

# **Efficacy of Penile Traction Therapy Using a Novel Device: A Controlled, Single-blinded, Randomized Trial**

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## 1 ABSTRACT

Peyronie's disease (PD) is a fibrotic condition of the penis, affecting 1-13% of the US male population. The disease results in penile curvature and significant psychosocial bother. Current preferred therapies for PD include repeated penile injections with bacterial enzymes and surgery. However, these therapies are expensive and in some cases result in permanent reductions in penile length and sensation. Penile traction therapy (PTT) is a relatively newer treatment which has been proposed as a treatment for PD with preliminary data suggesting a potential role. However, currently available PTT devices are primarily designed for penile lengthening and have many significant limitations including a requirement of use for 9 hours daily and significant difficulties in personal application. Given these limitations, a new penile traction device (RestoreX®) was created and funded through Mayo Ventures and was specifically designed to treat men with PD. The primary objective of the current study is to evaluate safety of the device using various dosing schedules, with secondary endpoints designed to assess efficacy and subjective outcomes. To accomplish the study, a population of PD men will be enrolled and will be randomized to utilize the device for varying amounts of time. Outcomes will be periodically assessed, and results are to be used with the intent to publish in a scientific journal.

## 2 SPECIFIC AIMS / HYPOTHESIS

### 2.1 Primary Objectives

1. Evaluate the safety of the RestoreX® device when used 30 minutes once daily, twice daily, three times daily, and in an open label fashion

### 2.2 Secondary Objectives

1. Compare changes in stretched penile length following completion of 3 months of RestoreX® therapy as well as following an open-label period within and among treatment groups.
2. Compare changes in penile curvature following completion of 3 months of RestoreX® therapy as well as following an open label period within and among treatment groups
3. Compare outcomes of subjective questionnaires assessing erectile function, PD disease-specific domains, satisfaction, ability to achieve sexual intercourse, and pain among treatment groups
4. Compare satisfaction with the RestoreX® device to alternative forms of PTT among treatment groups
5. Compare satisfaction with the RestoreX® device to alternative PD therapies among treatment groups

The current study hypothesis is that deformities relating to PD (penile length loss, curvature) can be treated with penile traction therapy.

## 3 BACKGROUND AND SIGNIFICANCE

Peyronie's disease (PD) is estimated to affect 1-13% of the male population and is associated with deposition of fibrous plaques within the tunica albuginea of the corporal bodies.[1-6] It is characterized by penile curvature, pain, shortening, impaired sexual function, and adverse effects on patient and partner well-being.[7, 8] While surgery remains the gold standard for the correction of penile curvature, multiple alternative treatment options including oral, intralesional injections, and mechanical vacuum or traction therapies are available, with variable success rates.[9, 10]

Penile traction therapy (PTT) consists of any treatment designed to lengthen or straighten the penis through mechanical forces. As a broad category, it also can include the use of vacuum erection devices (VED), which serve to expand the penis through application of hydrostatic forces, although the objective of the current study relates only to the more narrow definition of PTT.

Although various forms of PTT have likely been utilized to lengthen the penis for many years, the majority of data on its impact on penile length and curvature have only been reported recently. The increasing popularization of PTT as a treatment modality is likely secondary to several factors, including its relative non-invasive nature, adverse effects associated with alternative therapies, and the difficulty of treating conditions resulting in penile length loss. The scientific basis for use of traction therapy in general is well established, with mechanical stresses known to modulate multiple aspects of cellular function, including apoptosis, gene expression, and growth and differentiation.[11] In cases of fibrosis, such as with Dupuytren's contracture or Peyronie's disease (PD), continuous traction therapy has also been shown to reorient collagen fibrils and may have a differential effect on diseased versus non-diseased tissues.[12, 13]

PTT for the treatment of PD has been the subject of several studies.[14] While current evidence for PTT as monotherapy for PD is limited by small cohort sizes and low quality methodology, several studies have suggested significant improvements in stretched penile length (SPL), penile curvature (in acute phase of PD), and/or patient satisfaction.[15-17] PTT in conjunction with intralesional injections including verapamil and interferon has been assessed as well, with significant improvements found in SPL and no significant differences identified on penile curvature.[18-20]

### **3.1 Limitations with Current PTT Devices**

Currently available PTT devices have several notable limitations:

- The first and most important limitation is regarding regulatory approval. As a general class, orthotic-type devices intended to correct a deformity are considered Class I devices by the FDA. However, current devices are not designed to correct penile curvature, but are predominantly designed to lengthen the penis. As such, they fall outside of the Class I category and are therefore considered as novelty items with no claims as to role or efficacy. Only one PTT device (Andropenis®) has retroactively registered with the FDA as a 510k exempt Class II device (pending review by the FDA).

