A Minimally Invasive Jet Injector for Intravitreal and Subconjunctival Injection

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BACKGROUND AND OBJECTIVE: To evaluate a minimally invasive injector for intravitreal and subconjunctival administration of medications.

MATERIALS AND METHODS: The device has a microneedle that communicates with an internal formulation chamber. A piercing depth-limiting flange restricts microneedle penetration to a depth of less than 1 mm and defines the location of the pars plana from the limbus. The jet injector creates a force of up to 1,000 psi, forcing the medication through the remaining sclera/choroid thickness. The device was tested in 28 enucleated rabbit eyes and 9 experimental and 4 control rabbit eyes to define jet pressure for subconjunctival and intravitreal injection.

RESULTS: Injection pressures of 76 to 156 psi were needed for subconjunctival injection and 974 psi for intravitreal injection. Clinical and histologic examinations did not reveal damage to intraocular structures.

CONCLUSION: The semi-automated jet injector facilitated intravitreal/subconjunctival injection. The microneedle-assisted jet injector minimized the risk of wet injection by anchoring the microneedle in the sclera.

INTRODUCTION

Delivery of pharmacological agents to a specific organ or tissue can be achieved through systemic or local administration. In systemic administration, circulating blood delivers the agent to the target tissue by either passive or active transport. However, the agent must be administered at relatively high doses to reach the target area in sufficient quantity, with potential toxicity and side effects. In contrast, local therapy generally can avoid the side effects of systemic medication. Intravitreal administration of an agent typically requires strict
adherence to numerous safeguards to avoid mechanical injury to the lens and retina and to avoid potential toxicity of a medication to these structures. However, significantly lower concentrations of a medication can be injected with increased effectiveness inside the eye than would be possible with the systemic route. Subconjunctival injection is a routine technique for short- or long-term delivery of medication to the anterior segment. Despite the simplicity of the technique, care must be taken to avoid conjunctival or scleral perforation with the needle, which may result in retinal injury and serious toxicity to the retina. In addition, reflux of medication through the needle penetration site can reduce efficacy of the medication.

To explore and eliminate toxic effects, most nontoxic doses of various agents injected intravitreally have been evaluated. Intravitreal injection is currently used routinely by retina specialists to treat vitreoretinal and choroidal diseases involving the retina.

The current standard technique employs conventional syringes and needles. Despite minimal complications after intravitreal injection, injury to the lens, retinal injury, and endophthalmitis can occur and injection is disconcerting to patients. Our aim was to evaluate an alternative method of injection using a minimally invasive device (microneedle) that avoids needle entry inside the eye. Although dermal jet injectors without microneedles are commercially available, wet injection is a side effect of such a system. This short-term, proof-of-concept study demonstrates use of a jet injector in intravitreal and subconjunctival injection.

MATERIALS AND METHODS

Instrumentation

We developed a prototype jet injector that has a nozzle with an internal formulation chamber adapted to receive and contain the pharmacological agent formulation. A commercially available jet injector (Dermo-jet Polymedical; Robbins Instruments, Chatham, NJ) was modified by replacing the nozzle with a custom-made 27-gauge needle (Vita Needle Company, Inc., Needham, MA). The needle is in communication with the internal drug reservoir and extends 0.1 mm from a piercing depth limiter circular flange (6-mm diameter) that limits penetration of the centrally located microneedle into the sclera to less than 0.1 mm (Fig. 1). The concave edge of the platform conforms to the surface of the sclera. By placing the edge of the flange at the limbus, its center and the microneedle define the location on the pars plana, thereby eliminating guesswork by the practitioner (Fig. 2).

Although various means of creating jet pressure are available, in this first prototype we used springs of different strength to create the desired force in the plunger for expelling the pharmacological formulation.
from the nozzle through the microneedle. The injection pressures produced were between 30 and 1,000 psi, as evaluated from spring constants and video estimation of the speed of injection. When a spring is assembled inside the body of the instrument—coupled to the medical reservoir and the microneedle—an intravitreal jet injection device is formed. By depressing an actuation button located on the injector body, the pharmacological formulation is either directionally expelled from the microneedle through the remaining sclera into the intravitreal compartment of the eye (Fig. 2) or into the subconjunctival space, depending on the pressure generated.

Experimental Studies
The study was initially done on 28 enucleated rabbit eyes obtained from a local abattoir. Subsequently, using data from the in vitro study, we performed a short-term 24-hour in vivo investigation on nine albino rabbits (nine experimental and four control eyes); rabbits weighed 4 to 5 pounds. All animals were treated according to guidelines established by the Association for Research in Vision and Ophthalmology Resolution on the Use of Animals in Research. The rabbits were anesthetized and killed using an isofluorane anesthesia chamber.

