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Clinical evaluation of safety and human tolerance of electrical sensation induced by electric fields with non-invasive electrodes

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Abstract

This paper reports the first clinical safety study of human tolerance of electrical sensation using non-invasive, flexible surface-type electrodes and exponentially decaying electric pulses. The study evaluated the effect of electric fields in the absence of a drug and an anesthetic, and was performed in light of potential applications in the field of erectile dysfunction (ED). Twenty impotent patients who had previously received injection or intraurethral therapies were enrolled in the study. Voltage escalations from 50 to 80 V (in 10-V increments) with a single pulse of 3-ms duration were performed with meander-type electrodes placed on the shaft and part of the glans of the penis. The electric fields-induced sensation was assessed via a pain scale from 0 to 10. All 20 patients, who were free to withdraw from the study at any point, completed the voltage escalation study. No clinical safety concerns were apparent and no skin irritation was observed after electric treatment. Our initial study indicates that the pulses in the tested voltage range were well tolerated by most patients. In previous animal experiments under analogous experimental conditions, the application of 50 V has been found effective for transdermal drug delivery into the penis.

Keywords: Electrical sensation; Human; Skin; Electroporation; Impotence; Anesthesia

1. Introduction

Skin is a potentially attractive target tissue for local and systemic delivery of therapeutics. It is easily accessible, constantly regenerating, and provides a large surface area. Transdermal drug delivery also offers potential advantages over other delivery routes such as injection or oral medication: convenience, non-invasiveness, and potentially fewer side effects for local treatments. However, the skin's highly resistive outer layer, the stratum corneum, presents a strong barrier to the delivery of therapeutic levels of most drugs. Electroporation (EP) of skin is a powerful tool for decreasing the resistance of the stratum corneum and to enhance drug penetration. Recent progress in understanding the mechanism and effectiveness of EP in cutaneous drug delivery has been summarized in [1]. Although about 200 patients have been treated under local or general anesthesia with EP in the context of electrochemotherapy of tumors [2,3], very few studies have assessed the tolerability of EP on healthy skin without anesthesia [4]. For further clinical applications, it is important to answer key questions such as: How painful is EP? Is EP safe?

Since nerve sensations and pain are subjective experiences, the threshold of tolerability of the electrical treatment is expected to vary from subject to subject. Only human studies can provide direct answers to the question whether pain experienced during electrical treatment is acceptable or not.

The level of sensation or pain induced by equal stimuli depends largely on the concentration of sensory receptors in the skin, which varies with the anatomical location, as well as the individual's subjective threshold. The penile skin, especially at the glans, is one of the most sensitive locations in the human body due to the high density of nerve endings and vascularization. In cooperation with others, we had previously shown in rabbits that topical application of vasodilators to the penis, when followed by EP of the penile surface, caused various degrees of erection [5]. No erection was observed with the control groups (either EP alone no drug or drug alone no EP). It indicates that EP increases the permeability of the skin tissue for transdermal delivery. These encouraging results and the potential of providing an alternative treatment for impotent patients prompted us to assess the tolerability and safety of electric fields in patients

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suffering from erectile dysfunction (ED). ED is a medical disorder for men. It has been estimated that it is prevalent in 2% of men aged 40 years, and in 50% of the male population that is 70 years and older. ED affects more than 20 million men in the US. Intracavernosal injection of vasodilators, such as prostaglandin E1 (PGE1, alprostadil, CAVERJECT®), is still a commonly, though now less frequently, used treatment of ED. It is very painful and carries a high risk of corporal fibrosis at frequent usage [6]. Another approach is transurethral delivery of penile suppositories (alprostadil, MUSE®), which can also be painful and is less effective than injection [7]. More recently, an oral formulation of sildenafil citrate (VIAGRA®) has become available and is now the first line of treatment. However, the use of VIAGRA® is associated with side effects, and cannot be used without significant risk by ED patients with cardiovascular disease or patients who depend on medications containing nitrates.

The goal of the study reported here was to investigate the safety of electric field and the tolerability of electrical sensation in the absence of a drug and an anesthetic. This is the first clinical study approved by an Institutional Review Board (IRB) determining the sensation caused by electric field using non-invasive electrodes. Electrical sensation (pain) was assessed by 20 ED patients via a scale ranging from 0 to 10 following voltage escalations. In order to develop a clinical viable treatment with electroporation, we should consider both aspects: (1) maximize the efficiency of electroporation, and (2) minimize the pain associated with electrical sensation induce by electric fields. Therefore, the patients' response obtained from this study will be valuable information for determining the feasibility of further development in the field of electroporation with potential medical applications.

