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A Study Evaluating Intraoperative Application of Platelet-Rich Plasma to the Neurovascular Bundles During Nerve-Sparing Radical Prostatectomy: Initial Technical Description and Prospective Early Postoperative Outcomes Analysis

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Version No.	Date	Major Changes
1	09 Mar 16	Initial
2	08 Apr 16	UNK
3	08 Jun 16	UNK
4	16 May18	6.1: Updated baseline PSA and CBC w/differential documentation procedure; 6.2: AE assessment via medical record review; 6.3: AE assessment and vitals collected via medical record review; 6.4: visit 4 may be done on site or remotely Outside records for physical exam and vitals will not be requested if visits are done remotely. 6.5: visit 5 may be done on site or remotely. Outside records for physical exam and vitals will not be requested if visits are done remotely. Allowable PSA window is +/- 21d; 6.8: Protocol Schedule of Events was

		updated
5	11 June 18	6.4: visit 4 Outside records for physical exam and vitals will be requested if visits are done remotely. 6.5: visit 5 Outside records for physical exam and vitals will be requested if visits are done remotely

Table of Contents

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
ED	Erectile Dysfunction
EPIC	Expanded Prostate Cancer Index Composite
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IDE	Investigational Device Exemption
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
NVB	Neurovascular Bundle
PHI	Protected Health Information
PI	Principal Investigator
PRP	Platelet rich plasma
RP	Radical Prostatectomy
PSA	Prostate-Specific Antigen
SAE	Serious Adverse Event/Serious Adverse Experience
SHIM	Sexual Health Inventory for Men
SOP	Standard Operating Procedure

Study Summary

Title	A Study Evaluating Intraoperative Application of Platelet-Rich Plasma to the Neurovascular Bundles During Nerve-Sparing Radical Prostatectomy: Initial Technical Description and Prospective Early Postoperative Outcomes Analysis
Running Title	PRP Application During RP
Protocol Number	16-001320
Methodology	Open label
Overall Study Duration	18 months
Subject Participation Duration	18 months
Single or Multi-Site	Single site
Objectives	To evaluate the safety, tolerability, feasibility and efficacy of using platelet rich plasma to facilitate early nerve healing and decrease erectile dysfunction after nerve-sparing radical prostatectomy.
Number of Subjects	20
Diagnosis and Main Inclusion Criteria	Post-surgical erectile and urinary dysfunction. Main inclusion criteria are men, aged 50-60 years, with normal sexual function and regular sexual partner, undergoing RP for newly diagnosed prostatic adenocarcinoma.
Study Product, Dose, Route, Regimen	Autologous Platelet-Rich Plasma The dose is approximately 1,000,000 platelets/mL and the product is applied topically to the neurovascular bundle once during radical prostatectomy
Duration of Administration	One time drug administration with duration of drug application is approximately 4 hours.
Reference therapy	None
Statistical Methodology	The safety evaluation will focus on the number of adverse events including local reactions, expected serious adverse events and unexpected serious adverse events. All events will be collected, recorded and assessed for severity as a means to facilitate the reporting process. All patients will undergo an assessment of sexual and urinary function and oncologic outcomes at 3, 6, 9, 12 and 18 months after surgery. All patients will be evaluated for perioperative complications, length of stay, and need for blood transfusion.

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures. The described study will be conducted in compliance with the protocol and associated Federal regulations, and all applicable institutional research requirements.

1.1 Background

Prostate cancer is a common problem worldwide with an estimated incidence of 1.1 million cases and 307, 000 deaths in 2012. Advancing age, black race, and poor health literacy are known risk factors for development of prostate cancer. Radical prostatectomy remains the most common surgical treatment for prostate cancer with excellent oncologic outcomes. With the development of anatomic RP, ED after surgery has decreased but the risk is still a significant treatment concern. Even with nerve-sparing RP, a significant proportion of man can experience transient or even permanent ED. The etiology of ED after nerve-sparing RP is multifactorial, however common factors contributing to the problem related to nerve damage secondary to thermal or mechanical trauma.[1-3]

Recovery of sexual function after RP may depend on nerve healing or nerve-regrowth from the remaining NVB. Until now, this has been thought to be a time-dependent process. New evidence suggests that growth factors play an important role in this process. Platelets are known to contain many growth factors such as platelet-derived growth factor, insulin growth factor 1, vascular endothelial growth factor and transforming growth factor beta. At the time of RP, whole blood containing platelets and other hemostatic substances is observed to have an intraoperative impact on repairing the neurovascular bundle. At the time of RP, platelets are functioning in a homologous manner to counteract the surgical trauma required to remove the prostate. At the time of surgery, the platelets demonstrate a physiologic response by releasing growth factors to help repair the NVB.

