Low-Cost Platelet- Rich Plasma for Hemearthropathy

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May 2, 2024

STUDY PROTOCOL

Objectives

Hemophilic arthropathy, or hemarthropathy, results from recurrent accumulation of blood in the joints, leading to chronic pain, inflammation, and progressive joint damage. Effective nonsurgical treatment options for patients with hemophilic arthropathy are needed, but further research must be conducted to identify if safe conservative options, such as platelet-rich plasma (PRP) injections, can contribute to functional improvements and pain relief for this clinical population.

The objective of this study is to assess the feasibility of utilizing low-cost platelet-rich plasma (LC-PRP) preparation technique within the context of utilizing PRP for the treatment of hemophilic arthropathy. Specifically, this study aims to demonstrate the safety of this technique/treatment (no serious adverse events), evaluate LC-PRP composition (i.e., to assess if the prepared LC-PRP has similar cellular composition to reported values from commercially available PRP kits), and to measure patient improvement (e.g., pain, function, and satisfaction) following LC-PRP injection.

More specifically, this study will be guided by the following aims:

Aim 1: Prospectively evaluate clinical outcomes in a cohort of patients with bleeding disorders for pain and functional measures over six months. Hypothesis: Subjects who receive LC-PRP will demonstrate improvements in pain and function at three months, specifically on the WOMAC score (knee), American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot score (ankle), and the Quick Disabilities of Arm Shoulder and Hand (QuickDASH) score (elbow).

Aim 2: Evaluate the total cost of the procedure, including the cost of supplies, staff time, and pharmaceutical components. Hypothesis: The total cost of the procedure will be comparable to the standard-of-care injection, corticosteroid.

Aim 3: Evaluate the likelihood of adverse events related to the procedure, namely repeat bleeding into the joint or infection following the procedure. Hypothesis: Subjects who receive a LC-PRP injection will not have an increased risk of adverse events compared to the standard-of-care injection, corticosteroid.

METHODS

Study Design

This single-arm, prospective cohort pilot study is designed to evaluate the feasibility of using LC-PRP to treat pain and dysfunction from hemarthropathy. Consecutive patients eligible for a standard-of-care injection will be enrolled from the Utah Center for Bleeding and Clotting Disorders. A total of 20 joints (estimated 10-15 patients) will receive PRP injections, performed at day 0 and 3 weeks, for a total of two injections – two injections have demonstrated superior outcomes to one,[1] and will increase our number of injections to improve the proof of feasibility.

Sample

Adult patients with symptomatic hemarthropathy of the ankle, knee, or elbow, based on radiographs within the last 24 months will be eligible for inclusion. Patients must have failed at least six weeks of conventional conservative treatments (e.g., medication or physical therapy). Exclusion criteria will include recent (last two years) surgery to the affected joint, prior joint replacement, prior orthobiologic injection into the affected joint, thrombocytopenia, inability to receive factor prior to PRP injection, active systemic or local infection at the site of injection, non-ambulatory patients, body mass index (BMI) over 50, and recent (six month) or current corticosteroid injection/intake. Patients with hemarthropathy in multiple joints will be eligible for up to 2 joints if multiple fit the criteria.

LC-PRP Preparation

The full methodology is presented in the Appendix. To summarize, 45mL of blood will be collected and processed to result in 3-9 mL of neutrophil-poor PRP, depending on the joint injected (i.e., 3 mL for ankles/elbows, 9 mL for knees). Whole blood will be collected into three 20 mL syringes containing ACD-A anticoagulant. No platelet activators will be used in this process. The flange and the plunger of the syringes will be clipped off with shears and placed into a centrifuge with counterbalance. The centrifuge will run at 750 G for

five minutes. The three syringes will then be removed, and each will be consecutively attached to a 3-way stopcock. For each syringe, the platelet-poor (upper) portion of the plasma will be directed to a waste syringe, then the remaining platelet-rich (lower) portion of the plasma will be directed to a syringe containing the final PRP. This process will be repeated for the 3 syringes. No more than 5 minutes will elapse between stages of the procedure. No more than 30 minutes will elapse between completion of PRP preparation and injection; during that time, the PRP will be placed on a rocker to avoid layer separation. Blood will not be exposed to air at any point during this process, and all connections between syringes will be accomplished via Luer-Lok. PRP preparation/processing time will be monitored.

