

# ERYTHROPOIETIN TO ENHANCE RECOVERY OF ERECTILE FUNCTION IN MEN FOLLOWING RADICAL PROSTATECTOMY

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## **Johns Hopkins Medicine - eIRB Protocol (eForm A)**

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### **1. Abstract**

This research proposal aims to explore the efficacy of recombinant human erythropoietin versus placebo in promoting the recovery of erectile function in patients undergoing bilateral nerve-sparing radical prostatectomy for clinically localized prostate cancer. The proposal represents a translational objective deriving from findings from the Burnett urological laboratory that have defined neuroprotective and neurotrophic roles of erythropoietin involving the penile autonomic innervation following cavernous nerve injury. We have completed preclinical studies in a rat model of cavernous nerve injury that mimics the cavernous nerve trauma of radical prostatectomy in which we showed erythropoietin potently promotes the recovery of erectile function. We have also shown that the erythropoietin receptor is expressed in rat major pelvic ganglia and cavernous nerves and preliminarily confirmed similar findings in innervation of the human penis. This work suggests the potential benefit of using erythropoietin to promote erectile function recovery rates in men undergoing radical prostatectomy and other pelvic surgeries. A retrospective comparison of 36 patients at Johns Hopkins suggested a benefit in erectile function for patients receiving erythropoietin. Our hypothesis is that erythropoietin offers neuroprotection for the penile autonomic innervation in men undergoing nerve-sparing radical prostatectomy, and we plan to conduct a randomized controlled trial to demonstrate enhanced recovery of erectile function postoperatively.

**Specific Aim: To evaluate the effect of short-term perioperative recombinant human erythropoietin administration on erectile function recovery in men undergoing bilateral nerve-sparing radical prostatectomy.** The research proposal will test the hypothesis that erythropoietin exerts neuromodulatory effects that will result in a reduced time interval of erectile dysfunction and an improved rate of erection recovery after this surgery. The aim relates to the knowledge that nerve trauma occurs even during cavernous nerve-sparing radical prostatectomy and this neuropathic event affecting the penis largely accounts for the temporary or permanent erectile dysfunction observed in many men undergoing the surgery. The investigation will apply a single center, randomized, double-blind, placebo-controlled 12 month study design and employ validated instruments to assess erectile function, urinary continence, and health related quality of life status.

### **2. Study Procedures**

The study design will be a single center, randomized, double-blind, placebo-controlled, 2-arm study, comparing the effects of recombinant human erythropoietin vs. saline placebo on erectile function recovery in men after bilateral nerve-sparing radical prostatectomy. The dosing regimen: a three (3) day

Date: March 16, 2017

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intensive treatment of 300 units/kg subcutaneously and then 33,000 units intravenously was used in a previously reported clinical trial of erythropoietin for acute stroke. Similarly, the dosing regimen for this clinical trial will be ~300 units/kg subcutaneously for a 3-day treatment plan – the exact dose will be 20,000 units given as a subcutaneous treatment on the day prior to surgery and 20,000 units given subcutaneously on the day of and day after surgery.

The sample size will be 25 patients randomized to each study arm (50 patients total). Study procedures will involve screening and informed consent after initial consultation, baseline evaluation including medical clearance and completion of validated questionnaires, randomization, therapy (preoperative day dosing, dosing 0-2 hours prior to surgery, postoperative day 1 dosing), follow-up with blood draw for hematocrit and hemoglobin levels at 2 weeks post-op and then follow-up (completion of efficacy questionnaires at 3, 6, 9 and 12 months postoperatively). Assessment tools will consist of the following questionnaires which will be administered online using a REDCap site hosted by the Data Informatics Services Core within the Johns Hopkins Biostatistics Center or via mail per patient preference: IIEF questionnaire, the Quality of Erection Questionnaire (SEQ), and the version of the Expanded Prostate Cancer Index Composite (EPIC) that combines the Short Form Health Survey (SF-12) and AUA Symptom Index (AUA-SI). Standard practice associated with surgery, blood transfusion and postoperative laboratory testing will be performed. Patients will be prescribed a phosphodiesterase type 5 inhibitor (sildenafil, tadalafil or vardenafil) at 1 month following surgery to be used as conventional “on-demand” therapy. Adverse event monitoring will be performed. PSA monitoring is recommended at 3 and 12 months with the definition for biochemical recurrence set a PSA of 0.2ng/mL (rising from an undetectable level after surgery).