Growth factors such as vascular endothelial growth factor, insulin growth factor -1, and brain-derived growth factor have been shown to promote neuronal regeneration and increase the presence neuronal nitric oxide synthase in cavernosal nerve tissue.[1] A prior report has evaluated the use of dehydrated human amnion/chorion membrane allograft nerve wrap as a means to deliver growth factors and anti-inflammatory substances during RP. In this study, allograft enhanced functional recovery yet this approach required placement of a foreign body.[4]

1.2 Investigational Agent

PRP is prepared by specialized centrifugation of a patient's own whole blood.[5] The PRP product that is created is a platelet concentrate of approximately 1,000,000 platelets/mL. The morphology and function of the platelets in the whole blood sample used to create the product and morphology and function of the platelets in the prepared PRP sample are identical. In both instances during RP, the platelets are activated to release growth factors that help repair the NVB that is traumatized during surgery.

In general, platelets are known to contain many growth factors such as platelet-derived growth factor, insulin growth factor 1, vascular endothelial growth factor and transforming growth factor beta that can have a healing effect and regenerative effect on nerve tissue. By concentrating the number of platelets by volume, the healing and regenerative impact of PRP on the NVB is thought to be augmented. The basic function of the platelet is not changed, but the repairing effect on the NVB is increased by the fact that the concentration of the platelets compared to whole blood has been increased.

1.3 Preclinical Data

In animal models, application of PRP has promoted healing of cavernous nerves in an experimental nerve crush model when compared to controls.[1-3]

1.4 Clinical Data to Date

To date, there is no available clinical research data on use of PRP application to the NVB intra-operatively at the time of nerve-sparing RP. Clinical application of PRP using a similar topical application, however, has been found to be safe and efficacious for a variety of musculoskeletal indications including osteoarthritis, chronic tendinopathy, nerve injury and ligamentous injuries.[5-10]

1.5 Dose Rationale and Risk/Benefits

The PRP sample will be prepared in the operating room from a sample of whole blood while the patient is undergoing RP. The PRP sample will be prepared by trained personnel from the Mayo Clinic Division of Transfusion Medicine using a commercially available, FDA-cleared, platelet concentration device in accordance with the manufacturer's instructions ((510K# BK110046; Angel® Concentrated Platelet Rich Plasma [cPRP] System, Cytomedix, Inc., Gaithersburg, MD USA). The Division of Transfusion Medicine has developed a detailed SOP that all staff using the Angel® system must follow in order to operate the Angel® device (http://mayoweb.mayo.edu/txmed-docs/documents/002696.pdf).

At the present time, the Angel® device is used in routine clinical use in the department of orthopedics and physical medicine and rehabilitation at Mayo Clinic. The Angel® system yields platelet concentrations of approximately 1,000,000 platelets/ mL of plasma. This dose of PRP has been demonstrated to have clinical efficacy and safety for topical applications used in orthopedic and physical medicine and rehabilitation applications.

Clinical experience with the Angel® device has demonstrated that a sample of 180 mL of whole blood will yield approximately 10 mL of PRP. This dose would be divided equally and will permit even topical application to the NVB intra-operatively at RP. The study proposes a one-time dosage period and clinical studies to date report that the duration of action for PRP is approximately 4 hours.

Risks from study participation may be related to obtaining the whole blood to produce the PRP sample or the effects of the PRP sample on the healing process after surgery. The collection of

blood would be obtained under general anesthesia required for RP using sites needed for the general anesthetic. Obtaining the whole blood could results in pain, bruising, and infection at the needle site. Obtaining a collection of blood could also have an adverse effect the patient's circulating blood volume and could result in lightheadedness or hypotension after surgery. In some instances this could require that a blood transfusion be given. Since the risk of blood transfusion for RP ranges from <1 to 5%, the independent risk of the blood collection alone requiring a postoperative blood transfusion is very low.

Platelets contain growth factors and the hypothesis of the study is that the growth factors will augment healing of the NVB after surgery. There is a possibility that the growth factors could cause adverse healing of the NVB. There is also a possibility that if residual prostate tissue is present that growth of the tissue could occur. There is a low risk that if the residual prostate tissue were cancerous that the growth factors could contribute to a higher chance of cancer recurrence. The relatively short term effect (<4 hours) of PRP applied topically will significantly decrease the risk of promoting growth of prostate tissue. It is also defined approximately 15-20% of men undergoing radical prostatectomy can expect to have recurrence after surgery. Based on the physiology of growth factors, it is thought the risk of PRP independently increasing risk of prostate cancer recurrence is very unlikely.

