Chitosan-coated contact lens-based ophthalmic drug delivery system to manage Acanthamoeba keratitis: A preliminary hypothesis

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ABSTRACT

Background: *Acanthamoeba* species can cause devastating contact lens (CL)-related microbial keratitis. Its culture is less sensitive, and little evidence is available for the safety or efficacy profile of medications. Therefore, early diagnosis and optimal treatment remain difficult. The aim of this study was to present the hypothesis that a novel chitosan-coated CL-based ophthalmic drug delivery system has therapeutic and prophylactic effects on acanthamoeba keratitis.

Hypothesis: CL-based drug delivery is a popular sustained-release drug delivery that extends the drug release time, thus increasing its bioavailability and treatment efficacy. Chitosan, a derivative of chitin, has antioxidant and broad-spectrum antimicrobial properties against fungi, yeasts, and bacteria. It acts against microbial cells; however, whether its mechanism of action is microbiostatic or microbicidal remains unknown. It exhibits wound healing and film-forming properties. Chitosan composite films permit high transmittance of visible light, making it transparent and therefore desirable for the development of CLs. Chitosan/Ag/ZnO blend films exhibit antimicrobial activities. Further, soft CLs coated with chitosan, sodium hyaluronate, polylysine hydrobromide, and sodium alginate show drug delivery properties and reduced bacterial growth. Recently, concentration-dependent anti-amoebic activities of chitosan and nano-chitosan against the trophozoite and cystic forms of *Acanthamoeba* have been reported. Based on the existing evidence, we hypothesized that a chitosan-coated CL-based ophthalmic drug delivery system could have therapeutic and prophylactic effects on acanthamoeba keratitis or subsequent endophthalmitis.

Conclusions: CLs or intraocular implants with chitosan-based nanocoatings alone or in combination with routine treatment may be preventive or therapeutic for acanthamoeba keratitis or endophthalmitis. Experimental studies and further clinical trials are required to explore the efficacy and safety profile. Moreover, randomized controlled trials in healthy eyes with soft or hard CLs or orthokeratology lenses for refractive error correction may shed light on the prophylactic effect of this novel drug delivery system. Other forms of ophthalmic drug delivery systems using chitosan-based nanocoatings should be studied additionally.

KEY WORDS

microbial keratitis, acanthamoeba, chitosan, chitin, antimicrobial, bacteria, yeast, fungi, contact lens

INTRODUCTION

Keratitis is a sight-threatening contact lens (CL) complication. Its incidence rate depends on the lens type and wearing time and is higher with extended-wear soft CLs than with daily-wear rigid CLs. *Acanthamoeba* species is a dangerous offending microorganism causing keratitis [1]. Orthokeratology refers to the use of reverse geometry rigid gas-permeable CLs when sleeping to change the corneal shape and thereby reduce the refractive power. It is associated with infectious keratitis, particularly in young wearers, with a female preponderance [2].

Pseudomonas aeruginosa and *Acanthamoeba* are common ocular offending microorganisms isolated in overnight orthokeratology. Despite early intervention and treatment, most eyes develop corneal scars, and approximately 10% of the eyes require surgical intervention [2]. Furthermore, diagnostic culture is less sensitive for *Acanthamoeba* and positive in only 33% of cases [3]. Moreover, evidence is limited for the relative effectiveness and safety of topical biguanides, including chlorhexidine 0.02% and polyhexamethylene biguanide 0.02%. Therefore, early diagnosis and optimal treatment of acanthamoeba keratitis remain difficult [4].

Drug delivery systems include emulsions, ointments, suspensions, aqueous gels, nanomicelles, nanosuspensions, nanoparticles, dendrimers, liposomes, implants, CLs, microneedles, and in situ thermosensitive gels [5]. Among the various routes of drug administration, such as systemic administration, topical application, intravitreal injection, subconjunctival injection, and intraocular implants [6, 7], topical application is prominent. CLs are a popular sustained-release drug carrier offering increased drug bioavailability and treatment efficacy owing to the extended drug release time. Drug-loaded CLs have been employed to treat various ocular diseases by releasing anti-inflammatory, immunosuppressive, or ocular pressure-lowering agents. Manufacturing techniques for drug-loaded CLs include soaking, molecular imprinting, and colloidal nanoparticle and supercritical fluid technologies [8].

Soft CLs are preferable as an effective ophthalmic drug delivery system. Various polymers, whether drug-containing polymer nanoparticles or polymeric implants, are used as carriers for therapeutic CLs. Polymers used as therapeutic carriers include propoxylated glyceryl triacrylate, polycaprolactone, chitosan, polylactic glycolic acid, poly (D, L-lactide) dextran, poly (2-hydroxyethyl methacrylate), ethylcellulose, and fibrin. Each polymer has specific characteristics. Drug-loaded CLs offer advantages of enhanced bioavailability, solubility, penetration, and retention of ophthalmic drugs. Novel drug–polymer film-embedded CLs increase drug retention time. The coating polymer used to bind drugs to 2-hydroxyethyl methacrylate (a monomer used in soft CLs) is poly (lactic-co-glycolic acid)/polyvinyl alcohol with chitosan or ethyl cellulose with Eudragit S-100® [9]. Likewise, chitosan-based coatings are applied to medical implants because of their properties of biocompatibility and antibacterial activity [10].