2. Experimental

2.1. Study design

This IRB-approved clinical study was conducted by MDS Harris (Lincoln, NE) in Phoenix, AZ. Twenty ED patients were enrolled in this study. Each patient signed an Informed Consent Form prior to receiving the treatments. Subjects were divided into two groups: 10 subjects who had undergone the intracavernosal injection treatment, and 10 subjects who had used the transurethral therapy. During the screening period, subjects were given a demonstration of the Genetronics Transdermal Delivery Device (exponential pulse generator and a surface-type meander electrode) and received an electrical pulse on their forearm. Those subjects, who did not wish to continue, were free to withdraw at that time. Subjects who consented to continue proceeded with the screening process. The medical screening process involved medical history, physical examination, and clinical laboratory tests (hematology, serum chemistry, urinalysis, HIV antibody screen, and urine screen for alcohol and drugs of abuse). On the scheduled study day, subjects self-administered (under supervision) the Genetronics Transdermal Delivery Applicator which covers the penile shaft and part of the glans. Each subject initially received a single pulse at 50 V. If the subjects tolerated the 50 V without any severe or serious adverse experiences, they could continue with voltage escalation in 10-V increments up to a maximum of 80 V, depending upon their tolerance for the procedure. The pulse length was always set at 3 ms. There was at least a 1-h rest period between voltage escalation applications. After each pulse application, every subject filled out a form about the experienced sensation and rated the sensation of pain on a scale ranging from 0 to 10, with zero indicating no sensation and 10 indicating excruciating pain. Vital signs (blood pressure, pulse) were evaluated prior to, and following each treatment. Urinalysis was conducted from a sample obtained at the end of the voltage escalations for each subject. The subject used the same set of meander electrodes throughout the voltage escalation.

2.2. Pulse generator and electrode

The pulse generator was equipped for clinical use and delivers exponential pulses (Genetronics, San Diego, CA). The Transdermal Delivery Applicator consisted of two rectangular meander-type electrode patches (2×5 cm each), attached to the inside of an inflatable cuff which is normally used to measure the blood pressure on the arms of infants (Tycos Instruments, Arden, NC). The meander electrode patch consisted of an array of interweaving electrode fingers with alternating polarity [8]. Each electrode finger was 0.2 mm wide and was separated by a 0.2-mm gap from its neighboring electrodes. The gap was filled with insulator to eliminate some bypass current between the adjacent electrodes. The patient aligned the two meander electrode patches lengthwise along the sides of the mid-shaft such that the electrodes also extended onto the sides of the glans.

2.3. Test procedure

The pulse generator was calibrated before each pulse application. The surfaces of the electrodes were cleaned with alcohol swabs and allowed to dry thoroughly. The patient cleaned the penile skin surface on both sides (left and right) of the midshaft and on the glans with alcohol swabs and let the skin dry thoroughly. Next, the patient moistened the penile skin using a cotton ball wetted with the saline solution (sham drug). After that, the patient positioned the meander electrode patches as described above, wrapped the cuff around the penis and secured the cuff by closing the Velcro® fasteners. The patient then inflated the cuff slowly until the cuff and electrodes made uniform contact with the surface of the penis, usually at a pressure of 20–30 mm Hg. The electrodes were connected to the pulse generator and a single pulse was delivered. At the end

of the procedure, the cuff was deflated and removed together with the electrodes.

3. Results and discussion

Patients were subjected to single pulses of 50–80 V escalating in 10-V increments and delivered for 3 ms. The patients were asked to rate the pulse sensation on a scale of 0, no pain, to 10, excruciating pain. The results of this study are shown in Table 1. Pain scores up to and including level 5 were considered tolerable. The percentage of tolerability at each voltage level was calculated by multiplying the number of subjects rating the degree of sensation up to level 5 by 100 and dividing this result by 20 (the total number of patients enrolled). At 50 V, the tolerability of pulse sensation was 100%, and 65% of the ratings fell between no pain and mild (0 to 2). At 60 and 70 V, tolerability declined slightly to 93%, with 30% of the ratings still between 0 and 2. When the voltage increased to 80 V, the tolerability dropped to 75% due to the fact that 25% of the patients marked pain scores from 6 to 9. In summary, all patients passed the single pulse tests (50–80 V, 3 ms) without rating the sensation excruciating. Across the voltage escalation range from 50 to 80 V, the overall of the tolerability was 90% (72 out of 80 scores). No side effects of electrical treatment were observed or reported according to clinical examination of the patients before and after the tests.

