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Electrotherapeutic Device/Protocol Design Considerations for Visual Disease Applications

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Abstract—**One of the more interesting applications of electrotherapy involves its use in the treatment of visual disease; including retinitis pigmentosa, diabetic retinopathy and macular degeneration. The therapeutic efficacy of electrotherapy is highly dependent upon the incorporation of appropriate design choices for both the electrotherapeutic device and treatment protocol. Electrotherapeutic design drivers include electrode probe-tissue interface, device reliability, operational constraints, treatment protocol procedures, and safety. In FDA guided and FDA supervised clinical studies (FDA pre-IDE numbers 1980275 and 1000038 and FDA IDE number G020106) involving electrotherapeutic intervention for dry macular degeneration, 61% of a 400 patient cohort treated with electrotherapy achieved visual acuity improvements of two lines or more on the Snellen chart. Average electric current intensities in the range of 60 to 125 μA were utilized to achieve this level of therapeutic efficacy. With further improvements in the design of electrotherapeutic device waveforms, frequency selection, treatment protocols and electrode probe configurations; long-term visual acuity improvements of two lines or better on the Snellen chart can be anticipated for more than 60% of the patients who are in the early stages of retinitis pigmentosa, diabetic retinopathy and dry macular degeneration.**

I. Introduction

The use of electrotherapy in the treatment of visual disease has a long and interesting history. Some ophthalmological journals and hospital publications reported varying levels of success in the treatment of retinitis pigmentosa, choroidal disease, optical neuropathy-atrophy (amaurosis) and other visual disease problems more than 120 years ago [1]-[3]. Using direct current (DC) electrotherapy with currents between 0.1 and 1 mA, visual acuity and visual field-of-view improvements were achieved for a number of retinitis pigmentosa patients [4]-[6]. At that time, the electrotherapeutic device was nothing more than a wet cell battery with two electrode probes connected to the positive and negative terminals. For treatment purposes, one of the electrode probes was placed in contact with the tissue of a closed or partially closed eyelid (as shown in Fig. 1) and the other was attached to the wrist, top of the spine or back of the head. However, consistency and repeatability continued to be problematic. Part of the electrotherapy consistency problem appeared to be due to the use of treatment current levels that were too high [6]. Allen and Lowery reported successful results in reversing the progress of retinitis pigmentosa using a 10 Hz source at peak current levels of approximately 200 μA [7]. The lower current levels utilized by Allen and Lowery appeared to mitigate part of the consistency problem that was reported in earlier work.

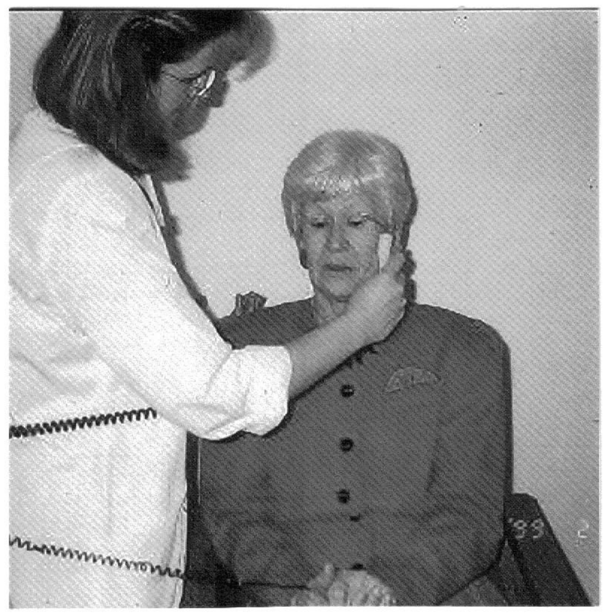

Fig. 1 A macular degeneration patient being treated with an electrotherapeutic device. The average current applied is in the range of 60 to 125 μA. One of the conductive electrode probes is shown being pressed against a partially closed eyelid. The other probe can be held in either hand or both hands.

Many of the electrotherapeutic devices recently used in visual disease applications appear to be simple signal generators with very poor current regulation, or converted transcutaneous electrical neural stimulation (TENS) devices. These devices have enjoyed some initial success in treating visual disease [7]-[9]. However, many commercially available TENS devices have limited frequency coverage for visual disease applications, they tend to have reliability problems under high volume production conditions and constant use, and they deliver average current levels that are much too high for lower contact-tissue impedances [10].

In 1998, an electrotherapeutic device was designed and developed specifically for visual disease applications [11]. It

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was designed with the needs of both patient and doctor in mind. The device employs a frequency control technique that is significantly different when compared with conventional devices and has been successful in its FDA guided Open Label clinical studies (FDA pre-IDE Nos. 1980275 and 1000038) and its FDA supervised double-blind Phase I clinical trial under FDA IDE No. G020106 (Phase I FDA Review held on January 18, 2005, Rockville, MD; FDA recommendation: begin Phase II clinical trials).