Benefits are thought to outweigh the risks of the study. Topical application of autologous PRP at the time of RP will permit supraphysiologic doses of growth factors to be present on the NVB. The growth factors may help promote healing and/or decrease the surgical trauma associated with RP. This may augment healing and recovery of erectile function after RP as measured during the 18 month study duration. Subjects will be asked to complete questionnaires regarding urological symptoms, quality of life (urinary control and ED) before and at 3, 6, 9, 12, and 18 months following the procedure.

2 Study Objectives

Primary Objective: To evaluate the safety and tolerability of using platelet rich plasma on the NVB after nerve-sparing radical prostatectomy.

Secondary Objective(s):

- To assess the feasibility of applying 1 dose of PRP intra-operatively at the time of bilateral nerve-sparing RP in 20 men with prostatic adenocarcinoma.
- To assess preliminary clinical benefit/efficacy of using PRP in facilitating early nerve healing and decreasing ED at 3, 6, 9, 12 and 18 months after nerve-sparing RP.To assess change in urological function by measuring urinary control before and at 3, 6, 9, 12 and 18 months after PRP treatment during nerve sparing surgery.

3 Study Design

3.1 General Design

This is an open label, human study evaluating the safety and tolerability, feasibility, and efficacy, s of PRP applied in topical fashion intra-operatively during RP. Subjects will be screened at outpatient clinic visit appointments and interested qualified subjects will be

consented and offered participation in this trial. The study aims to enroll 20 men with newly diagnosed prostatic adenocarcinoma that are planning to undergo bilateral nerve-sparing RP. Once written consent has been obtained baseline functional and laboratory assessments will be obtained and patients will be followed for the expected duration for study participation of 18 months.

Since the present study is a single-arm study, evaluation of safety and efficacy parameters will have to be performed using benchmark outcomes from historical controls. At Mayo Clinic, all patients undergoing RP are included in the Mayo Clinic Prostatectomy Registry. The prostatectomy registry is prospectively maintained by study nurses. The prostatectomy registry maintains detailed oncologic and quality of life data using PSA testing and the same validated questionnaires proposed by the current study. The comparator for the present study would be other subjects from the Mayo Clinic Prostatectomy Registry that underwent bilateral nerve-sparing RP within the same study dates and met all of the other inclusion and exclusion criteria for the present study but did not have PRP applied intraoperatively to the neurovascular bundles.

3.2 Primary Study Endpoints

Primary Objective:
To evaluate the safety and tolerability of using platelet rich plasma on the NVB after nerve-sparing radical prostatectomy.

3.3 Secondary Study Endpoints

Secondary Objective(s):

- To assess the feasibility of applying 1 dose of PRP intra-operatively at the time of bilateral nerve-sparing RP in 20 men with prostatic adenocarcinoma.
- To assess preliminary clinical benefit/efficacy of using PRP in facilitating early nerve healing and decreasing ED at 3, 6, 9, 12 and 18 months after nerve-sparing RP.
- To assess change in urological function by measuring urinary continence before and at 3, 6, 9, 12 and 18 months after PRP treatment during nerve sparing surgery.

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

The study involves men newly diagnosed with prostatic adenocarcinoma that are selecting RP for treatment. The men identified for the study would be from the outpatient clinic setting and all men would be able to give appropriate informed consent.
The following are inclusion criteria for the study:

- Newly diagnosed, clinically localized prostatic adenocarcinoma
- Age 50 – 60 years
- Male gender
- Normal preoperative sexual function (as defined by Sexual Health Inventory for Men questionnaire score > 19; see attachment)

- Normal urinary continence (as defined by Expanded Prostate Cancer Index Composite, question 5, response = none, see attachment)Regular sexual partner

4.2 Exclusion Criteria

- Unable or unwilling to provide informed consent
- Vulnerable study populations
- Active systemic infection
- Diabetes Mellitus diagnosis
- Preexisting ED or urinary incontinence
- Metastatic or locally advanced prostatic adenocarcinoma on preoperative evaluation
- Men found grossly or pathologically to have locally advanced or metastatic disease at the time of RP
- An estimated blood loss of >750 mL at the time of RP
- Treatment prior to surgery with any form of hormones, antiandrogens or androgen deprivation therapy
- Use of an antidepressant, beta blocker or ED medication at the time of study
- Screening Men without a regular sexual partner
- Use of aspirin or heparin 2 weeks before RP
- Need for use of aspirin or heparin for 2 weeks or more after RP.