Many different factors affect the sensation generated by electrical pulses delivered to the skin, including voltage, current, current density, pulse length, frequency, waveform, and body location. In this study we evaluated one of the most important factors, i.e., voltage. Aside from its direct effect on nerve stimulation, voltage also influences the amount of current flow. It is known that above the perception threshold, the quality of sensation changes with increasing current and the degree of pain increases nonlinearly [9]. One effect of delivering an electrical pulse of the magnitude we applied in this study is the breakdown of the insulating layer of the skin, the stratum corneum, thus allowing higher current flow into and through the skin [10]. This, in turn, increases the level of sensation. With increasing applied voltages, the electrical resistance of the skin decreases significantly. Therefore, it is not surprising that the level of sensation can escalate substantially with a relatively small increase in applied voltage. This phenomenon was observed in our study when the voltage was elevated from 50 to 80 V. For electroporation enhanced transdermal drug delivery, a high degree of breakdown of the skin impedance is desirable. However, in the treatment of patients a compromise has to be found that allows sufficient drug permeation through the porated skin tissue while not generating unacceptable pain in creating the pores. In experiments with rabbits under similar pulsing conditions, an applied voltage of 50 V was effective in delivering a sufficient amount of PGE1 transdermally into the penis to cause a full or partial erection in all treated animals (n=9). The application of the same voltage to humans was tolerable to 100% of the patients tested. Knowing that the thickness of human penile skin differs from the rabbit's, and even if the voltage has to be increased to 80 V in order to achieve effective drug delivery in humans, that voltage would still be tolerable to 90% of the patients we tested.

Besides voltage and current, another important factor is anatomical location. As mentioned, the penis is one of the most sensitive areas of the body and the application of 80 V caused significant distress to 25% of the patients. On the contrary, in a different study on topical delivery of lidocaine, where we tested the pain response to electroporation with meander electrodes targeting the forearm skin, the pain scores were mostly below levels 2 and 3 [4]. In that study, the pulse conditions were actually more intense (80 V, 10 ms, two cycles of six pulses each). Both in the study just mentioned and in the study reported here, no skin irritation was observed post electrical treatment. However, in a rat study with caliper electrodes, where the skin-fold was electroporated between two flat, parallel metal plates, the appearance of erythema was reported [11]. In this case, not only were the upper-most layers, including the stratum corneum affected by the electrical pulses, but also the

Table 1
Summary of electrical sensation assessment in ED patients

Set voltage	Pain score						
	0	1 to 2	3 to 4	5	6 to 7	8 to 9	10
	No Pain	Mild	Discomforting	(Between)	Distressing	Horrible	Excruciating
50 V	3	10	6	1	0	0	0
60V	1	8	10	0	1	0	0
70V	1	2	10	5	1	1	0
80V	0	1	10	4	2	3	0
Total subjects per score	5	12	36	10	4	4	0
Tolerability (%)	(50 V) 100%		→				
	(60 V-70 V) 93%		→		5% →	2% →	
	(80 V) 75%		→		10% →	15% →	

Twenty patients were given one electrical pulse each at escalating voltages from 50 to 80 V. After each pulse, every patient scored his subjective sensation (pain) according to the scale given above. Pain scores up to and including level 5 were considered tolerable.

underlying tissue. This points out the advantage of electrode designs such as the meander electrodes which allow the initial electric fields to be mostly localized within the superficial layers of the skin, thereby avoiding undesirable effects, including pain, in underlying tissues.

In summary, this study provides evidence that electrical treatment with the purpose of enhancing transdermal drug delivery appears feasible, even in sensitive areas like the penis. Previous studies mentioned above, which included actual drug delivery by electroporation in animals and humans, make it likely that under the pulsing conditions we found acceptable in this study, effective drug delivery may be achieved even in the absence of anesthesia. The electrode applicators and delivery conditions used here can be optimized further depending on the disease target and medical requirements.

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