- A second limitation is that the devices are very difficult to use and often result in mild, temporary patient pain and discomfort. The clamping portion of the device alone often results in pinching of skin and transient pain with device application. In the largest (n=96) randomized controlled trial (RCT) performed of the device in men with PD, the authors noted penile erythema occurring in 2% and transient pain in 25%.[17]
- A third limitation is the duration of use required. Currently, the Andropenis® device is recommended to be used for 9 hours daily over a period of at least 3 months. This duration of use is clinically very challenging to achieve, and in our practice we have found that most patients are not able to utilize the device for over 1-2 hours daily.
- The Andropenis® device achieves very minimal traction on the penis. In assessments of patients utilizing the device, often no traction is achieved.
- Existing PTT devices do not have a mechanism by which curvature can be corrected. They are restricted to lengthening alone. They also are not allowed to make any claims specifically on lengthening in the US.
- With the exception of one device, existing PTT systems have not undergone clinical testing.

Given these numerous limitations, a novel PTT device has been developed at Mayo Clinic (Figure 1). The primary objective of the device was to assist in the treatment of PD, either as a primary or adjunctive therapy. The device addresses each of the above bullet points, and is designed to be a minimally-invasive alternative to existing treatments.

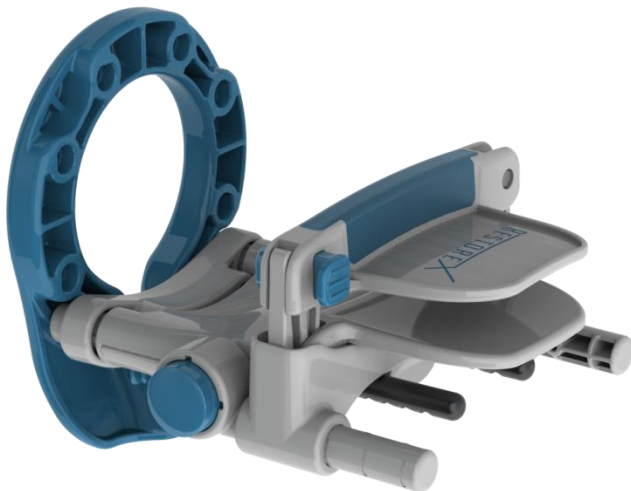


Figure 1 – RestoreX® device

### 3.2 Preliminary Data

Currently, there is a small amount of preliminary data available on the RestoreX® instrument. During the developmental phase of the device, a quality improvement project was performed to evaluate the clamping portion (see **Attachment – Quality Improvement Summary**). It was felt that the clamp represented the most critical aspect of the device, as this was where the majority of discomfort occurred with other devices. Additionally, the clamp needed to provide sufficient friction to allow adequate traction without having the glans of the penis dislodge from the device.

A total of 15 patients participated in the quality improvement project and had the clamps applied under direct supervision for 30 minutes. After the 30 minutes, all patients reported 0/10 pain, and only minimal transient erythema was documented by the physician. The clamp was again applied, and traction forces were administered to determine if the clamp was able to remain intact despite stretching forces applied. This also resulted in a successful outcome, with all patients able to successfully achieve a minimum required tension of 1 kg, with a 36% safety factor achieved before any discomfort was reported among any patient. During the testing, patients reported improved comfort with the use of a wrap such as gauze or Coban, which permitted additional traction in all patients.

### **3.3 Significance**

The development of a novel PTT which addresses the above limitations is a significant milestone. As previously noted, no PTTs are currently designed to correct PD curvature, and only limited data are available on PTT use in this manner. In the absence of a more conservative therapy, the most common current first line treatment for PD is collagenase clostridium histolyticum (Xiaflex®). This therapy requires 10 physician visits over a 5 month period and costs >\$50,000 for a full treatment series. It also results in notable adverse events including risk of penile fracture and significant penile ecchymoses. The only other viable alternative is surgical management. This is associated with multiple undesirable adverse effects including penile shortening, penile edema, loss of penile sensation, and recurrence of curvature over time.

Traction therapy has been used in many applications including limb and dental orthotics (braces) with success for many years. It however has not been successfully applied in the case of chronic PD, as this has previously not been an area of legitimate scientific research and treatment. If the current study demonstrates the safety and efficacy of the current therapy on improving penile curvature, it has the possibility of displacing other treatments as a first line option for the treatment of PD. This would not only be very cost-effective (for patients and the overall healthcare system), it would also provide a less-invasive option for treatment with fewer long-term risks. It therefore has the possibility of changing the entire paradigm for managing the condition of PD.