HYPOTHESIS

Chitin is a ubiquitous natural nitrogenous polysaccharide found in the exoskeleton and endogenous regions of invertebrates and fungal mycelia. Chitosan is a derivative of chitin that is produced by incomplete N-deacetylation of chitin [11, 12]. Manipulating solution conditions, such as temperature, pH, ion strength, concentration, and solvent, controls the physicochemical properties of chitosan solutions [13]. Chitin fibers have unique features, including biocompatibility, non-toxicity, biodegradability, and low immunogenicity. Combined with good mechanical properties, chitin fibers are candidate materials for manufacturing sutures for use in the human body [14].

Chitosan exhibits antioxidant and broad-spectrum antimicrobial properties against bacteria, yeasts, and fungi by inhibiting microbial cells via two main mechanisms. First, owing to its polycationic nature, it interacts with anionic groups on the cell surface of microbes, forms an impermeable layer around the cell, and prevents the transportation of essential solutes. Chitosan with a higher positive charge binds to the bacterial cell walls more strongly. Second, it inhibits RNA and protein synthesis by permeating the cell nucleus, depending upon the molecular weight. Additionally, it can act as a chelating agent, rendering metals, trace elements, and essential nutrients inaccessible for microorganisms, thereby inhibiting microbial growth. Other mechanisms have been proposed; however, whether the mechanism of action is microbiostatic or microbicidal remains unknown [15].

Chitosan/Ag/ZnO blend films have a higher antimicrobial activity than chitosan/Ag or chitosan/ZnO blend films, indicating that Ag and ZnO nanoparticles enhance the antimicrobial activities of chitosan [16]. Chitosan exhibits wound healing and film-forming properties. Chitosan films are transparent and exhibit mechanical stability, oxygen permeability, wettability, and immunological compatibility. These properties are desirable for the fabrication of CLs [11, 12]. Chitosan composite films with high transmittance of visible light show good compatibility between chitosan and gelatin. This implies that chitosan/gelatin composite films may be suitable for implementation in CLs [17].

Chitosan binds to the CL surface through polydopamine crosslinking. It is also used to culture rabbit limbal epithelial cells. Epithelial cells form multilayers on the modified biocompatible chitosan-coated CL. This may be an effective delivery method for human corneal tissue and useful in the management of severe ocular surface diseases [18]. Voriconazole loaded onto a hydrogel CL composed of quaternized chitosan, graphene oxide, and silver nanoparticles showed a rapid and strong therapeutic effect on fungal keratitis in an animal model [19]. Chitosan, sodium hyaluronate, polylysine hydrobromide, and sodium alginate were crosslinked using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride and coated layer by layer on a silicone-based soft CL. The drug delivery properties and coats of CL reduced bacterial growth [20]. ZnO nanoparticles, chitosan, and gallic acid are coated on CLs using the sonochemical method, which imparts improved surface properties and enhanced antibacterial activity against *Staphylococcus aureus* [21].

Based on the existing evidence, we hypothesized that a chitosan-coated CL-based ophthalmic drug delivery system could have therapeutic and prophylactic effects on CL-related acanthamoeba keratitis or subsequent endophthalmitis.

