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Brief Reports

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DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY EVALUATING THE USE OF PLATELET-RICH PLASMA THERAPY (PRP) FOR ACUTE ANKLE SPRAINS IN THE EMERGENCY DEPARTMENT

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□ **Abstract—Background: Over 23,000 people per day require treatment for ankle sprains. Platelet-rich plasma (PRP) is an autologous concentration of platelets that is thought to improve healing by promoting inflammation through growth factor and cytokine release. Studies to date have shown mixed results, with few randomized trials. Objectives: To determine patient function among patients randomized to receive standard therapy plus PRP, compared to patients who receive standard therapy plus sham injection (placebo). Methods: Prospective, randomized, double-blinded, placebo-controlled trial. Patients with severe ankle sprains were randomized. Severity was graded on degree of swelling, ecchymosis, and ability to bear weight. PRP with lidocaine and bupivacaine was injected at the point of maximum tenderness by a blinded physician under ultrasound guidance. The control group was injected in a similar fashion with sterile 0.9% saline. Both groups had visual analog scale (VAS) pain scores and Lower Extremity Functional Scale (LEFS) on days 0, 3, and 8. LEFS and a numeric pain score were obtained via phone call on day 30. All participants were splinted, given crutches, and instructed to not bear weight for 3 days; at this time patients were reevaluated. Results: There were 1156 patients screened and 37 were enrolled. Four withdrew before PRP injection was complete; 18 were randomized to PRP and 15 to placebo. There was no statistically significant difference in VAS and LEFS scores between groups. Conclusion: In this small study, PRP did not provide benefit in either pain control or function over placebo.** © **2015 Elsevier Inc.**

□ **Keywords—ankle sprain; platelet rich plasma; sports medicine**

INTRODUCTION

Over 23,000 people per day require treatment for ankle sprains, resulting in loss of workdays and training for athletes. Over 2 million ankle sprains occur each year in the United States. Health care costs for this seemingly simple injury are considerable, and long-term disability affects up to 60% of patients (1–3).

Platelet-rich plasma (PRP) therapy is an emerging treatment for soft tissue injuries. PRP therapy involves an autologous injection of a high concentration of platelets derived from the patient's own blood into or near the site of injury. PRP, when injected into the site of injury, is thought to improve healing by promoting inflammation through growth factor and cytokine release. Studies to date have shown mixed results, with few randomized or placebo-controlled trials.

Numerous animal and human studies have demonstrated the safety and efficacy of PRP therapy for a variety of conditions. Unfortunately, the majority of these studies are limited due to small sample sizes or nonrandomized methodology (4–9). Mishra et al. performed a retrospective review of 20 patients with chronic

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epicondylar elbow pain (tennis elbow) who had failed conservative treatments (4,5). Similar pilot studies have demonstrated the efficacy of PRP for the treatment of plantar fasciitis, and as an augment to surgically repaired Achilles tendons and rotator cuffs (7–9).

There is a paucity of well-designed prospective clinical trials comparing PRP therapy to standard therapy for acute musculoskeletal injuries. Likewise, we are unaware of any studies of this therapy in the emergency medicine literature. This investigation was a collaborative effort between the departments of Orthopedic Surgery and Emergency Medicine to advance the knowledge base on this potentially beneficial treatment for the patients that we serve. The purpose of this prospective, randomized, double-blinded, placebo-controlled trial was to evaluate the benefit of PRP therapy in treatment of ankle injuries in an emergency department (ED) setting.

Objectives

Our primary objective was to determine patient function as defined by the Lower Extremity Functional Scale (LEFS; Figure 1) at days 0, 3, 8, and 30 among patients randomized to receive standard therapy plus PRP compared to patients who receive standard therapy plus sham injection (placebo). Our secondary objective was to compare pain scores at 0, 3, 8, and 30 days in the two groups.

MATERIALS AND METHODS

We conducted a randomized, double-blind, placebo-controlled study conducted in an urban Level I trauma center. Clinical Research Assistants (RA) present in the ED 24/7 screened and enrolled patients in the study. We screened patients presenting with traumatic ankle pain. Patients were eligible if they were age 18 years or older, had severe ankle sprain based on clinical criteria from Coughlin, and ankle radiograph was negative for fracture (10). Exclusion criteria were pregnancy and lactation, history of peripheral vascular disease, current anticoagulation therapy, current antiplatelet therapy, history of thrombocytopenia, allergy to study medications, evidence of active infection, and prior surgery at the site of injury.