The device was filled with a blue dye solution (mix of FD&C Blue 1 and Red 40 in water, Escofoods.com), diluted 1:50 in sterile saline. For injection, the edge of the platform was applied at the limbus of an enucleated eye or anesthetized albino rabbit eye so that the microneedle was positioned at the pars plana. The microneedle was then pressed inside the sclera using gentle manual force. The eye was injected with 0.1 mL of dye solution using the microneedle jet injector. By choosing various springs, the jet injector produced a range of pressures from 30 to 1,000 psi to identify the most desired range of pressure for intraocular and subconjunctival injection. Four control eyes were also injected intravitreally with 0.1 mL of dye solution using a tuberculin syringe and a 27-gauge needle. Immediately following injection, the eyes were evaluated clinically by flashlight and ophthalmoscope for signs of penetration of dye in the anterior chamber and visible retinal injury. Thereafter, the animals were killed and the eyes were enucleated. All eyes from both experiments were fast frozen and then dissected to evaluate the quality of injection and potential damage to the lens or retinal

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structures. All eyes from the in vivo experiment were initially examined and then fixed in formaldehyde and submitted for histology examination (Excalibur Pathology, Inc., Moore, OK). The sections were stained with hematoxylin–eosin.

RESULTS

Tables 1 (in vitro) and 2 (in vivo) show pressure results needed to consistently achieve either an intravitreal or a subconjunctival injection. In this experiment, a pressure of approximately 974 psi was necessary to consistently achieve an intravitreal injection. Subconjunctival injection could be reproducibly achieved using a range of intermediate pressures of 74 to 156 psi. Results were comparable using enucleated eyes or in vivo. Low injection pressure (< 29 psi) yielded inconsistent results with a large number of wet injections where medication spread outside and under the conjunctiva.

No macroscopic or microscopic damage to structures of the eye were noted after either subconjunctival or intravitreal injections (Figs. 3 and 4).

DISCUSSION

This was a preliminary experiment to evaluate the potential application of a jet injector for subconjunctival and intravitreal injections. We developed a microneedle jet injector to improve safety with reduced pressure, as compared to needleless injectors, and to minimize wet injection, which is observed frequently with dermal jet injectors that are not equipped with a microneedle and a positioning platform.

In this experiment, a microneedle jet injector combined with a positioning platform showed potential as an alternative technique to the standard syringe or needle for automated intravitreal or subconjunctival injection. Placement of the edge of the platform at the corneoscleral limbus allowed precise positioning and application of the microneedle on the pars plana.

Figure 3. Representative cross-sections of frozen rabbit eyes following in vivo intravitreal (A and B) and subconjunctival (C and D) injection of blue dye. (A) Microneedle-assisted jet injection (974 psi). Inset shows bluish injection area. (B) Control intravitreal injection using a 27-gauge needle and syringe. (C) Microneedle-assisted jet injection (156 psi). (D) Control subconjunctival injection using a 27-gauge needle and syringe.
area. In general, a microneedle that penetrates partly through the sclera allows the use of lower pressures for minimally invasive intravitreal jet injection compared to conventional jet injection without the microneedle. Using appropriate jet pressure of approximately 74 to 156 psi, subconjunctival injection could be performed with ease at any desired location. However, higher jet pressure of approximately 974 psi was needed for intravitreal injection in this experiment. The amount of the pressure required for intravitreal injection is influenced by the thickness of the sclera and the diameter and the length of the microneedle. Change in any of these parameters would require investigation to determine required pressure.

Despite these unknowns, we found that under specific conditions the microneedle-assisted jet injector showed promise for simplifying both intravitreal and, more significantly, subconjunctival injection. Because scleral thickness is not a factor for subconjunctival injection, the remaining parameters (length and diameter of the microneedle) can be easily evaluated with experiments in animals. Shortcomings of the current prototype are bulkiness of the instrument, size of the microneedle, and the need for sterilization. Therefore, it cannot be used in its present form in humans. Disposable instruments are now commonly used in ophthalmology to avoid potential infection. A disposable prototype of this system can be created for certain frequently used medications that guarantees proper dosing and sterilization.

Our objective was to evaluate an alternative method to the standard syringe or needle for intravitreal/ subconjunctival injection using a jet injector system that provides semi-automated injection of therapeutic agents. Use of a conventional needleless jet injector is technically challenging. If the needleless jet injector is not positioned perpendicular to the tissue interface or if poor contact is established between the nozzle and the tissue at the time of injection, a “wet” injection may occur. A wet injection is characterized by loss of a significant fraction of medication outside the surface of the tissue. A long needle penetrating the eye wall cannot be used with a jet injector because its position inside the eye would require more finely controlled pressure, and could damage the retina. Along with a positioning flange, a microneedle that partially penetrates the sclera acts as a guide for the jet stream, creates an effective seal, and excludes air and fluids present at the surface of the conjunctiva. This could potentially minimize the risk for aspiration of contaminated fluid from the surface of the eye. We believe that avoiding needle penetration through the wall of the eye should increase the safety margin with respect to accidental and abrupt eye and/or device movement. This configuration might also alleviate patient fear about having a needle inside his or her eye.

With the development of new pharmacological treatments for retinal diseases, vitreoretinal specialists are faced with the responsibility of providing an ever-in-
creasing number of intravitreal injections of pharmacological agents with attendant potential complications. A method and device to standardize and simplify the intravitreal/subconjunctival injection process would improve patient comfort and safety and increase the efficiency of the process. Each injection requires several steps to prepare the eye and safely perform the injection. The process of injection can become time-consuming in a busy practice and may result in unexpected prolongation of patient waiting times.

The microneedle-assisted, semi-automated jet injector has the potential of facilitating an intravitreal/subconjunctival injection. It also minimizes the risk of wet injection as a result of anchoring the transfer mechanism microneedle beyond the conjunctiva, inside the sclera.

REFERENCES