#### EPO Erection Recovery following RRP Protocol

	Consult	Baseline Eval	Pre-Op Day	Surgical Day	Post-Op Day 1	Post-Op Day 2	Two Weeks Post-Op	One Month Post-Op	Three Months Post-Op	Six Months Post-Op	Nine Months Post-Op	Twelve Months Post-Op
Informed Consent	✓											
Medical Clearance		✓										
IIEF <sup>1</sup>		✓						✓	✓	✓	✓	✓
SEQ		✓						✓	✓	✓	✓	✓
EPIC, SF12, AUASI <sup>1</sup>		✓						✓	✓	✓	✓	✓
Randomization	✓											
Blood work (HCT)			✓	✓	✓	✓	✓					
EPO Administration			✓	✓	✓							
RX – (Phosphodiesterase type 5 inhibitor)								✓				
AE monitoring <sup>2</sup>			✓	✓	✓	✓		✓	✓	✓	✓	✓
PSA monitoring									✓			✓

<sup>1</sup>Questionnaires will be administered online using REDCap or via mail per patient preference

<sup>2</sup>Postoperative AE monitoring will be performed by an RN or MD via telephone

**An IND# application has been filed and approved by the FDA for this protocol, IND 100,709.**

Date: March 16, 2017

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Application Number: IRB00048594

### 3. Inclusion/Exclusion Criteria

#### Inclusion Criteria:

1. Male sex 40 to 65 years of age with localized prostate cancer (clinical stage  $\leq$  T2a, Gleason grade  $\leq$  3+4=7 (Gleason 8 or 4+3=7 will be excluded), PSA  $<$  10 ng/mL)
2. Scheduled to undergo curative radical prostatectomy applying bilateral nerve-sparing procedure
3. Intact pre-surgical erectile function (International Index of Erectile Function [IIEF]-5 / Sexual Health Inventory for Men (SHIM) score  $\geq$  22)
4. Willingness to attempt intercourse at least 5 times per month following surgery.
5. Has a sexual partner of at least 6 months with current sexual activity (within the past 4 weeks)
6. Pre-surgical hematocrit  $\leq$  48.

#### Exclusion criteria:

1. Known penile deformity or a history of Peyronie's disease
2. Pre or post operative androgen therapy
3. Pre or post operative radiation therapy
4. Taking anticoagulation therapy
5. History of sickle cell anemia
6. History of high or low blood pressure that is not controlled
7. Taking nitrates medications
8. History of heart problems such as angina, heart failure, irregular heartbeats, or myocardial infarction
9. History of drug or alcohol abuse
10. Current smoker has a 20 pack/year history of cigarette smoking
11. History of acute or chronic depression
12. History of liver problems or kidney problems
13. History of retinitis pigmentosa or severe vision loss, including a condition called NAION
14. History of spinal trauma or surgery to the brain or spinal cord
15. Other contraindications to the use of PDE 5 inhibitors
16. Patient is currently participating in another clinical investigation that would serve as a contraindication to administering erythropoietin.

### 4. Drugs/ Substances/ Devices

Erythropoietin (EPO) is a cytokine-hormone that stimulates erythropoiesis under hypoxic conditions. Recently, EPO protein and its receptor have been found to be abundantly expressed within the central and peripheral nervous systems.<sup>6, 7</sup> Exogenous administration of EPO in animal models focusing on brain, spinal cord, and sciatic nerve injury has resulted in attenuated neuronal damage and hastened recovery.<sup>8-10</sup> In humans, a recent clinical trial confirmed the therapeutic efficacy and safety of recombinant human EPO (rhEPO) administration in patients suffering from acute ischemic stroke.<sup>11</sup> The recently established role of EPO as a neurotrophic factor makes it an attractive drug to evaluate in the context of neurogenic erectile dysfunction.

Date: March 16, 2017

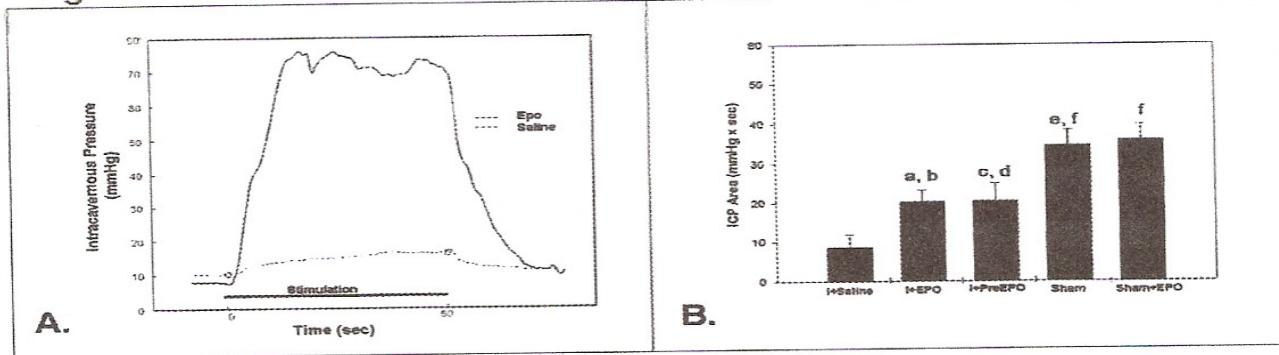
Principal Investigator: Mohamad E. Allaf, M.D.