EVALUATION OF THE HYPOTHESIS

The effectiveness of the combined *Nigella sativa* aqueous extract and chitosan nanoparticles in experimentally induced acanthamoeba keratitis suggests the potential for the development of an effective and safe therapeutic alternative for this vision-threatening disease [22]. Recently, an in vitro study demonstrated the time- and concentration-dependent anti-amoebic activity of chitosan against the trophozoite and cystic forms of *Acanthamoeba* genotype T4, revealing a more potent activity of nano-chitosan [23]. Considering the reemergence of infectious trophozoites from dormant cysts, which is a treatment challenge in acanthamoeba
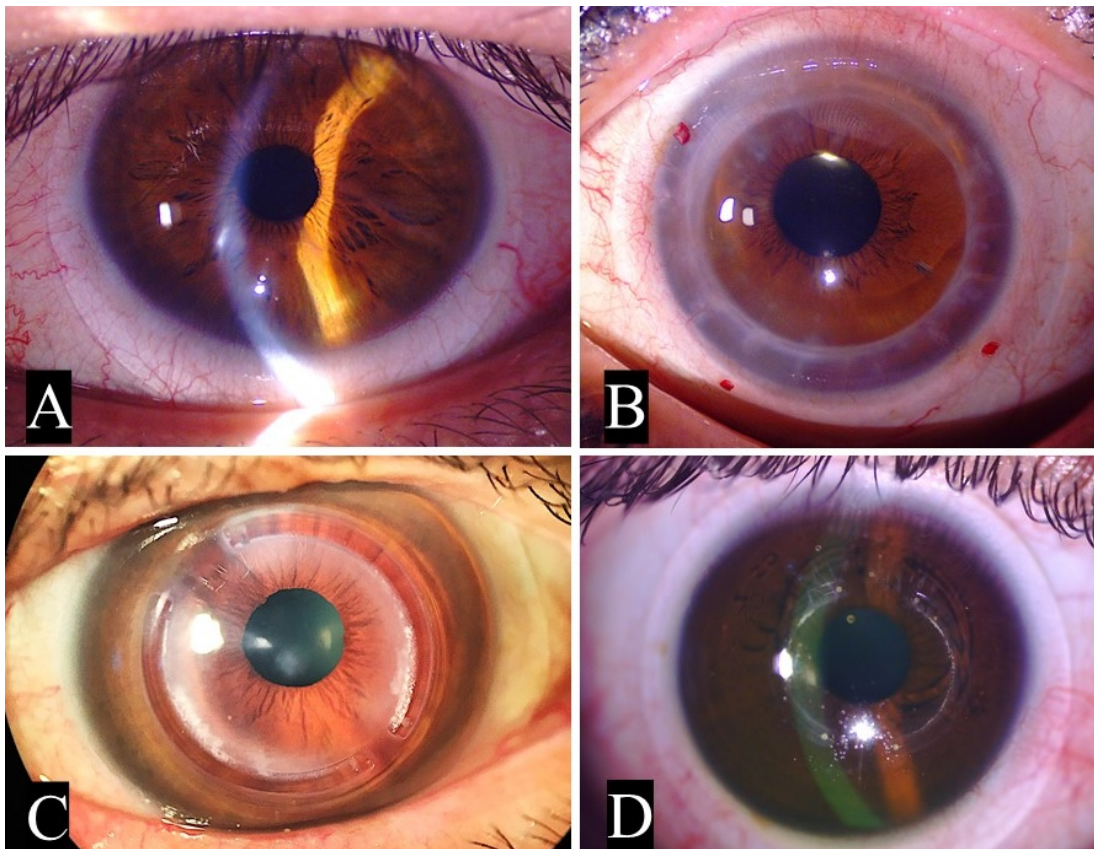
Figure 1. (A) Scleral contact lens in an eye with advanced keratoconus and central corneal scarring caused by previous gas-permeable contact lens use. (B) Toric scleral contact lens in an eye with high astigmatism after penetrating keratoplasty for keratoconus and high myopia. (C) Scleral contact lens in an eye with INTACS® intracorneal ring segment (ICRS) insertion for laser in situ keratomileusis-induced keratectasia. (D) Scleral contact lens in an eye with keratoconus for final visual rehabilitation after Kerarings® ICRS insertion for corneal remodeling. This figure has been reused with the permission of *Med Hypothesis Discov Innov Ophthalmol* [26].

keratitis [24], the effectiveness of chitosan and nano-chitosan against the trophozoite and cystic forms of *Acanthamoeba* is promising. Chitosan-based nanocoatings for CLs are under evaluation [25]; however, we hypothesized that chitosan-based CLs, independently or combined with routine medications, may be effective against *Acanthamoeba* species. The proposed CL may enhance the safety of orthokeratology in myopia control and visual rehabilitation by minimizing or eliminating the incidence of acanthamoeba keratitis, which is sight-threatening in CL wearers.

This hypothesis should be evaluated by in vitro studies although it is limited by difficulty in adopting the slow-release characteristics of the delivery system. Subsequently, the effectiveness of this on-demand novel nano-chitosan-coated CL or CL with chitosan-based nanocoating in combination with anti-*Acanthamoeba* medications should be tested in animal models. Randomized controlled trials in healthy eyes with CLs or orthokeratology lenses to reduce the refractive error could shed more light on the clinical impact of this novel CL as a prophylactic measure in acanthamoeba keratitis. To achieve a better clinical safety profile, further studies on patients with decompensated corneas fitted with CL for visual rehabilitation (Figure 1A–D) [26] are warranted. This hypothesis introduces a concept for minimizing or eliminating vision-threatening keratitis in CL wearers. We hope that it will stimulate further research on this topic.

CONCLUSIONS

We presented our hypothesis of adopting CLs or intraocular implants with chitosan-based nanocoating alone or in combination with usual medications against *Acanthamoeba*. Recently, an in vitro study revealed the concentration-dependent anti-amoebic activity of chitosan against the trophozoite and cystic forms of *Acanthamoeba* genotype T4, which is more potent in nano-chitosan. Considering the reemergence of infectious trophozoites from dormant cysts, the effectiveness of chitosan and nano-chitosan against the trophozoite and cystic forms of *Acanthamoeba* is promising for its therapeutic potential. The application of this hypothesis may be in the treatment or prophylaxis of CL-related acanthamoeba keratitis or subsequent endophthalmitis. However, the safety, tolerability, and efficacy of the chitosan-coated CL-based ophthalmologic drug delivery system should be evaluated.

ETHICAL DECLARATIONS

Ethical approval: Not required.
Conflict of interests: None

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