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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.