4.3 Subject Recruitment, Enrollment and Screening

Subjects will be recruited for the study in the outpatient clinic environment by the PI and Co-Investigators. Identified subjects will discuss the study with a Study Coordinator. At that time, the inclusion and exclusion criteria will be discussed as well as the rationale, the potential benefits, and potential risks associated with the study. The recruitment, enrollment, and screening procedures will occur in the outpatient clinic setting. If subjects want to proceed with the study, informed consent will be obtained by the study coordinator or investigator.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

A subject may withdraw at any time prior to RP. There are no adverse safety considerations in the study for those deciding to withdraw from the study. Subjects may choose to discontinue study participation after RP surgery and will be counted as withdrawn

A subject consenting to the study will receive PRP at the time of RP unless the surgical team decides intra-operatively to withdraw a subject from the study in the following situations:

- Estimated blood loss greater than 750 mL

- Evidence of disease grossly and/or pathologically that the prostate cancer is locally advanced or metastatic

- Documentation of the reason for withdrawal will be retained in the study files.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

As part of normal clinical care, subjects that have withdrawn from the study will still have routine postoperative monitoring after RP. Any collected study data from withdrawn subjects will not be included in the data analysis. Since all patients have their outcomes tracked after RP at Mayo Clinic, postoperative data would be available should this be needed as part of another study protocol.

4.4.3 Replacement of Subjects

If subjects withdraw from the study, they will be removed from the final study cohort. In the situation of a subject withdrawing from the study, we will continue to recruit subjects such that 20 total subjects complete the entire study with 18 months of follow-up.

5 Study Drug

5.1 Description

The PRP product will appear as a liquid.

5.2 Treatment Regimen

The PRP product will be created intra-operatively by personnel from the Division of Transfusion Medicine from a **180** mL sample of the patient's whole blood. An FDA-cleared platelet concentration device (Angel® Concentrated Platelet Rich Plasma [cPRP] System, Cytomedix, Inc., Gaithersburg, MD USA) in routine clinical use at Mayo Clinic in Rochester, MN will be used to create the sample of PRP that will be given one time in topical fashion onto the NVB during nerve-sparing RP. The application of PRP will take approximately 1 minute to perform and the treatment duration for the PRP product is estimated at 4 hours.

5.3 Method for Assigning Subjects to Treatment Groups

Not applicable.

5.4 Preparation and Administration of Study Drug

The PRP sample will be prepared in the operating room from a sample of whole blood while the patient is undergoing RP. The PRP sample will be prepared by trained personnel from the Mayo Clinic Division of Transfusion Medicine. The Division of Transfusion Medicine has developed a detailed SOP that all staff using the Angel® system must follow in order to operate the device (http://mayoweb.mayo.edu/txmed-docs/documents/002696.pdf). At the present time, the Angel® device is used in routine clinical use in the department of orthopedics and physical medicine and rehabilitation at Mayo Clinic in Rochester, MN. In many instances, the Angel® system yields platelet concentrations of approximately 1,000,000 platelets/ mL of plasma. During our planned study we will follow SOP 002696 prior to administration and confirm that the concentration of platelets over baseline be at least 2. This dose of platelets has been

demonstrated to have clinical efficacy and safety for topical applications used in orthopedic and physical medicine and rehabilitation applications.

In addition, the Division of Transfusion Medicine is accredited by the American Association of Blood Banks to perform perioperative activities at Mayo Clinic. Perioperative activities by definition include the intraoperative preparation of PRP. To achieve accreditation, an institution "shall have a structure that clearly defines and documents the parties responsible for the following activities: intraoperative acute normovolemic hemodilution; collection, storage, and administration of autologous blood products obtained during intraoperative and postoperative autologous blood recovery; and perioperative autologous product production. Products covered under these activities include but are not limited to autologous plasma for reinfusion, injection, or topical application, thrombin for topical application, and bone marrow aspirate concentrate for topical application."

The Angel® Concentrated Platelet Rich Plasma (cPRP) System is cleared for use in the U.S. by the FDA as an automated blood cell separator. The device operator's manual states it's indications for use specifically include the following: "To be used in the clinical laboratory or intra-operatively at the point of care for the safe and rapid preparation of platelet poor plasma and platelet concentrate (platelet rich plasma) from a small sample of whole blood or a small mixture of blood and bone marrow. The platelet rich plasma can be mixed with autograft and/or allograft bone prior to applications to an orthopedic site." The Angel device is contraindicated in cases where there is active systemic infection or systemic heparinization. In preparation of this research application we have reviewed the United States government electronic CFR (accessed March 3, 2016 and current as of March 1, 2016) part 1271 entitled "Human Cells, Tissues, and Cellular and Tissue Based Products." We believe that the PRP created in the study would be solely regulated under Section 361 of the Public Health Service Act on the basis of meeting all criteria included in part 1271.10:

- The PRP product created by the Angel® device is minimally manipulated.
- The PRP product created by the Angel® device is intended only for homologous use, following the labeling, advertising, or other indications of the manufacturer's objective intent.
- The PRP product created does not involve the combination of cells or tissues with another article except for water, crystalloid, or a sterilizing preserving or storage agent provided that addition of water, crystalloid, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the product.
- The PRP product created does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function.