II. Scientific Background

A. Organ-Tissue Standpoint

The use of electrotherapy in visual disease can be thought of as a special branch of wound healing (which includes the healing of lacerations, ulcers, fractures and tumors). In the late nineteenth century, a number of medical doctors theorized that the mechanism behind the visual acuity and visual field improvements achieved with electrotherapy were due to electrically induced improvements in optic nerve conduction, electrically stimulated enhancement of retinal vascular system function and enhanced dilation capabilities of retinal blood vessels [12].

Endogenous (internal) injury potentials in the range of 17 to 42 mV, with endogenous injury currents of 2 to 25 μA, have been measured at wound sites [13]. Fowles, Edelberg and Chakkalakal *et al*. provide models for uninjured and injured tissue [14]-[16]. In research related to ophthalmology, Zhao and Reid followed with similar wound healing models for corneal epithelium and corneal wounds [17], [18]. Nordenström published results on vascular porosity and absorption that occurs with very low level endogenous and exogenously (externally) applied electric fields, along with the influence of electro-osmosis for the movement of water in wound healing and cancer remission [19]. Nordenström's theory appears to be relevant to ophthalmology and optometry. Fischbarg *et al*. reported that endogenously driven electro-osmosis is the mechanism that supports fluid transport across the corneal epithelium. [20], [21]. Recent work by Fischbarg, and others, indicates the presence of endogenous local corneal circulating current densities in the 15 to 25 mA / cm^2 range [21].

B. Cellular-Molecular Biology Standpoint

The influence of exogenous electrical currents and electric fields, and their influence on various cell plasma membrane receptors, has been well documented [17], [22], [23]. By activating these cell receptors, biochemical events within the cell cytoplasm and nucleoplasm can be influenced through a number of plasma membrane interactions and in different cellular signaling pathways.

Young *et al*. and Cheng *et al*. reported that endogenous and exogenous electrical stimulation supports production and release of the nucleoside/nucleotide derived family of molecules including adenosine triphosphate (ATP) and cyclic adenosine monophosphate (cyclic AMP); along with promoting protein synthesis, amino acid transport and cellular Ca^{++} influx [22], [24]. ATP is known to act as a neurotransmitter in the retina. and it influences rhodopsin conversion in retinal rod cells. Cyclic AMP participates in the cellular signaling pathway that influences gene expression. The activities associated with ATP and cyclic AMP have a strong influence on function, structure, growth, regulation, immune response and healing at the cellular, tissue and organ level.

Research at the organ-tissue and cellular-molecular biology levels indicates that endogenous electrical activity is an integral part of a variety of naturally occurring growth, regulation and healing events that involve the transport of ions (over mm and cm distances for tissues and organs) and electrons (over nm and μm distances for molecules and cell membranes). Therefore, the process of healing can be enhanced by an exogenous electrotherapeutic source to accelerate and enhance the electrically driven healing processes that occur naturally in the human body.

III. Electrotherapeutic Device/protocol Design Drivers

A. Output Current, Safety Issues and Side Effects

One of the first electrotherapeutic device design issues that must be addressed involves safe levels of output current. Many electrotherapeutic wound healing treatment protocols utilize average currents in the range of 200 μA to 1 mA. For visual system applications, current levels in this range are not recommended. Current levels beyond 200 μA can destroy retinal cells in culture [10].

Current density at the retina is also a safety issue. If the current is considered to be distributed within the confines of an 83^o cone, extending 1.7 cm from the eyelid to the retina, the current density at the retina would be approximately 25 μA / cm^2 for a treatment current of 120 μA. Data from Agnew, McCreery and Shannon indicate the possibility of dry tissue burn at much higher current density levels of 500 μA / cm^2 and current levels above 2,500 μA [25], [26].

In order to provide a margin of safety for visual system applications, average current levels should be less than 200 μA. Most patients report some discomfort (a pinching or mild burning sensation on the eyelid) at average treatment current levels above 150 μA. In order to maintain a wide margin of safety and avoid any patient discomfort or damage to retinal tissue, the average value for treatment current can be restricted to levels below 150 μA.

By maintaining appropriate constraints on treatment current levels, no significant side effects were experienced during the FDA guided and supervised clinical trials. One patient condition that does need to be addressed involves potential interactions between the electrotherapeutic device and pacemakers.

B. Device Output Frequency Range

Over the past 120 years, the therapeutic efficacy of direct current in the treatment of visual disease provides a strong indication that a non-zero average current component is desirable over short time frames [1]-[6], [10]. With respect to the eyelid contact point, both positive and negative polarities have proven to be effective.

Rectangular (pulsed) waveforms, from several Hz to 300 Hz, have been successfully employed in wound healing and connective tissue disease applications. Frequency choice is based, to some degree, on the history of successful electrotherapeutic applications. A considerable amount of research has been reported on the effects of electric field and electric current stimulation of cells, tissues and organs at different frequencies. Rectangular waveforms with frequencies close to 10 Hz promote enhanced levels of DNA and increases in fibroblast proliferation [27]. Clinical studies for wound healing show positive results for frequencies above 40 Hz. Research and clinical results indicate that frequencies in the range of approximately 0.1 Hz to 100 Hz should be useful in visual system disease applications.

