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Local transdermal delivery of phenylephrine to the anal sphincter muscle using microneedles

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ABSTRACT

We propose pretreatment using microneedles to increase perianal skin permeability for locally targeted delivery of phenylephrine (PE), a drug that increases resting anal sphincter pressure to treat fecal incontinence. Microneedle patches were fabricated by micromolding poly-lactic-acid. Pre-treatment of human cadaver skin with microneedles increased PE delivery across the skin by up to 10-fold *in vitro*. *In vivo* delivery was assessed in rats receiving treatment with or without use of microneedles and with or without PE. Resting anal sphincter pressure was then measured over time using water-perfused anorectal manometry. For rats pretreated with microneedles, topical application of 30% PE gel rapidly increased the mean resting anal sphincter pressure from 7 ± 2 cmH_2O to a peak value of 43 ± 17 cmH_2O after 1 h, which was significantly greater than rats receiving PE gel without microneedle pretreatment. Additional safety studies showed that topically applied green fluorescent protein—expressing *E. coli* penetrated skin pierced with 23- and 26-gauge hypodermic needles, but *E. coli* was not detected in skin pretreated with microneedles, which suggests that microneedle-treated skin may not be especially susceptible to infection. In conclusion, this study demonstrates local transdermal delivery of PE to the anal sphincter muscle using microneedles, which may provide a novel treatment for fecal incontinence.

1. Introduction

Fecal incontinence is described as the loss of regular control of hard feces, loose feces, and gases of the bowels in an individual [1]. Incontinence occurs in about 2–18% of the adult population and in about 15% of healthy independent adults over the age of 50 [2,3]. The frequency of fecal incontinence is considerably higher in patients with neurological problems [4]. For instance, fecal incontinence is the second leading cause of placement in nursing homes in the United States [5,6]. Individuals with fecal incontinence suffer from an embarrassing condition that causes social isolation and difficulties in employment. In 2004 patients spent US$400 million on adult diapers, and an additional $1.5–7 billion was spent on care for the incontinence of institutionalized patients [6]. Nevertheless, these persons are frequently reluctant to visit a hospital to discuss their symptoms [7,8].

The most common cause of fecal incontinence appears to be a degenerative disorder of the anal sphincter [9]. Fecal incontinence is also experienced by patients with an ileoanal reservoir [10], and it can also develop after low anterior resection in patients with rectal cancer [11]. Especially in women, fecal incontinence is mainly caused by structural anal sphincter damage associated with childbirth [12,13]. Damage to the anal sphincter muscle leads to loss of control, causing the urgent fecal incontinence [14].

Treatment of fecal incontinence can be determined and categorized based on its pathogenesis [15]. There are many surgical ways to treat fecal incontinence [16], including sphincteroplasty, postanal repair, total pelvic floor repair, dynamic graciloplasty, and artificial bowel sphinctery. Sphincteroplasty is carried out when the anal sphincter is damaged. An improvement in anal pressure was found in up to 88% of patients in the short-term after surgery. However, only 6% of patients experience improvement 10 years after surgical treatment. Postanal repair is a method that recovers bowel movement by decreasing an anorectal angle, but there are no reports of a well-designed study. Dynamic graciloplasty involves transferring the gracilis muscle into the anus, with implantation of stimulating electrodes and a pulse generator. Unfortunately, this surgery often leads to infection, pain, and constipation. An artificial bowel sphinctery is an implantable

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device used to treat patients with severe fecal incontinence who are not candidates for less-invasive forms of restorative therapy. If this device is inserted improperly, it can cause infection, skin erosion, and pain after the surgery [17,18].

Drug treatment can be administered in two ways. One is oral administration and the other is topical application of drugs to the anal canal. Oral drugs that control bowel mobility are loperamide, diphenoxylate, difenoxin, and amitriptyline. Loperamide acts directly on the intestine to inhibit peristalsis by controlling muscle contractions in the intestine [19]. Diphenoxylate and difenoxin inhibit intestinal motility and propulsion. Amitriptyline is an antipsychotic drug that affects the functions of the colon, rectum, and anal sphincter and increases colonic transit time, leading to the formation of a firmer stool [20]. However, these drugs have side effects as well. Loperamide is a typical narcotic anti-diarrheal drug and makes stools harder. An overdose of loperamide may result in central nervous system (CNS) depression and paralytic ileus. Diphenoxylate and difenoxin in high doses can cause adverse CNS effects, and the adjunctive atropine may produce constipation. Amitriptyline can cause the common side effects of antipsychotic drugs [21,22].

Recently, topical delivery of the drug phenylephrine (PE) into the sphincter muscle without surgery has been studied. PE is a selective alpha-1 agonist that causes sphincter contraction *in vitro* [23,24] and PE elevates anal resting pressure in animal studies [25]. In current clinical practice, phenylephrine is widely used as a decongestant. The hydrochloride salt form of phenylephrine has been used because of physiological acceptance of the chlorine ion and increased solubility [26]. The hydrochloride salt of phenylephrine has water solubility greater than 1000 mg/ml and a melting point of 144 °C [27]. The internal anal sphincter exists in a state of tonic contraction and is the main factor responsible for the generation of anal resting pressure [28]. When the sphincter becomes fibrotic and weak, maximum anal canal resting pressure is reduced, causing episodes of passive fecal incontinence. In several studies, a high concentration (10%–30%) of PE gel was applied to the anal canal for delivery of PE into the sphincter muscle [17,22,29,30]. In some cases, topical application of PE gel increased maximum resting anal sphincter pressure [17,31,32]. However, in another study, high concentrations (10%–30%) of PE did not significantly increase resting anal pressure [30]. A study of patients who had a low anterior resection found that topical application of PE gel did not help relieve the patients' fecal incontinence [29].