Application Number: IRB00048594

This body of work stimulated a study in our laboratory to investigate the effects of EPO administration on a validated cavernous nerve injury rat model of erectile dysfunction.<sup>12</sup> Male Sprague-Dawley rats underwent unilateral CN transection with excision of a 5mm segment of the contralateral CN, as described previously.<sup>13</sup> A group of animals received daily EPO treatment, and a group received EPO pretreatment (24 hours and 1 hour prior to injury). The appropriate control groups consisting of saline treatment and pretreatment as well as a sham group (nerve dissection but no injury) were also included in this study. On day 14 following the injury, the rats underwent electrical stimulation of the transected nerve with simultaneous intracavernous pressure (ICP) and systemic arterial pressure monitoring. This model of nerve injury endures a reproducibly exact peripheral nerve injury while preserving the alignment of the CN permitting nerve recovery and simultaneously serving to connect the measured erectile response exclusively to the recovery of the injured nerve supply.

Exogenous treatment with daily doses of rhEPO starting 24 hours prior to CN injury preserved erectile function to a greater extent than saline treatment at 14 days following injury (Figure 1). Erection recovery, calculated as stimulated ICP area above the baseline pressure indexed to systemic pressure, was significantly greater for rats treated with daily rhEPO than for controls treated with saline ( $20.3 \pm 2.9$  versus  $8.6 \pm 3.2$ ,  $p < 0.05$ ). Daily treatment for 14 days resulted in a significant increase in the hematocrit values of treated animals (51.4 vs. 65.8,  $p < 0.01$ ). Because of the clinical ramifications of this effect and in light of data supporting the efficacy of pretreatment regimens in the context of nerve injury, a group of rats underwent a pretreatment protocol. Pretreatment with rhEPO (24 hours and 1 hour prior to CN injury) resulted in erection recovery comparable to that of daily treatment ( $20.3 \pm 4.0$  versus  $20.3 \pm 2.9$ ,  $p = 0.99$ ) without significant changes in hematocrit values (48.9 vs. 48.2,  $p = 0.56$ ). Treated animals achieved recovery of erections to approximately 60% of those achieved by sham treated rats. Treatment of sham animals with daily rhEPO had no effect on erectile responses after 14 days.

**Figure 1.**



- Representative tracing showing ICP responses to CN electrical stimulation. In the rhEPO treated animal, stimulation of the transected CN produced substantial erection recovery in contrast to the saline treated animal.
- Mean ICP area normalized to the systemic pressure  $\pm$  SEM when stimulating transected right CN after treatment with saline, rhEPO daily, and rhEPO pretreatment versus sham treatment. (I+Saline=CN injury treated with saline, I+EPO=CN injury treated with daily rhEPO, I+PreEPO=CN injury pretreated with rhEPO, Sham=Sham animals treated with saline, Sham+EPO=Sham animals treated with daily rhEPO). a,  $p < 0.02$  vs. I+Saline; b,  $p < 0.01$  vs. Sham; c,  $p < 0.04$  vs. I+Saline; d,  $p < 0.02$  vs. Sham; e,  $p = 0.94$  vs. Sham+EPO; f,  $p < 0.001$  vs. I+Saline.

To identify the presence of EPO receptors in major pelvic ganglia (MPG) and penile tissues, we performed immunohistochemistry on rat tissue sections. EPO receptor was localized to the neuronal

Date: March 16, 2017

Principal Investigator: Mohamad E. Allaf, M.D.

Application Number: IRB00048594

bodies within the MPG. RT-PCR confirmed the presence of EPO receptor mRNA in MPG tissue. EPO receptor mRNA levels were unchanged one day after injury and saline treatment but were increased by approximately 7 fold with injury and EPO treatment at the same time point. EPO receptor immunoreactivity in the penis was observed in the penile dorsal nerves, sinusoidal endothelium of the corpus cavernosum, and endothelial cells lining the dorsal vein and arteries. In addition, preliminary immunolocalization studies of human tissues reveal positive staining for the EPO receptor in the axons of widely excised neurovascular bundles. All slides processed without primary antibody or with blocking peptide showed no staining.

