Local delivery of phenylephrine using hollow microneedles as a treatment of fecal incontinence

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ABSTRACT SUMMARY

A hollow microneedle was used to deliver a phenylephrine (PE) solution into the sphincter muscle locally with minimal pain. PE was administered at two spots, on the left and the right of the anus of a rat, through perianal skin. Increasing the dose of PE using the new method increased resting anal pressure but it did not increase blood pressure. The local delivery of PE using a hollow microneedle system demonstrated a promising method for the treatment of fecal incontinence with few side effects.

INTRODUCTION

Fecal incontinence is described as the loss of regular control of hard feces, loose feces, and gases of the bowels in an individual. Our previous study demonstrated that the delivery of phenylephrine (PE) to perianal muscles using solid microneedles increases resting anal sphincter pressure [1].

The solid microneedles used in the previous study have the advantage of increasing skin permeability. However, the uses of solid microneedles has limited clinical application for several reasons: inconsistent delivery of PE because the holes close up quickly, clearance of the drug on treated skin, long application time required to deliver a therapeutic dose, and possible infection because of the number of holes generated by the solid microneedle array [2]. To overcome these limitations of treatment using solid microneedles, a hollow microneedle system was utilized. In this study, resting anal pressure was investigated after locally injecting PE using hollow microneedles into the anal sphincter muscle. The side effect of this new method was also studied and compared with other administration methods by measuring blood pressure.

EXPERIMENTAL METHODS

A hollow microneedle 1 mm in length and with an inner diameter of 150 μm (Figure 1(a)) was inserted at two spots (left and right) on either side of the anus of a rat as shown in Figure 1(b), and 50μl of PE solution with various concentrations was injected at a constant rate using a syringe pump.

Figure 1. (a) Optical image of a hollow microneedle. (b) Image showing two injection sites on the left and right side of a rat’s anus.

Changes in resting anal pressure were investigated as a function of PE dose by using an Urodynamic system with a T-DOC catheter after injection with hollow microneedles. The therapeutic efficacy of hollow microneedles was compared with that of subcutaneous (SC) and intramuscular (IM) injection methods at same dose of 50μg. To study the side effects of microneedle administration of PE, blood pressure was measured in relation to the dose of PE administered by using a non-invasive blood pressure measurement system. These findings
were compared with blood pressure resulting from conventional administration methods (SC, IM). The drug distribution in tissue was observed after the injection of Rhodamin B (M.W 479 KD) as a function of time using IVIS (an in-vivo imaging system).

RESULTS AND DISCUSSION

A comparison of the efficacy of SC, IM and hollow microneedle methods of injecting PE (50μg) found that the hollow microneedle system enhanced mean resting anal pressure most effectively over 3hr (ANOVA, P < 0.05). When PE was applied with hollow microneedle injection locally, resting anal pressure increased over up to 6hr and gradually decreased to certain level till 12hr (Figure 2). The increase of PE dose by hollow microneedles caused an increase in resting anal pressure over 6 hr after injection (t-test, P < 0.05, n=5 respectively). Treatment with a hollow microneedle system did not cause an increase in blood pressure like S.C and I.M (ANOVA, P > 0.1); however, an IV injection led to a serious increase in mean blood pressure within 1hr (ANOVA, P < 0.05).

As shown in Figure 3, Rhodamin B was locally delivered into the anal sphincter muscle and a fluorescent intensity lasted for over 5 hr. In comparison with other administration methods, the hollow microneedle method provides more efficacious local delivery of a small volume of a sample drug solution into a targeted region, resulting in locally high concentration and distribution of drug in tissue.

CONCLUSION

A hollow microneedle system induced significant contraction of internal anal sphincter pressure at least 6hr after injection. Locally targeted delivery of a small volume of PE solution with high concentration into the sphincter muscle can increase resting anal pressure and reduce side effects of the drug. This new administration system using hollow microneedles could potentially provide treatment of fecal incontinence by painless topical delivery of PE into muscle through perianal skin.

REFERENCES


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