Transdermal drug delivery is a method of delivering drugs through the skin without injection or oral administration. It is becoming a popular system different from conventional methods. To improve transdermal drug delivery, iontophoresis, ultrasound, and chemical enhancers have been studied, but either require secondary equipment or have slow onset times [33,34]. Microneedles, in contrast, have been shown to painlessly and quickly pierce the skin's outer barrier, the stratum corneum, and can enable self-administration [35–37]. In addition, microneedles are inexpensive and disposable [38]. Microneedle patches can deliver a variety of drugs that cannot usually be transferred because of the impermeability of the skin [39]. For example, microneedles can increase transdermal delivery of small-molecule drugs, proteins [40], DNA [41], and vaccines [42,43]. Previous studies with microneedles have focused primarily on systemic drug delivery via the skin or for vaccination. In this study, we introduce the use of microneedles for locally targeted delivery of drugs to the anal sphincter muscles by piercing holes in the perianal skin.

Because most patients with fecal incontinence are advanced in age, treatments based on drugs are preferred to surgery. However, there is no efficient drug therapy to repair fecal incontinence, which is especially induced by weakness of the anal muscle. We propose the novel treatment of fecal incontinence by topical application of PE on perianal skin pretreated using simple and economical treatment of microneedles. This treatment can carry PE into the local sphincter muscle efficiently with minimum pain and without resistance of the stratum corneum of the perianal skin. We performed the delivery study of PE across the perianal skin by pretreating it with microneedles (Fig. 1). The drug delivery property was investigated as a function of the number of needles and concentrations of PE qualitatively and quantitatively. Also, the change in resting anal sphincter pressure of rats was measured *in vivo* after treatment. Efficiency of various treatments was compared to demonstrate the feasibility of combining microneedle pretreatment with topical application of PE on the perianal skin as a potential treatment of fecal incontinence.

2. Materials and methods

2.1. Fabrication of microneedles for drug delivery to perianal skin

As described previously [44], a female master microneedle mold was prepared using a photolithographic process with SU-8 epoxy photoresist (MicroChem, Newton, MA) and used to prepare a male master structure. Next, a PDMS female mold was prepared from the male master structure using the molding process again.

To make the final microneedle devices, the female molds were covered with pellets of poly-lactic acid (L-PLA, 1.1 dl/g, SurModics Pharmaceuticals, Birmingham, AL) and placed in a vacuum oven (Eyeler, Tokyo, Japan) under −70 kPa vacuum for 5 min at 190 °C. PLA microneedles on a PLA solid base were removed from the PDMS mold

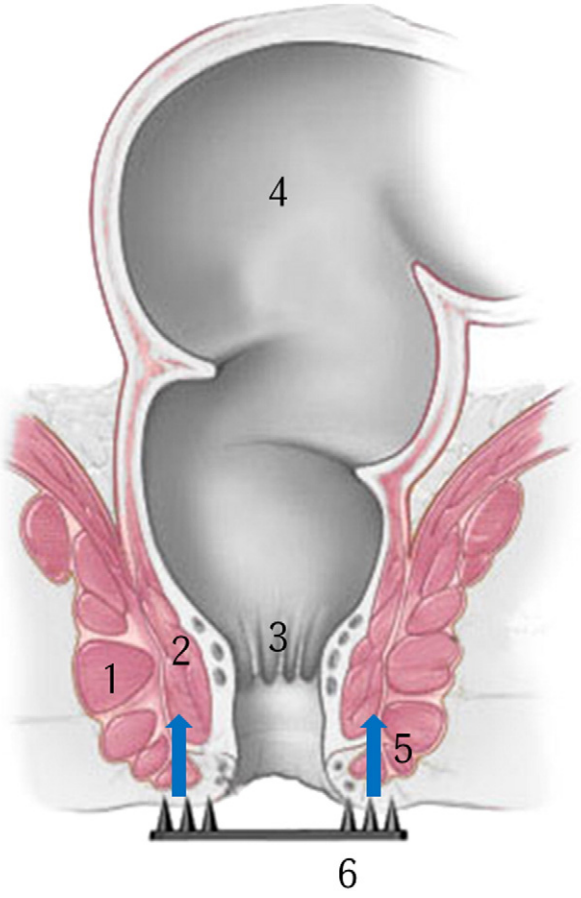

Fig. 1. Diagram of locally targeted delivery of PE into anal sphincter muscle through perianal skin using microneedles. Microneedles generate holes on perianal skin to make local delivery pathways for PE to the sphincter muscles. 1. External sphincter muscle. 2. Internal sphincter muscle. 3. Anal canal. 4. Rectum. 5. Path of PE delivery. 6. Microneedles. (The picture of the anus is copyrighted by the Mayo Foundation for Medical Education and Research and is used with permission.)