## **4 STUDY DESIGN AND METHODS**

### **4.1 Subject Selection**

#### *4.1.1 Inclusion Criteria*

- Males with previously diagnosed PD
- >18 years old

#### *4.1.2 Exclusion Criteria*

- Prisoners
- Curvatures <30 degrees
- Stretched penile length <7 cm

- Currently undergoing intralesional injections for PD
- Erectile dysfunction (ED) unresponsive to phosphodiesterase-5 inhibitors or intracavernosal injection therapies
- Diabetes mellitus with evidence of end-organ damage (peripheral neuropathy, retinopathy, CKD stage III or higher, etc.)

#### *4.1.3 Setting*

The current study will be conducted at the Mayo Clinic in Rochester, MN on Gonda 7 South (Dept of Urology). All patients will be recruited from Dr. Landon Trost's clinical practice, as Dr. Trost is the only Andrologist treating men with PD at Mayo Clinic Rochester. All aspects of recruitment, education, and objective assessments will occur within Dr. Trost's practice.

#### *4.1.4 Recruitment and Pre-Screening*

Recruitment will occur from patients treated at Mayo Clinic for Peyronie's disease. Contact will occur via mailers and provider-initiated telephone calls after assuring that the patients meet the appropriate inclusion / exclusion criteria. Patients who would be interested in proceeding with the trial will be invited to an introductory meeting, at which time details of the study itself would be reviewed. No financial incentives will be provided to participate in the trial, however, participants would be given a RestoreX® device at no charge. Patients will not be charged for any visits related to the study, and no labs or other testing will be obtained which require payment.

Patients indicating that they would wish to participate will be reviewed to again assure that they meet the appropriate inclusion and exclusion criteria.

#### *4.1.5 Consent and Enrollment*

Following initial recruitment, patients will be scheduled for an introductory and orientation appointment. Specific study details and requirements will be reviewed at that time, and if the patients express interest in participating, a formal consent will be reviewed.

If the patient successfully completes the consenting process, they will undergo initial assessments as described later in the protocol. At enrollment, all patients will be assigned a study identifier, with a master list maintained in a password protected database (Mayo server) linking the patient to the identifier. A goal of 25 patients will be enrolled into each arm of the study, with an estimated 120 enrolled to achieve this number (due to anticipated dropouts, failure to comply). It is estimated that 250 patients will need to be screened to enroll the 120 patients.

## **4.2 Study Schema**

Once patients have agreed to receive further information on the study, an initial consult will be established. Patients who are currently taking other therapies for PD will be requested to stop these therapies for a minimum of 4 weeks prior to the appointment to assure an adequate washout period prior to being enrolled.

During the initial appointment, the patient will receive a description of the study, initial education on how to use the device properly, and informed consent. Those consenting to the procedure will

receive initial study assessments (see below). Those wishing additional time to consider enrollment may be rescheduled to a later date if desired. Once consent is completed, the patients will be randomized into one of four groups: PTT 30 min 1x/day, 30 min 2x/day, 30 min 3x/day, or control (no treatment).

Patients will then begin using the devices as previously instructed for the times appropriate to their group. After 3 months (+1.5 months permitted), patients will return for subsequent assessments (see below). After completion of the subsequent assessments, patients will begin a 3-month, open-label phase of the trial. During this period, the patients will be allowed to use the device for 30 minutes at a time, with a frequency to be determined by the patient.

After completion of the open-phase portion of the trial, patients will undergo final assessments, which are identical to the 3-month assessments. Patients will then be encouraged to self-report any additional adverse events (AE's) that they encounter over the subsequent 3 months after discontinuing the therapy and will be contacted by telephone for a final question / adverse event assessment (9 months after study initiation).

