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Peer Review File

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Review Comments

This is an important topic, however, this review is incomplete. There are number of ways to improve this:

1. Begin with a more focused review (ie. musculoskeletal use of PRP)

Reply: we have modified our text as advised (see Page 1, line 23)

Changes in the text: "In this review, we focus on the administration of PRP in musculoskeletal recovery."

2. Build support with some key pre-clinical studies in that specific area

Reply: we have modified our text as advised (see Page 9, line 159-161)

Changes in the text: Qu et al. conducted animal studies to show that PRP can promote osteoarthritis cartilage repair in rabbits. Wang et al. established 30 rabbits model of arthritis and verified the effect of PRP on promoting cartilage repair and inhibiting MMP13.

3. Current Level I or II supportive clinical studies.

Reply: we have modified our text as advised (see Page 9, line 161-165)

Changes in the text: Xiu et al. performed a randomized controlled trial on 60 patients comparing the clinical effects of articular cavity injection of PRP and sodium hyaluronate. Their results showed that the score of each dimension of the PRP injection group was better than that of the HA group, suggesting that intra-articular injection of PRP can more effectively reduce the pain degree of patients with knee osteoarthritis, improve their joint function, regulate the level of NO and MMP13, and have higher safety.

4. Inadequacies with current PRP preps (ie. variability between patients, variability between different preparation methods, lack of cell counting data, etc...).

Reply: we have modified our text as advised (see Page 3 line 67--Page 5 line 108)

Changes in the text: PRP preparation

There are many ways to make PRP, different centrifugal times, centrifugal force, and centrifugal time, PRP produced are different. In addition, the platelet recovery and activation rate in PRP can also be affected by factors such as different length of axis,

different diameter and length of the centrifuge tube, the material of centrifuge tube (glass or plastic), and even different body positions or blood drawing at different times of the day. At present, there is commercial equipment to make PRP on the market. The concentrations of platelets, white blood cells, and growth factors are all different in the PRP produced. Since the concentration of growth factor and white blood cells can significantly affect the effect of PRP, the concentration of PRP components produced by the machine is relatively stable, compared with manual production. The key tricky of PRP preparation is to use twice centrifugation method. After the first slow and short centrifugation, the red blood cells with the largest sedimentation coefficient are discarded. Then, with the second high-speed and long centrifugation platelet is collected as many as possible. To obtain a better efficiency of platelet collection, it is necessary to develop a matching centrifuge method, rather than the centrifugal force and centrifuge time reported in the literature.

At the same time, there is a study focused on centrifugation times. This study indicate that PRP prepared by the Landesberg method has high platelet concentration and low activation rate. Thus, we recommend that the preparation of PRP should follow the centrifugation method two times, and centrifuge the red blood cells with the largest sedimentation coefficient to the bottom of the tube for the first time, and then remove the red blood cells; The second high speed long centrifugation is designed to collect as many platelets from the serum as possible to the bottom of the tube.

Simultaneously, there are several studies on platelet concentrations. Three different PRP separation methods were used: a single-spin process yielding a lower platelet concentration (PRPLP), a single-spin process yielding high platelet and white blood cell concentrations (PRPHP), and a double-spin that produces a higher platelet concentration and lower white blood cell concentration (PRPDS). As the result, the "more is better" theory using higher platelet concentrations does not work. And in another study, indicated that after PRP extraction, the platelet count should be more than 4 times higher than that of whole blood. Studies have shown that 4-5 times of platelet concentration can effectively promote bone and soft tissue repair, higher concentration does not show better repair effect, and more than 4 times of concentration can be obtained manually, without the need for special preparation instruments.

At present, there is no unified preparation standard for PRP, and the platelet collection rate of different preparation systems is different due to the great differences in various PRP collection and preparation processes. Usually will collect whole blood with

anticoagulant factors (such as sodium citrate, dextran and ethylenediamine tetraacetic acid) hybrid, and centrifugal separation of red blood cells (RBC), poor plasma (PPP), and contains concentrated platelet "blood sedimentation layer" buffy, remove the RBC and the PPP layer, further separation of platelet concentrate layer. PRP can be injected directly into the affected area or "activated" by adding calcium chloride or thrombin, which degranulates the activated platelets and releases growth factors and differentiation factors. After activation, about 70% of stored growth factors were released within 10min, and almost 100% were released within 1h. The remaining few growth factors were released within 8 ~ 10d of platelet survival.

5. Future directions

Reply: we have modified our text as advised (see Page 10 line 199-- Page 11 line 204)

Changes in the text: Although PRP has been in use for a long time, there is still confusion over how to define, classify, and describe the different variants of platelet concentrate. In addition to the lack of accurate characterization of the products under test in most articles on the subject, there are wide variations in reporting protocols for the standardization and preparation of PRP. In addition, the high cost of PRP kits, which are commercially available, prevents their use in a larger population. In the future, our goal should be to find a safe, simple, and standardized PRP preparation protocol, and to follow this protocol to obtain the best stable platelet yield.