LC-PRP Injection

Peri-procedure factor management (if applicable) will be directed by the participant's primary hematologist. Injections are to be performed on day 0 and at 3 weeks, for a total of two injections per joint. This process will involve an ultrasound-guided intra-articular knee, ankle, or elbow injection by an experienced sports medicine provider (PI Daniel Cushman) with a 23 g needle after local anesthesia with 1% lidocaine to the extra-articular structures, namely the skin and joint capsule, to increase comfort.

Blood Analysis: LC-PRP Composition

All subjects will have less than 1mL of their whole blood and prepared PRP analyzed, with a complete blood count (CBC) with differential for each injection. Importantly, we will include all data required in the PRP minimum reporting standards,[2] including “platelet, differential leukocyte, and red cell analysis of all samples.”

Questionnaires

We will collect demographic information along with baseline and follow-up (i.e., 1 month, 3 months, and 6 months following second injection) patient reported outcomes, namely the WOMAC (knee), FAOS (ankle), and the QuickDASH (elbow). Surveys will be administered, and data will be stored, in REDCap.[3–5] Additionally, patient surveys will assess any adverse events, pain, global satisfaction, global injection satisfaction, and medications. At 3 and 6 weeks, we will inquire about adverse events related to the procedure, monitoring closely for any reported joint bleeds or infections following PRP injections.

DATA ANALYSIS

Statistical Analysis Plan

Whole blood and LC-PRP outcomes (e.g., platelet concentration, platelet count) will be summarized with descriptive statistics (i.e., mean and standard deviation). Patient reported outcome measures (e.g., global assessment, EQ-5D, WOMAC [including total score and pain, stiffness, and function subscores], QuickDASH, FAOS) will be described via median and interquartile range (IQR) at baseline and follow-up (i.e., 1, 3, and 6-months). Frequencies and percentages will be used to summarize patient satisfaction with the study joint (at baseline and all follow-up points) and adverse events. As this is a feasibility study and therefore is not intentionally powered for clinical outcomes, no statistical hypothesis testing will be performed. See example tables 1 through 6 below for further details pertaining to planned analyses and study reporting.

Example Table 1: Demographics

	n	%	Mean	SD
Total patients				
Joints				
Elbows				
Knees				
Ankles				
Age				
Body mass index (kg/m^2)				
Duration of symptoms (y)				
Sex				
Female				
Male				
Hemophilia type				

Hemophilia type A			[redacted]
Hemophilia type B			
Hemophilia severity			
Mild			
Moderate			
Severe			
Baseline satisfaction with joint			
Very unsatisfied			
Unsatisfied			
Neither satisfied nor unsatisfied			
Satisfied			
Very satisfied			

Example Table 2: Whole blood and PRP cellular composition

	Whole blood		**PRP**	
	Mean	**SD**	**Mean**	**SD**
Volume				
Platelet concentration, 10^3 per uL				
Platelet count (billion)				
Platelet extraction (%)				
Concentration factor				
WBC concentration, 10^3 per uL				
- Neutrophils				
- Lymphocytes				
RBC concentration, 10^6 per uL				
Hb concentration, g/dL				

Example Table 5. Satisfaction with study joint at baseline and and follow-up

	Baseline	**1 Month**	**3 Months**	**6 Months**
Satisfaction with Joint				
Very unsatisfied				
Unsatisfied				
Neither satisfied nor unsatisfied				
Satisfied				
Very satisfied				

Example Table 6. Adverse events associated with study PRP injections.

	n (%)
Adverse Event	
New joint bleed	
Increased pain in the joint	
Bruising	
Fever/Chills	
Redness in the area	
Reduced joint range of motion	
Other	