Six trained investigators performed the research intervention. All investigators were board certified or eligible emergency physicians with experience using emergency bedside ultrasonography. Investigators underwent a structured training course in musculoskeletal ultrasonography prior to the start of the study and reviewed the techniques with the primary investigator periodically during the study period. The investigators also underwent a structured review of PRP injection before the investigation began and periodically during the study.

We defined severe ankle sprains as diffuse tenderness and swelling and inability to walk. Both the treating physician and the investigator performing the procedure reviewed three-view ankle radiographs to rule out any fracture prior to enrolling the subject. The RA consented patients and randomized them to receive either PRP or placebo. The RA also obtained a baseline visual analog scale (VAS) for pain and LEFS prior to the procedure. An ED technician or a nurse drew 50 cc of blood directly into a syringe using an 18-gauge butterfly needle for both groups. The blood of the placebo group was discarded and the treatment group's blood was processed to produce 3–4 cc of PRP. The unblinded RA utilized a disposable Magellan Autologous Platelet separator Kit (Arteriocyte, Cleveland, OH), which included citric acid anticoagulant for use in the syringe. The patients and investigators were blinded to the blood draw and processing of PRP.

The unblinded RA prepared the injection using a sterile syringe, and then taped it to blind both the investigator and patient to the contents. Placebo injections consisted of 4 cc of sterile normal saline and 1 cc of 1% lidocaine and 1 cc of 0.25% bupivacaine. Treatment injections consisted of 3–4 cc of PRP and 1 cc of 1% lidocaine and 1 cc of 0.25% bupivacaine. Local anesthetics were added to the infusion to help with blinding and decrease possible pain associated with the procedure.

Investigators used real-time ultrasound and standard sterile practices to place the injections. The investigators examined the ankle using a 6–13-MHz linear array probe (Sonosite, Bothell, WA) to determine the nature of injury. When an injured ligament could be identified, the injection was placed adjacent to the injury. When no injury would be identified, the injection was placed at the site of maximal tenderness. Ultrasound guidance also allowed for avoidance of vessels.

The investigator applied a posterior splint to the affected ankle after the injection was given. The treating physician provided participants with crutches and training. The treating physician also prescribed pain medication at his or her discretion and instructed them to avoid nonsteroidal anti-inflammatory drugs. The participants were asked to come back at 2–3 days, 7–8 days, and had a phone interview at day 30.

The RA scheduled the first follow-up visit for 2–3 days after the primary ED visit. The investigator re-evaluated the patient, removed the splint, and the patient was asked to bear weight on the affected leg as tolerated. The RA also assessed the LEFS and VAS for pain during this visit. The RA scheduled the second follow up 7–8 days after the primary ED visit to assess the LEFS and VAS for pain. The RA contacted the participants by phone at day 30 for a numeric pain score and LEFS.

THE LOWER EXTREMITY FUNCTIONAL SCALE

We are interested in knowing whether you are having any difficulty at all with the activities listed below because of your lower limb problem for which you are currently seeking attention. Please provide an answer for **each** activity.

Today, do you or would you have any difficulty at all with:

(Circle one number on each line)

Activities	Extreme Difficulty or Unable to Perform Activity	Quite a Bit of Difficulty	Moderate Difficulty	A Little Bit of Difficulty	No Difficulty
Any of your usual work, housework, or school activities	0	1	2	3	4
Your usual hobbies, recreational or sporting activities	0	1	2	3	4
Getting into or out of the bath	0	1	2	3	4
Walking between rooms	0	1	2	3	4
Putting on your shoes or socks	0	1	2	3	4
Squatting	0	1	2	3	4
Lifting an object, like a bag of groceries from the floor	0	1	2	3	4
Performing light activities around your home	0	1	2	3	4
Performing heavy activities around your home	0	1	2	3	4
Getting into or out of a car	0	1	2	3	4
Walking 2 blocks	0	1	2	3	4
Walking a mile	0	1	2	3	4
Going up and down 10 stairs (about 1 flight of stairs)	0	1	2	3	4
Standing for 1 hour	0	1	2	3	4
Sitting for 1 hour	0	1	2	3	4
Running on even ground	0	1	2	3	4
Running on uneven ground	0	1	2	3	4
Making sharp turns while running fast	0	1	2	3	4
Hopping	0	1	2	3	4
Rolling over in bed	0	1	2	3	4
Columns Total:					

SCORE: ____/80

Error (single measure): ±5 scale points
MDC: 9 scale points
MCID: 9 scales points

Figure 1. The Lower Extremity Functional Scale (LEFS). Binkley et al.: the Lower Extremity Functional Scale (LEFS): scale development, measurement properties, and clinical application. Phys Ther 1999; 79:371–383 (11).