C. Electrode Probe-Tissue Interface; From the Standpoint of Device and Protocol Design

One of the electrode configurations for visual disease and wound healing applications involves the combination of a cotton-gauze tip soaked in saline solution.

Gelled cotton-gauze in a hollow metal tip offers a relatively convenient and comfortable electrode configuration for treating visual disease [10]. Gel contacts can minimize chemical dissociation and allergic reaction problems. However, when used as conductive coatings on metal electrodes, gels will often push away from the contact area and dry out. As a result, the quality of the electrode probe-tissue contact interface can degrade rapidly.

The probe-tissue load impedance can have a significant effect on the intensity and shape of the source output waveform. The time constant associated with the leading and trailing edge spikes of the output current waveform will vary significantly with electrode probe contact quality.

IV. Impact of Results on Device/protocol design

The first response to electrotherapy that macular degeneration patients often notice involves the reduction of visual "haze" that interferes with their peripheral vision. This effect often occurs by the end of the second treatment. Significant visual acuity improvements occur by the end of the third treatment. After the end of the fourth treatment, some patients report that they can see bright colors again.

Clinical test results can have an impact on device and/or protocol design. In the FDA guided Open Label clinical study, patients were treated with average current levels of approximately 120 μA. And 52.2% to 61% of those patients achieved two lines or better of Snellen chart visual acuity improvement over a 24 month treatment time period, as shown in Table I (The Snellen chart is the conventional 11 line 10 letter visual acuity examination chart used by ophthalmologists and optometrists).

The macular degeneration patients who participated in the FDA Phase I clinical study were treated with approximately 62 μA of average current. And 18% of those patients achieved two lines or more of Snellen chart visual acuity improvement by the end of the first week of treatment. By the end of the second week, 26.7% of the patients achieved two lines or more of visual acuity improvement (Table II). This represents an eight percent increase for just one additional week of electrotherapy treatment.

TABLE I
MACULAR DEGENERATION ELECTROTHERAPY RESULTS: COMPARING FDA GUIDED OPEN LABEL STUDY DATA & FDA SUPERVISED DOUBLE-BLIND PHASE I CLINICAL TRIAL DATA

Factor	Open Label Study	Phase I Clinical Trial
Total number of patients	High (400)	Low (41)
Average electric current	~ 120 μA	~62 μA
Treatment time frame	Several years	2 weeks
Visual acuity improvement for % of patients treated	61% ≥ 2 lines on Snellen chart	26.7% ≥ 2 lines on Snellen chart
Was dose-time response observed with continuous treatment?	Yes	Yes, an 8.7% improvement over just one week
Was double-blind used?	No	Yes
Control group	Patients not receiving electrotherapy just focused on nutritional supplementation	Sham treatment

TABLE II
MACULAR DEGENERATION ELECTROTHERAPY RESULTS: PERCENTAGE OF PATIENTS ACHIEVING TWO LINES OR BETTER VISUAL ACUITY IMPROVEMENT ON SNELLEN CHART; INDICATION OF A DOSE-TIME RESPONSE

	After 1 week of treatment	After 2 weeks of treatment	After ~ 24 months of treatment
Patients treated with electrotherapy	18%	26.7%	~ 52.2% to 61%
Patients not treated with electrotherapy (controls)	11%	11%	~ 2%
Difference in Visual acuity improvement between treated and untreated patients, showing evidence of dose-time response	7%	15.7%	~ 50.2% to 59%

Tables I and II show a pronounced dose-time response between the end of weeks one and two, and at the end of two years of treatment. The results indicate that lower treatment currents should be considered.

V. DISCUSSION

Some of the first electrotherapeutic device/protocol design tasks to be considered involve legal/litigation issues, patient health care, doctor concerns, safety and reliability. In 1998, when considering electrotherapeutic devices that were available at the time for visual disease applications, the design driver that served as the primary motivator for a new device was the effect that poor device reliability had on therapeutic efficacy and safety.

One of the more critical design driver issues for any biomedical device involves the doctor and the person who administers the therapeutic intervention. Ophthalmologists and optometrists cannot be expected to embrace a therapeutic intervention unless it satisfies certain patient control requirements including revenue stream issues, safety/liability concerns and follow-up capability.

A therapeutic device for visual disease applications will involve take-home units, where patients self-administer electrotherapeutic treatments for the rest of their lives. In order to address the patient control issues of concern for medical doctors and other health care practitioners, a data acquisition capability can be incorporated into the device design. This feature provides assurances that the patient will visit the doctor periodically, allowing the doctor to correlate patient progress with data stored in the device. With this information, the doctor can make adjustments in the treatment protocol that will enhance the therapeutic efficacy of the patient's home treatment regimen. Based on historical progress and recent improvements in device and protocol design (waveform structure, frequency choices, average current level, treatment schedule/duration, patient position, etc.), we anticipate that approximately 70% of the dry macular degeneration patients, who have 20/100 or better visual acuity, will be able to improve at least two lines on the Snellen chart after several months of treatment.

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