standard drug delivery methods, prolong the duration of medication action, improve drug absorption in the retina, reduce drug cytotoxicity, and facilitate gene therapy. Research on NPs is illuminating new paths for the diagnosis and therapy of several retinal disorders. Unfortunately, most NP research is still in the experimental phase, and even fewer make it into the clinic, so there are still many problems to be overcome. Retinal diseases are the only ones for which certain nanoparticles are appropriate due to their dose-dependent cytotoxicity or size-dependent cytotoxicity. Certain nanoparticles may be poisonous and cause damage to the retina, thus it's crucial to be aware of the risks associated with NPs. In conclusion, NPs show promising potential in the retina, and further study is needed to fully realize this potential.

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