This was a pilot study and sample size was not predetermined. We compared the two groups for baseline pain scores and LEFS. We then compared them for differences in pain scores and LEFS at days 2–3, 7–8, and 30. We performed independent and paired sample *t*-tests using SPSS version 21 (IBM, Armonk, NY).

RESULTS

We screened 1156 patients screened for enrollment; 37 patients agreed to participate; 982 patients did not meet inclusion criteria and 137 patients declined study participation. Four patients withdrew before study procedures

Table 1. Baseline Demographics

	Race (AA)	Gender (F)	Age in Years (Mean, Min–Max)	BMI in Kg/m^2 (Mean, Min–Max)
PRP	13	14	30.3	31.6
	72.2%	77.8%	19–54	22.7–48.5
Placebo	9	9	35	32.2
	60%	60%	18–61	22–49.9

AA = African American; F = Female; BMI = body mass index; PRP = platelet-rich plasma therapy.

were performed. Of the 37 participants enrolled, 18 were randomized to PRP and 15 to placebo. We did not find any statistically significant differences in baseline demographics of both groups (Table 1).

We found no statistical differences in LEFS or pain scores at each of the time intervals between the two groups. Results of the independent sample *t*-test are illustrated in Table 2. We also performed paired sample *t*-tests to assess significant improvement in LEFS and pain scores over time for each patient in both groups. Both groups showed a statistically significant improvement over time.

We performed a post hoc power calculation. The power of our study to detect a significant difference in LEFS at day 3 between the PRP and placebo groups was 17.8%.

DISCUSSION

Ankle sprains are a common injury and reason for ED visits. They result in substantial direct cost, and loss of function and workdays. Likewise, they also contribute to lost time for education and participation in organized athletics and general recreation (1). Any therapy that can accelerate healing and ability to return to function may be of benefit from a public health standpoint and for the individual patient (2).

PRP is not a new therapy. For nearly 20 years, physicians have safely used PRP therapy to augment wound hemostasis and wound healing in many fields of medicine and surgery, including dentistry, otolaryngology, neurosurgery, orthopedic surgery, physical medicine and rehabilitation, and cardiothoracic surgery. The mechanism of action of PRP for the treatment of soft tissue injuries is theorized to involve enhanced healing and tissue regeneration resulting from the release of numerous immunologically active proteins found in platelets (4,5).

In the setting of soft tissue injuries, PRP therapy is a novel approach using the patient's own blood derivatives. Blood typically contains 93% red blood cells, 6% platelets, and 1% white blood cells by volume. The theory behind PRP therapy lies in reversing the aforementioned ratio by decreasing red blood cells (which are not helpful in wound healing) to 5% and increasing platelets to 94% to stimulate recovery (4). Although this physiological background may support the effectiveness of using PRP in management of ankle sprains, we failed to show statistically significant benefit from PRP injection for acute ankle sprains in either function or pain compared to standard therapy. Difference in functional improvement, measured on a LEFS, was not statistically significant between treatment group and control group at days 0, 3, 7, and 30. Pain measured on a VAS at days 0, 3, and 7 was not significantly different between treatment and control groups. Difference in the numerical pain scale at day 30 was not statistically significant between groups.

Limitations

Our study had some significant limitations. The small sample size may have resulted in the low power of the study to detect any significant difference in LEFS or VAS scores between the two groups. Another limitation of the study was a nonstandardized pain medication regimen for patients enrolled in the study. The type and amount of pain medications consumed by the subject would have played a significant role in symptomatic improvement of subjects. Further, the high refusal rate and the lack of data on characteristics of these patients may have biased our results. A discussion of the nature of these biases is beyond the capacity of this study.

