Microneedle Delivery of Propranolol and Timolol to Treat Infantile Hemangiomas

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INTRODUCTION

Infantile hemangiomas are one of the most common benign vascular tumors in pediatric patients. These tumors are often self-limiting over several years, but they can be a concern both cosmetically and functionally for the parents and child. A small percentage of hemangiomas require treatment due to possible obstruction of airways or eyes, and cosmetic scarring or disfiguring of the child’s face, hands, or other critical areas. Current treatment options include oral corticosteroids and propranolol or topical treatment with timolol eye drops or compounded propranolol ointment. 

The use of oral beta-blockers such as propranolol are associated with many systemic side-effects that include hypotension, bradycardia, hypoglycemia, and bronchospasm. Such side-effects are dangerous in children (especially infants) who cannot describe to their caregivers the signs/symptoms that they are experiencing. Studies have shown that topical timolol and propranolol are good alternatives compared to oral therapies when treating smaller, superficial infantile hemangiomas. However, while these topical formulations can aid in superficial lesions, they cannot improve deeper subcutaneous hemangiomas and the formulations have not been specifically optimized for skin delivery. This is where microneedle (MN) technology can help. Microneedles are micron-scale projections that can deliver the drug into the skin and still avoid dangerous systemic effects.

HYPOTHESIS

Microneedle delivery of propranolol and timolol will increase the skin’s concentration of the drug in vitro compared to topical propranolol and timolol eye drops.

METHODS

Polyvinyl alcohol/polyvinyl pyrrolidone (PVA/PVP) Microneedles

PVA/PVP are a propranolol and timolol loaded dissolvable microneedles were formulated for evaluation of drug delivery into excised skin. 25% w/v propranolol and timolol were loaded into the PVA/PVP microneedles. Polyvinyl alcohol is water-soluble and biodegradable, and is subject to swelling upon contact with moisture. This is desirable because it serves to open a diffusion channel for the medication to partition from the microneedles to the skin. PVP and Polyethylene Glycol-400 (PEG-400) Microneedles

2.34% w/v propranolol and 1.58% v/v timolol were loaded into these microneedles. PVP is also water-soluble and biodegradable. Polyvinylpyrrolidone is known to assemble into branched hollow fibers in aqueous solutions, and this aids in creating a strong and sharp microneedle.

Microneedle Formulation Procedure

The polymer solution and medications were formulated into a microneedle patch with 350 micron length, 100 micron needle mold by centrifugation and drying. Microneedle formulations were tested for efficacy through diffusion studies with standard thickness excised pig skin.

Transdermal Water Loss Tool (TEWL)

Used to test microneedle permeation into the skin

The microneedles permeation into the skin was tested through transdermal water loss tests (TEWL) to evaluate if they are breaking through the stratum corneum layer to deliver drug. The experimental microneedles were compared to controls, which are known to break the skin, and to intact skin treated with current topical propranolol and timolol formulations used to treat infantile hemangiomas.

RESULTS

PVA/PVP Microneedles

The diffusion study with 25% v/v drug in PVA/PVP matrix was not successful in delivering drug into the skin. The drug in skin levels and receiver solution concentrations were below the limit of quantification.

TEWL

The TEWL test showed that the PVA/PVP microneedle matrix did not penetrate the skin. The p-value comparing the water loss of intact skin to PVA/PVP microneedle treated skin was 0.0849, which is non-significant. However, the PVP only formulation microneedles all showed a significant increase in water loss compared to intact skin. This suggests that PVP formulated microneedles have desirable properties to penetrate the skin. The PVP MN resulted in a sharper, although more brittle, dissolvable microneedle. The PVP treated skin resulted in a water loss similar to the 250µm dermaroller treated skin. This shows that this formulation can break through the epidermis. However, the lower concentrations of PVP without PVA MNs were very brittle and prone to breaking upon insertion. The 250µm and 500µm dermarollers all resulted in a significant increase in water loss.

CONCLUSIONS/FUTURE DIRECTIONS

- PVP MNs were successful at delivering propranolol and timolol into the skin while minimizing receiver solution concentrations.
- Formulations developed and performed in this experiment suggest microneedles can aid in topical drug delivery as the pores penetrating the dermis creates a route for delivery.
- MNs are useful for hydrophilic formulations/drugs such as timolol which would otherwise have difficulty penetrating through the epidermis.
- Future studies are needed to optimize the dissolvable microneedle formulations to fabricate a strong and sharp microneedle capable of penetrating the epidermis and providing therapeutic slow and sustained drug release.

REFERENCES

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Image 1: Microneedles

Image 2: Image of a microneedle

Image 3: Image of a microneedle