REFERENCES

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3. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381. doi:10.1016/j.jbi.2008.08.010
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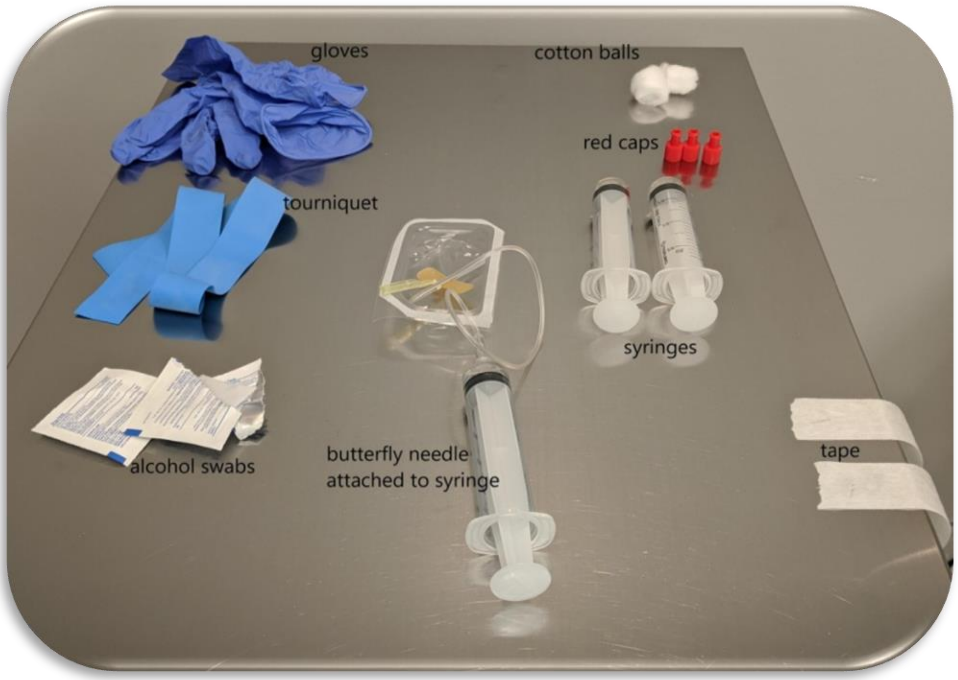
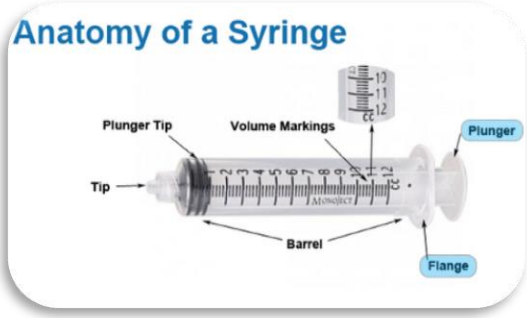
APPENDIX – LOW-COST PLATELET-RICH PLASMA (LC-PRP) PREPARATION METHOD

Step	
1	Ensure name and date-of-birth of subject.
2	Put stickers on all syringes, ensuring proper name & DOB throughout procedure
3	Add 2mL of ACD-A into 3 x 20mL syringes

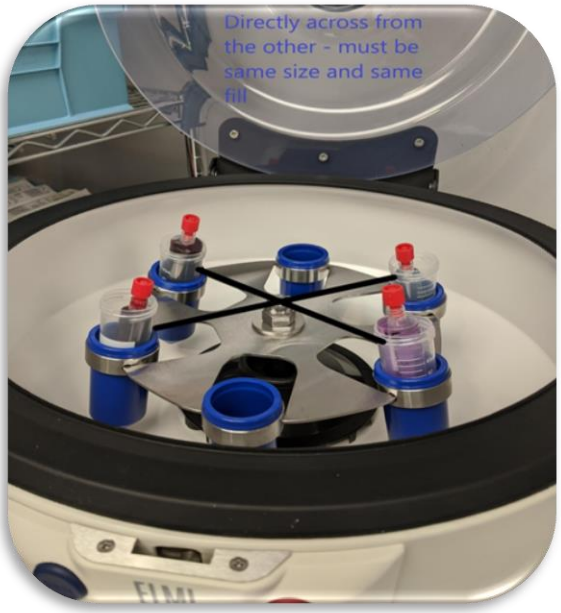
4	Venipuncture using butterfly needle



5	Draw 13mL blood (15mL total including 2mL ACD-A) into 20mL syringe - syringe 1
6	Draw 13mL blood (15mL total including 2mL ACD-A) into 20mL syringe - syringe 1
7	Draw 13mL blood (15mL total including 2mL ACD-A) into 20mL syringe - syringe 1
8	Draw 1-2mL blood into 5mL syringe for complete blood count (CBC) testing
9	If extra blood is drawn up on any needle, properly dispose of extra blood to leave exactly 15mL
10	Cap each syringe (qty 4) - 3 for PRP and 1 for CBC
11	Mix all syringes by themselves with a rocking motion, back and forth
12	Using shears, cut off the plunger and both flanges from each syringe