Furthermore, according to part 1271.15 from the CFR, we note that our proposed use of PRP would fulfill item (b) that states, "You are not required to comply with the requirements of this part if you are an establishment that removes human cell tissue/products (PRP is an example) from an individual and implants such human cell tissues/products into the same individual during the same surgical procedure.

Since we meet all of the criteria established in part 1271.10 and also meet exception criteria listed in part 1271.15, we believe that the PRP created in this study would be solely regulated

under section 361 of the Public Health Safety Act and that regulation of the created product as a drug under section 351 of the Public Health Service Act would not apply. Accordingly, the need to pursue an IND application for the proposed use was not felt to be applicable. However, upon request for an exemption from IND regulations, FDA subsequently decided to regulate this study under an Investigational Device Exemption, (IDE) for the investigational use of an approved blood separation device.

5.4.1 Specifics of PRP Sample Preparation

To prepare the sample, **180** mL of whole blood will be obtained from the patient by venipuncture during the RP by Anesthesia personnel. The whole blood will be placed in the platelet concentration device and centrifuged following manufacturer's instructions. After final processing, the final PRP sample will consist of 10 mL of product that will be used for intra-operative application. The PRP created intra-operatively would be placed into a syringe labeled "PRP." Samples of whole blood and PRP will also be sent to the laboratory for analysis for quality control purposes, in accordance with Division of Laboratory Medicine SOP.[10]

During the RP procedure, PRP will be applied to the NVB after completion of the vesicourethral anastomosis and after conventional techniques have been performed to achieve adequate hemostasis. Conventional techniques for hemostasis include the placement of surgical clips or suture as required to bleeding sites on the neurovascular bundle. No additional hemostatic products will be applied to the neurovascular bundles during the study. PRP will be applied evenly to the entire length of the NVB by mechanical transfer of product. For robotic procedures, a laparoscopic spoon instrument will be used to deliver the PRP directly to the NVB. For open procedures, delivery of PRP will occur via PRP-labelled syringe. After application of PRP, the surgical team will then complete RP in standard fashion.

5.5 Subject Compliance Monitoring

Not applicable.

5.6 Prior and Concomitant Therapy

The following concomitant medicines are not permitted during the study:

- Any type of androgen deprivation therapy
- Aspirin and heparin for 2 weeks before or 2 weeks after the date of PRP application
- Use of an antidepressant, beta blocker or ED medication at the time of study screening

5.7 Packaging

The PRP will be made intra-operatively and will be placed into a syringe labelled PRP. The PRP will be created from the patient for autologous use and none of the created PRP will be removed from the operating room.

5.8 Masking/Blinding of Study

Not applicable

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

Not applicable

5.9.2 Storage

Not applicable

5.9.3 Dispensing of Study Drug

Not applicable

5.9.4 Return or Destruction of Study Drug

Not applicable

6 Study Procedures

6.1 Visit 1; Screening and Baseline

Potential study subjects will be identified by study staff, will be provided ample time to review the informed consent document, discuss the study procedures and contents of the ICF, have all questions answered, have their medical history reviewed, vitals taken, and a physical examination performed. The baseline quality of life assessments with Sexual Health Inventory for Men and the Expanded Prostate Cancer Index Composite will be completed by the subject at this visit, if not done earlier. Baseline CBC with differential and platelet count and serum PSA samples will be obtained. If a PSA and CBC with differential and platelet count have not been performed during clinic visits at Mayo Clinic within the year prior to the screening visit and the subject has scheduled clinical labs before the screening visit, an order will be placed for the baseline PSA and CBC with differential and platelet count to ensure there is proper record of test result in the Mayo Clinic medical record. If a PSA and CBC with differential and platelet count have been performed outside of Mayo Clinic within the year prior to the screening visit and the subject does not have scheduled clinical labs before the screening visit, outside results may be used to satisfy this study visit with copies retained in study files. The study coordinator will confirm the contact information of the outside laboratory facility at the time of the screening visit and will request outside laboratory results if not already available in the Mayo Clinic medical record. However, all study eligibility requirements; including a review of current medical conditions and medications as well as written informed consent must be documented by study staff and reviewed for acceptability by an Investigator prior to enrolling the subject into the study. Documentation of any subjects who were consented but subsequently failed the screening requirements, including the reason for screen failure, will be retained in study files. A screening/enrollment log will be maintained.

6.2 Visit 2; Surgery

At the time of radical prostatectomy, topical PRP will be prepared and applied topically to the NVB. An assessment of adverse events will be conducted via medical record review by the study coordinator.