#### *4.2.1 Initial Study Assessments*

- Obtained prior to randomization
- Objective assessments – to be obtained by providers blinded to study arm
  - Penile length – measured from pubic symphysis to glanular corona and penile tip
  - Penile curvature
    - Measured in A/P and lateral planes using a goniometer (per standard protocol)
    - Direction of curvature also assessed
    - Curvature document as uniplanar (i.e. 60 degrees dorsal, 30 degrees lateral) and composite (i.e. 90 degrees composite)
  - Distance to curve – measured from concave portion of curvature to corona of glans
  - Indentations / hourglass deformities noted
  - Where possible (patients may decline), photographs obtained of the penis in the lateral and dorsal curvature after a pharmacologic erection has been obtained (per routine curvature assessment protocol). Images will be de-identified.
- Questionnaire on prior relevant disease history
- Subjective questionnaires
  - IIEF-15
  - PDQ
  - Additional questions pre-treatment

#### *4.2.2 Subsequent Study Assessments*

- Obtained at 3 and 6-month time points
- Objective assessments – individual obtaining assessments will be blinded to study arm
  - Penile length – measured from pubic symphysis to glanular corona and penile tip
  - Penile curvature
    - Measured in A/P and lateral planes using a goniometer (per standard protocol)
    - Direction of curvature also assessed

- Distance to curve – measured from concave portion of curvature to corona of glans
- Indentations / hourglass deformities noted
- Photographs (if previously obtained and where possible) will be taken at the 3 and 6 month visits
- Subjective questionnaires (attached)
  - IIEF-15
  - PDQ
  - Additional questions (3 and 6-month form)

#### 4.2.3 *Randomization and Blinding Protocol*

Following enrollment and completion of the initial curvature assessment, patients will be categorized into one of six strata based on baseline variables (curvature 30-60 degrees, >60 degrees by dorsal primary, lateral primary, and ventral primary). Each strata will have a separate randomization table provided such that one of four possible outcomes will occur no less frequently than every four cases. This is done to better account for baseline variables that may impact outcomes and to assist with matching groupings appropriately.

The explanation of which grouping the patient is assigned will then be reviewed, and the patient will be provided with a RestoreX® device (if applicable).

#### 4.2.4 *Assessment of Curvature and Length*

To assure blinding of outcomes, where possible, men will have photographs obtained of the penis in the lateral and dorsal curvature after a pharmacologic erection has been obtained (per routine curvature assessment protocol). Images will be de-identified, and curvatures will be assessed in two planes (lateral and dorsal).

Penile length measurements will be obtained by two individuals using a standardized ruler prior to beginning the pharmacologic erection. Where possible, the same individuals will perform the measures at each visit.

### **4.3 Statistical Methods**

#### 4.3.1 *Data Handling*

All data will be recorded either by the patient themselves or by the provider directly onto printed forms. The information will then be entered into spreadsheets using the assigned study identifier. Information will remain de-identified throughout the remainder of the study period and will remain on password protected, Mayo servers.

#### 4.3.2 *Power Analysis*

This is the first study which will be performed for this specific device. As such, the objectives are to assess safety with various dosing protocols. Regarding our secondary end points of penile length and curvature improvement, prior studies evaluating the role of PTT in the early phase of PD have



demonstrated significant improvements with study sizes of 96 patients, which is consistent with the current study schema.[17]

A power analysis was also performed using ANOVA with anticipated sizing of 25 individuals into 4 arms. This provides an effect level of 0.3370 using 80% power, with 0.05 significance established for curvature assessment. Therefore, the study is likely powered to demonstrate large changes in curvature but may not be adequately powered to identify small or medium differences in curvature between groupings. The study is adequately powered to detect reasonable changes in penile length.

#### 4.3.3 *Statistical Analysis*

All data will be entered into JMP Pro 10.0.0 (SAS Institute, Cary, NC). Differences between groupings will be analyzed using tests appropriate to the specific conditions: Wilcoxon, matched-pairs, student's t-test, ANOVA, ANCOVA, chi-squared, or Fisher's tests. All relevant tests will be 2-sided, with a p-value of <0.05 defined as significant. Differences in AE's will be determined based on total number of reported events as well as individual assessments of each individual event.

During the first phase of the study, results will be analyzed as a whole to determine the percentage of men who were non-compliant (both in methods of utilizing the device and percentage of time spent using the device) or dropped out. These data will determine the ability of men to utilize the device as recommended. Data will be analyzed both with and without these non-compliant / dropout men included. Non-compliance will be determined by failure to bury the white indicator line regularly with straight stretch, failure to achieve 90 degree bending during majority of uses, and failure to perform traction for at least 90% of days recommended.

Analyses will be performed using comparisons within patients (changes from baseline to 3 months, from 3 months to 6 months, from baseline to 6 months) and between groupings. ANCOVA will be used (adjusting for baseline values of curvature direction, curvature degree, and baseline penile length). Additional analyses will be performed to analyze the impact of prior treatments (such as intralesional injections) on outcomes. The use of ANCOVA is anticipated to increase the effect size slightly to 0.302 (assuming R<sup>2</sup> value of 0.2 for curvature direction, curvature degree, and baseline penile length).