Table 2. Lower Extremity Functional and Scale Visual Analog Scale Between Groups

	Lower Extremity Functional Scale			Pain Scores		
Day	PRP Mean (SD)	Placebo Mean (SD)	*p*-Value	PRP Mean (SD)	Placebo Mean (SD)	*p*-Value
0	12.9 (9.5)	18.6 (12.2)	0.14	8.8 (1.8)*	7.7 (2.2)*	0.11
3	24.2 (16.1)	30.1 (16.4)	0.31	5.72 (2.7)*	4.8 (2.1)*	0.14
8	51.3 (22.2)	53.1 (15.8)	0.8	2.4 (2)*	1.8 (1.7)*	0.37
30	68 (9.1)	64.1 (14)	0.45	1.1 (1.6)†	1.6 (2.6)†	0.6

PRP = platelet-rich plasma; SD = standard deviation.
* Visual analog scale in centimeters.
† Numeric pain score measure on a scale of 1 to 10.

CONCLUSIONS

PRP injections are commonly used in elite and professional athletes, and have drawn attention in the lay media. Despite the growing popularity of PRP, very few controlled trials have been done to investigate the effectiveness of PRP. This small, randomized controlled trial showed no effectiveness of PRP over placebo in an urban population presenting to the ED with undifferentiated ankle sprains. Further studies might be needed to determine utility of this intervention.

REFERENCES

1. Waterman BR, Owens BD, Davey S, Zacchilli M, Belmont PJ Jr. The epidemiology of ankle sprains in the United States. J Bone Joint Surg Am 2010;92:2279–84.
2. Gerber JP, Williams GN, Scoville CR, Arciero RA, Taylor DC. Persistent disability associated with ankle sprains: a prospective examination of an athletic population. Foot Ankle Int 1998;19:653–60.
3. Yablon CM. Ultrasound-guided interventions of the foot and ankle. Semin Musculoskelet Radiol 2013;17:60–8.
4. Sampson S, Gerhardt M, Mandelbaum B. Platelet rich plasma injection grafts for musculoskeletal injuries: a review. Curr Rev Musculoskelet Med 2008;1:165–74.
5. Mishra A, Woodall J Jr, Vieira A. Treatment of tendon and muscle using platelet-rich plasma. Clin Sports Med 2009;28:113–25.
6. Marx R, Garg A. Dental and craniofacial applications of platelet rich plasma. Carol Stream, IL: Quintessence Publishing Co., Inc; 2005.
7. Barrett S, Erredge S. Growth factors for chronic plantar fasciitis. Podiatry Today 2004;17:37–42.
8. Sánchez M, Anitua E, Azofra J, Andía I, Padilla S, Mujika I. Comparison of surgically repaired Achilles tendon tears using platelet-rich fibrin matrices. Am J Sports Med 2007;35:245–51.
9. Randelli PS, Arrigoni P, Cabitza P, Volpi P, Maffulli N. Autologous platelet rich plasma for arthroscopic rotator cuff repair. A pilot study. Disabil Rehabil 2008;30:1584–9.
10. Coughlin M, Saltzman CL, Anderson RB. Mann's surgery of the foot and ankle. 9th edn. Philadelphia: Mosby; 2013.
11. Binkley JM, Stratford PW, Lott SA, Riddle DL. The Lower Extremity Functional Scale (LEFS): scale development, measurement properties, and clinical application. Phys Ther 1999;79:371–83.

ARTICLE SUMMARY

1. Why is this topic important?

Administration of platelet-rich plasma has gained popularity for treatment of various sports medicine-related injuries. Not many studies to date are done with the scientific rigor needed to prove cause and effect of the benefits of these treatments. Our group of investigators wanted to take the first step in trying to determine the efficacy of these treatments. We believe negative studies should be published so that the physicians who might be considering those specific treatments for their patients can better inform themselves and their patients of their decision.

2. What does this study attempt to show?

Our hypothesis was that patients receiving the platelet-rich plasma treatment would return to normal function faster than patients receiving placebo.

3. What are the key findings?

There were no statistically significant differences in the function scores or pain as measured by a visual analog scale. The platelet-rich plasma group used less opioid medication, which did not achieve statistical significance.

4. How is patient care impacted?

Based on our results, we will recommend that further studies need to be done to determine whether there is any benefit in the use of platelet-rich plasma on patients with moderate and severe ankle sprains.