6.3 Visit 3: Post-operative Day 2 (POD 2)

Subjects will undergo a review of their medical status and a physical examination. There will be a blood draw to assess CBC with differential and platelet count. An assessment of adverse events will be conducted by the study coordinator via medical record review. For visit 3 only, vital sign readings taken as part of standard of care will be abstracted via medical record review by the study coordinator.

6.4 Visit 4: Week 1

At approximately 1 week after surgery, the urinary catheter placed at the time of RP will be removed. This visit is timed at one week post RP to allow for the typical healing period prior to removal of catheter. If clinically indicated, the healing period may require more than 7 days, therefore this study visit may occur up to 21 days following the RP. This visit may be completed remotely rather than on-site, if the subject decided to have urinary catheter removal done locally. Contact with the subject may be by telephone or email, depending upon subject preference. The subject will undergo a postoperative check by study staff where quality of life status will be assessed with questionnaires. The Questionnaires may be mailed to the subjects (if visit is done remotely) with a self-addressed, postage paid, return envelope for completion and return to the study site by email, fax or regular mail and will be retained with subject study files. A physical examination by a Study Investigator will be performed and vitals will be taken if visit is completed on-site. An assessment for adverse events and concomitant medications review will be conducted by the study coordinator. Outside records for physical exam and vitals will be requested if visit is done remotely. The RP date will be considered Day 0 for determining future study visit windows. Per protocol, serum PSA has not been collected at this point and will continue to not be collected for remote visit

6.5 Visit 5: Week 12

At approximately 12 weeks after surgery, with an allowable visit window of +/- 14 days, subjects will undergo a postoperative check by study staff where quality of life status will be assessed with questionnaires. The Questionnaires may be mailed to the subjects with a self-addressed, postage paid, return envelope or emailed to the subjects for completion and return to the study site by email, fax or regular mail and will be retained with subject study files. This study visit may be completed remotely rather than on-site, if more convenient for the subject. Contact with subject may be by telephone or email, depending upon subject preference. Subjects will undergo a physical examination by a Study Investigator, have vitals taken, and have a serum PSA sample drawn. Adverse events will be assessed and concomitant medications will be reviewed by study coordinator. Outside records for physical exam and vitals will be requested by study staff if visit is done remotely. For subjects returning to the institution, the PSA sample will be drawn in the Mayo Clinic clinical laboratory. For subjects completing a remote visit, serum may be collected locally using a “mail-in” PSA kit mailed to the subject by study staff. This kit will be mailed back to Mayo Clinic for testing. The allowable PSA testing window is +/- 21d.

6.6 Visit 6: Month 6

At approximately 6 months after surgery, with an allowable visit window of +/- 14 days, subjects will undergo a study visit which may be completed remotely rather than on-site, if more convenient for the subject. Contact with subject may be by telephone or email, depending upon subject preference. The Questionnaires may be mailed to the subjects with a self-addressed,

postage paid, return envelope or emailed to the subjects for completion and return to the study site by email, fax or regular mail and will be retained with subject study files. For remote visits, the subject will be contacted to assess changes in concomitant medications and to assess if any adverse events have occurred since the previous study visit. Information obtained during telephone calls or other contact will be documented in the subject's study file. A serum PSA sample will be obtained. For subjects returning to the institution, the PSA sample will be processed in the Mayo Clinic clinical laboratory. For subjects completing a remote visit, serum may be collected locally using a "mail-in" kit to be mailed to the subject by study staff. This kit will be mailed back to Mayo Clinic for testing. Venipuncture may be obtained by a local physician or clinic. The allowable PSA testing window is +/- 21d.

6.7 Visits 7, 8 and 9: Months 9, 12 and 18

At approximately 9, 12 and 18 months after surgery, with allowable visit windows of +/- 14 days, subjects will undergo a study visit which may be completed remotely rather than on-site, if more convenient for the subject. For remote visits, the SHIM and EPIC Questionnaires may be sent to the subjects for completion and returned to the study site by mail, fax or email. A telephone call to the subject will be made to assess changes in concomitant medications and if any adverse events have occurred since the previous study visit. A serum PSA sample will be obtained. For subjects returning to the institution, the PSA sample will be analyzed in the Mayo Clinic clinical laboratory. For subjects completing a remote visit, the PSA sample may be obtained with venipuncture obtain locally and returned using a "mail-in" kit with analysis to be performed by the Mayo Clinic laboratory. The allowable PSA testing window is +/- 21d.