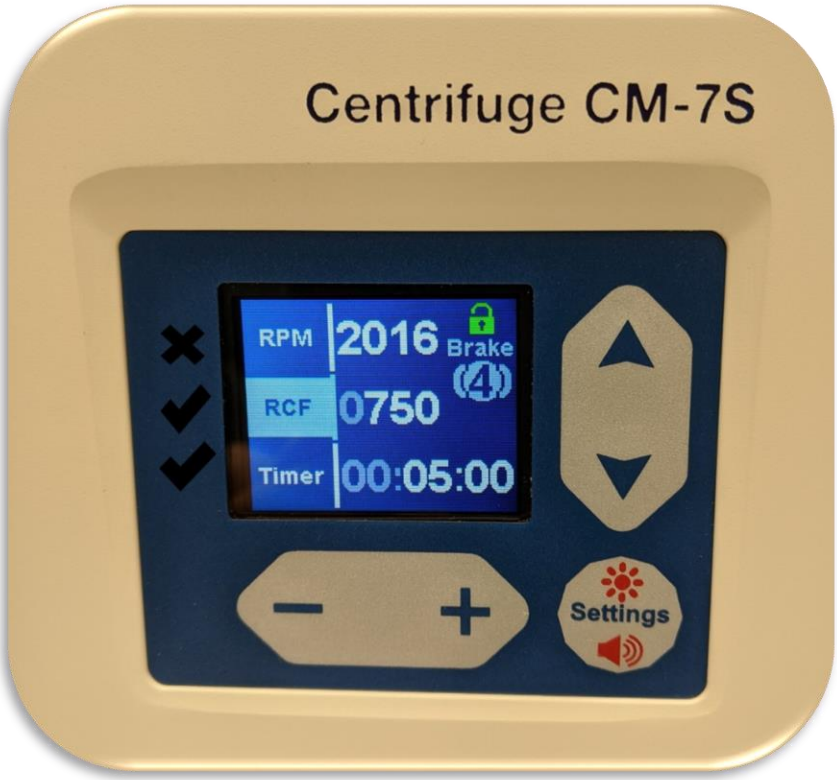


13 Place syringes in the centrifuge, opposite each other



14 A fourth syringe will be used as a counterbalance, filled with saline

15 Using a scale, syringes will be emptied (~0-0.5mL) to match weights for counterbalance
16 Close centrifuge lid
17 Centrifuge at 750G for five minutes



18 Ready stopcock - one "waste" syringe (20mL) and one "PRP" syringe (10mL)

19 For each of 3 syringes, perform the following:

20 - Hold syringe upright and attach to bottom of stopcock

21 - Distribute upper portion of plasma into "waste" syringe, leaving 3mL of plasma
22 - Rotate stopcock from "waste" syringe to "PRP" syringe
23 - Distribute remaining 3mL of plasma into "PRP" syringe

24 This will leave 9mL in the "PRP" syringe
25 Mix syringe with rocking motion (to ensure homogeneity)
26 From the "PRP" syringe, inject 1mL into separate 5mL syringe for CBC testing
27 This will leave 8mL in the "PRP" syringe
28 Physician will perform injection after local anesthetic administration, name/DOB verification, and sterile preparation
29 Perform CBC testing on both PRP and whole blood samples

<u>Important points to note</u>:

1. Sterility will be ensured
2. Appropriate storage of sodium citrate
3. Will not use single-use vials multiple times
4. Will use gloves and mask at all times

5. Only use sterile syringes, stopcocks, needles
6. Filling syringes to exact amounts is imperative. Will avoid over- or under-filling.
7. If a syringe becomes contaminated in any way, it will be disposed of appropriately and not continue to use it in the PRP preparation process.
8. All blood must have a label on it to ensure that no patient receives another patient's blood

Supplies:

- Alcohol wipes
- Gloves
- Elastic tourniquet
- Butterfly/winged infusion set
- 20 mL BD syringes (dual ribbed)
- 18G blunt tip filling needles
- Anticoagulant (single use vials): 4% sodium citrate
- 50cc conical tubes
- Red caps
- Shears
- 3-way stop cock
- Injection syringe with needle
- Centrifuge