Assessments will also be performed comparing any degree of traction (i.e. groups 2-4) against no traction. Additional assessment will also be performed based on the total duration of traction applied (time per day multiplied by number of days used) to assess for differences in outcome variables.

## 5 SAFETY AND ADVERSE EVENTS

### 5.1 **Definition of Adverse Event**

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO) - any unanticipated problem or adverse event that meets the following three criteria:

Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4)

disability/incapacity - persistent or significant; (5) breach of confidentiality and (6) other problems, events, or new information (i.e. publications, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, AND

Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND

Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event - an untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event - adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include:

- Death
- Life threatening adverse experience
- Hospitalization
- Inpatient, new, or prolonged; disability/incapacity
- And/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All AEs that do not meet any of the criteria for serious, should be regarded as non-serious AEs.

## **5.2 Adverse Event Reporting Period**

For the current study, the treatment follow-up period is defined as 3 months following the last administration of study treatment or 9 months from the initiation of the study, whichever is greater.

## **5.3 Preexisting Condition**

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

#### **5.4 Post-study Adverse Event**

All unresolved AEs will be followed by the study team until the events are resolved, the subject is lost to follow-up, or the AE is otherwise explained. A review of AEs which the subject or subject's physician believe might reasonably be related to participation in the study will be performed at the 6 month follow-up as well as via telephone up to 3 months following study completion.

#### **5.5 Hospitalization, Prolonged Hospitalization or Surgery**

Any AE related to the study intervention that results in hospitalization or surgery should be documented and reported as a serious AE.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- *Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.*

#### **5.6 Recording of Adverse Events**

The study team will seek information on adverse events by specific questioning between baseline and the 3 month and 6 month visits. At 9 months from the date of study initiation, the patient will be contacted via telephone for an additional assessment of any adverse events experienced. Information on all adverse events will be recorded immediately in the adverse event section of the specific questionnaire as well as in an adverse event form (see **Attachment – Adverse Event Form**).

All adverse events occurring during the study period will be recorded. The clinical course will be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period will be followed up, to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be at least possibly related to the study treatment or study participation will be recorded and reported immediately.

#### **5.7 Reporting of Serious Adverse Events and Unanticipated Problems**

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Adverse Event Form. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

##### *5.7.1 Sponsor-investigator Reporting: Notifying the Mayo IRB*

An adverse event form will be completed for any serious adverse event. This will be reported to the Mayo IRB in a de-identified manner.

The study team will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

Information collected on the adverse event form (and entered into the research database)

- Subject's ID
- Description of adverse event
- The date the adverse event occurred and resolved (if applicable)
- Intensity
- Outcome
- Action taken to address
- Relationship to study
- Impact on study withdrawal
- Classification as serious or not

The sponsor-investigator will review all adverse event reports to determine if specific reports need to be made to the IRB. The sponsor-investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UIRTSOs will be reported to the IRB.

#### *5.7.2 Stopping Rules*

Any serious adverse event which is determined to reasonably be related to the study device by the sponsor-investigator will result in immediate discontinuation of the therapy. If 5 patients develop serious adverse events, the study will be halted with re-review required by the Mayo IRB prior to consideration of study resumption.

#### *5.7.3 Medical Monitoring*

Medical monitoring of serious adverse events will be performed by the study investigator on a monthly-basis if serious adverse events have been reported.

## 6 OTHER ISSUES

### **6.1 Conflicts of Interest**

Dr. Landon Trost is the inventor and developer of the RestoreX® device and is currently the only consultant-level provider specializing in the treatment of PD at Mayo Clinic Rochester. The potential conflict of interest with publishing studies of this nature has been reviewed with the Mayo Clinic Conflict of Interest Review Board, and following review, it has been determined that Dr. Trost is able to conduct these studies as a Primary Investigator.

### **6.2 Regulatory Information**

PathRight Medical has registered the RestoreX® device with the FDA as a Class I device, similar to limb orthotics. The device is available without a prescription and may be purchased by the general public. As such, clinical studies are not required prior to its routine use, and the current studies are being done as an investigator-initiated project to determine its potential role in treating PD. The device's FDA registered indication is for the correction of deformity associated with PD, and the current study falls within the labeling of the device.

## 7 LEGEND OF ABBREVIATIONS

AE – Adverse event  
ED – Erectile dysfunction  
PD – Peyronie's disease  
PTT – Penile traction therapy  
RCT – Randomized controlled trial

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