6.8 Protocol Schedule of Events

Study Activity	Screen/ Baseline	RP	POD 2	Wk 1	Wk 12	Mo 6[2]	Mo 9[2]	Mo 12[2]	Mo 18[2]
Visit number	**1**	**2 Day 0**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Allowable Visit Window from RP				+21d	+/- 14d	+/- 14d	+/- 14d	+/- 14d	+/- 14d
Consent	X								
Medical History	X								
Concomitant Meds	X			X	X	X	X	X	X
Eligibility Review	X								
Physical exam[3]	X		X	X	X				
Vital signs[2,3]	X		X	X	X				
Questionnaires[1,4]	X			X	X	X	X	X	X

CBC w/diff, platelets	X		X						
Serum PSA[4]	X				X	X	X	X	X
PRP topical application		X							
Adverse events evaluation		X	X	X	X	X	X	X	X

[1] SHIM and EPIC
[2] Vitals will be abstracted from the medical record for visit 3, post-operative day 2
[3] Week 1 and week 12 visits may be done on-site or via telephone interview or email. Physical exam and vitals will be performed for these visits if participant is able to return to Mayo Clinic. Outside records for physical exam and vitals will be requested if visits are done remotely.
[4] The 6, 9, 12 and 18 Month visits may be done remotely via telephone interview or email. Completed SHIM/EPIC Questionnaires may be returned to study site by mail, email or fax. PSA testing: A local clinic may be used for venipuncture, using mail in lab kit for sample return to Mayo Clinic. PSA testing window for week 12 and 6, 9, 12, 18 month visit is +/- 21d

7 Statistical Plan

7.1 Sample Size Determination

For the proposed trial, a sample of 20 subjects is proposed. This sample will permit a statistical description of that is required for the primary and secondary objectives. Use of 20 subjects is in the range normally enrolled for trials of this nature.

7.2 Statistical Methods

Descriptive Statistics

Univariate descriptive statistics and frequency distributions will be calculated, as appropriate for all variables. Baseline values for demographic, clinical, and outcome variables (primary and secondary) will be tabulated. Temporal trends in recovery of erectile function and urinary continence will be assessed. Normal sexual function will be defined as a Sexual Health Inventory for Men score of >19. Normal urinary continence will be defined as a response of "none" on question 5 of the Expanded Prostate Cancer Index Composite.

Handling of Missing Data

Subjects that miss follow-up appointments where data is gathered will be contacted to forward missing data records.

Multiplicity

Not applicable

7.3 Subject Population(s) for Analysis

Data from all subjects consented for the study and completing postoperative visits will be evaluated.

8 Safety and Adverse Events

8.1 Definitions

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) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, 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 IB, 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
- persistent or significant birth defect/anomaly

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 adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period
For this study, the study treatment follow-up period is defined as 18 months following the topical application of PRP at the time of RP.

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.

General Physical Examination Findings
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 AE must also be recorded and documented as an AE.

Post-study Adverse Event
All unresolved AEs should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the AE is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an AE if the serum hemoglobin on postoperative day 2 is <8 g/dL. If hemoglobin level is considered an AE, then patient should have hemoglobin monitored and if there is a downward trend or if clinical symptoms are associated with the value then blood transfusion should be considered.

Hospitalization, Prolonged Hospitalization or Surgery
Any AE that results in rehospitalization or prolonged hospitalization (greater than 1 week) should be documented and reported as a serious AE unless specifically instructed otherwise in this protocol. Any condition requiring surgery should be documented as an AE if the condition meets the criteria for an AE.

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

- The planned hospitalization for RP.
- The prolonged hospitalization for diagnosis not related specifically to RP.
- Surgical procedure not related to RP.

8.2 Recording of Adverse Events

At each contact with the subject, the study team must seek information on AE by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate AE section of an electronic adverse event worksheet. All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should recorded in the document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should 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 must be followed up, to determine the final outcome. Any serious AE that occurs after the study period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

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

8.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

For any SAE, an AE worksheet will be sent to the IRB. In this situation the PI and study coordinators will document the data related to the SAE on the event worksheet and notify the IRB using the standard reporting procedure. The sponsor-investigator will specifically report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

Information collected on the adverse event worksheet (*and entered in the research database)*:

- Subject's name:
- Medical record number:
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, surgery, or other intervention):
- If the adverse event was expected:
- The severity of the AE: (use a table to define severity scale 1-5)
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

8.3.2 Sponsor-Investigator reporting: Notifying the FDA

The sponsor-investigator will report to the FDA all unexpected, serious suspected adverse events and reactions according to the required safety reporting timelines, formats and requirements.

Unexpected fatal or life threatening suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the AE, will be reported as a serious suspected adverse reaction. This will be reported to the FDA by telephone or by fax using FDA Form 3500A, no later than 5 calendar days after the sponsor-investigator's initial receipt of the information about the event and the report will also be made in writing within 10 days as required under 21 CFR 812.150.