Electron microscopy was used to examine the CN distal to the site of injury and to assess axonal regeneration. The number of axons per Remak bundle in addition to the morphology of these axons was used to determine regeneration within the CN. Sham (intact) animals had a mean of  $4.9 \pm 0.2$  axons per Remak bundle while injured animals treated with saline had a mean of  $1.0 \pm 0.1$  ( $p < 0.001$ ). Daily rhEPO treatment resulted in a greater recovery of axons per Remak bundle when compared to saline treated animals ( $2.7 \pm 0.2$  versus  $1.0 \pm 0.1$ ,  $p < 0.001$ ). Sprouting of unmyelinated fibers typically passes through a phase in which Remak bundles contain very small unmyelinated axons or axons in polyaxonal pockets.<sup>14</sup> Such profiles were evident in all rhEPO treated animals, suggesting neuronal regeneration.

Thus, we have shown that EPO promotes the recovery of erectile function in a rat model of nerve injury and that the EPO receptor is expressed in penile nerves and endothelium of penile blood vessels.

## 5. Study Statistics

The primary outcome variable is the patient's score on the IIEF questionnaire (erectile function domain) at 3, 6, 9, and 12 months post-surgery.

The secondary outcome variables will be the patient's scores on the QEQ, combined EPIC/SF-12/AUASI questionnaires, other domains of the IIEF questionnaire, and change in hemoglobin.

For statistical analysis based on ANOVA, the sample size is powered for a power of 80% with one-sided alpha of 0.05 showing a sample size of 23 patients in each arm is necessary to detect an expected difference of 5 points in IIEF scores (i.e. 20 vs. 15) at 6 months post-surgery. Therefore, the study is planned to enroll 25 patients in each arm.

## 6. Risks

Completion of the questionnaires and administration of EPO are the only 2 procedures from this protocol that are outside of the realm of standard of care for the radical prostatectomy patient. All of the questionnaires will be completed by the participants pre-operatively allowing them time to assess if this activity is something they are willing to complete 4 times post-operatively. If the questionnaires cause any type of discomfort or uneasiness at that time or any time during the study, the participant can decide to end their involvement with the protocol.

Date: March 16, 2017

Principal Investigator: Mohamad E. Allaf, M.D.

Application Number: IRB00048594

Possible adverse effects of EPO include pain, redness or swelling at the injection site, headache, joint or muscle pain, nausea, vomiting, indigestion, stomach pain, diarrhea, constipation, runny nose, sneezing, difficulty falling or staying asleep, excessive sweating, or rash.

Serious adverse effects associated with EPO (extremely rare) include anaphylaxis, cerebrovascular accident, deep venous thrombosis, hypertension, acute left ventricular failure, myocardial infarction, pulmonary embolism, seizure, thrombotic disorder, hemoptysis, chronic cough, production of antibodies causing severe anemia, transient ischemic attack, aphasia, confusion and death.

The occurrence of any serious adverse effects will end the patient's participation in the study and halt enrollment in the study to determine the safety of continuing the study. Each and every possible adverse effect of EPO will be investigated and treated individually to minimize the participant's discomfort. The safety of having the individual complete the study will also be assessed on an individual basis. At any time the participant can decide to terminate his participation in the study and no penalty or loss of benefits to which they are entitled.

## **7. Confidentiality**

Paper consent forms, enrollment check sheets, and other source or study documentation will be kept in a study binder. This binder will be stored in a locked office available only to the study team. Electronic data will be housed in a secure password protected REDCap database maintained by the Data Informatics Services Core within the Johns Hopkins Biostatistics Center. Only the study team will have access to this secure database. Of note, to maintain the protected healthy information of patients enrolled in this study, only the study Principal Investigator and primary coordinators will have the ability to export data containing identifying information from this master database. For the purposes of analysis, only de-identified data will be exported.

## **8. Benefits**

The patients' conditions may improve as a result of participation in this study, specifically as related to erectile function. However, there is no guarantee of this. The information from this research study may lead to a better treatment in the future for people with prostate cancer. The patients may not benefit from participation in this study. Their conditions may not get better or may become worse while they are in this study.

## **9. Payment and Remuneration**

There will be no payment or remuneration for the participants in this study.

## **10. Costs**

The cost of the EPO will be covered by the study. There are no other anticipated costs outside of usual care. The participant's insurance, as part of routine care after radical prostatectomy, will be charged for

Date: March 16, 2017

Principal Investigator: Mohamad E. Allaf, M.D.

Application Number: IRB00048594

the PDE5 inhibitor drugs such as Viagra, Cialis or Levitra. If the PDE5 inhibitor (Viagra, Cialis or Levitra) is not covered by the participants insurance, they will be responsible for the bill.

Date: March 16, 2017

Principal Investigator: Mohamad E. Allaf, M.D.

Application Number: IRB00048594

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