Other unexpected serious suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than

15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Any clinically important increase in the rate of serious suspected adverse reactions over those listed in the protocol or product insert will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Findings from other studies in human or animals that suggest a significant risk in humans exposed to the drug will be reported. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the sponsor-investigators initial receipt of the information about the event.

8.4 *Unmasking/Unblinding Procedures*

Not applicable

8.5 Stopping Rules

Not applicable

8.6 Medical Monitoring

It is the responsibility of the PI to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

Since the present study is a single-arm study, evaluation of safety and efficacy parameters will also be performed using benchmark outcomes from historical controls. At Mayo Clinic, all patients undergoing RP are included in the Mayo Clinic Prostatectomy Registry. The prostatectomy registry is prospectively maintained by study nurses. The prostatectomy registry maintains detailed oncologic and quality of life data using PSA testing and using the same validated questionnaires proposed by the current study. By using other subjects from the Mayo Clinic Prostatectomy Registry that underwent bilateral nerve-sparing RP within the same study dates (and those that met all of the other inclusion and exclusion criteria for the present study but did not have PRP applied intraoperatively to the neurovascular bundles), another means to compare the safety and preliminary evidence of efficacy will be achieved.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of HIPAA. Those regulations require a signed subject authorization informing the subject of the following:

- What PHI will be collected from subjects in this study
- Who will have access to that information and why

- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

9.4 Data Management

The process for managing data will be standardized for each patient using Case Report Form. Information will be recorded on the CRF directly at the time of study visits or completed based on entries made in the electronic medical. In situation where data is missing, subjects will be contacted to reconcile the missing data entries.

9.4.1 Data Processing

Data will be maintained in accordance with institutional research standards in an electronic format.

9.4.2 Data Security and Confidentiality

Data will be kept in an electronic format with confidentiality maintained by having only the study coordinators and investigators with access to the data. Subjects will not have their name recorded on the database and identification will only be made by registration/study code number and/or subject initials.

9.4.3 Data Quality Assurance

Study staff will cross check the accuracy of the database to the CRFs entries and source data.

9.4.4 Data Clarification Process

If there are concerns about the accuracy of the reported data, then the medical record will be reviewed for clarification. Subjects may be contacted as part of ongoing regular clinical care as part of their postoperative management of prostate cancer.

9.5 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports for the longest of these time frames:

1. If conducted under an IND, until 2 years after the marketing application is approved for the drug; or, if a marketing application is not submitted or approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified. OR
2. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

Periodic study monitoring will be provided on behalf of the Sponsor by staff from the Mayo Clinic Office of Research Regulatory Support. Monitoring may include but will not necessarily be limited to review of the study regulatory documents, source data and database entries throughout the duration of the study to help ensure the completeness, validity and integrity of the data. Original signed informed consent forms will be reviewed. Written monitoring reports with findings and recommended and suggested corrective actions will be provided to the sponsor, who will subsequently provide them to the IRB at time of annual continuing review.

The PI, assisted by delegated study staff, will also monitor study conduct and documents. PI and study staff meetings will be held bi-weekly.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, internal audits by the IRB, and external inspections governmental regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

12 Study Finances

12.1 Funding Source

This study will be funded internally by Mayo Clinic.

13 Publication Plan

The primary responsibility for the publication of results will be the principle investigator. No information from the study will be passed on to third parties. The study will be registered to ClinicalTrials.gov prior to subject recruitment and results will also be reported within 12 months of final data collection for the primary outcome.

14 References

1. Ding XG, Li SW, Zheng XM, Hu LQ, Luo Y. The effect of platelet-rich plasma on cavernous nerve regeneration in a rat model. Asian J Androl 2009; 11: 215-21.

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6. de Vos RJ, Weir A, van Schie HT, Bierma-Zeinstra SM, et al. Platelet-rich plasma injection for chronic Achilles tendinopathy: a randomized controlled trial. JAMA 2010; 303:144-9.

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9. Farrag TY, Lehar M, Verhaegen P, Carson KA, Byrne PJ. Effect of platelet rich plasma and fibrin sealant on facial nerve regeneration in a rat model. Laryngoscope 2007; 117: 157-65.

10. Finnoff JT, Fowler SP, Lai JK, Santrach PJ, Willis EA, Sayeed YA, and Smith J. Treatment of chronic tendinopathy with ultrasound-guided needle tenotomy and platelet-rich plasma injection. PM R 2011; 3: 900-11

14.1 Attachments

14.1.1 Expanded Prostate Cancer Index Composite (EPIC)

14.1.2 Sexual Health Inventory for Men (SHIM)