



Role of Platelet Rich Plasma Therapy on Rotator Cuff Disease

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

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LIST OF ABBREVIATIONS

| | | |
|-------------------------------|-------|---------------------------------------|
| AC | | Acromioclavicular |
| ACD | | Anticoagulant Citrate Dextrose |
| ADP | | Adenosine Di-Phosphate |
| ARC | | Angiogenesis-Related Cytokines |
| ATP | | Adenosine Tri-Phosphate |
| C | | Cervical |
| CBC | | Complete Blood Picture |
| ECM | | Extracellular Matrix |
| ELIZA | | Enzyme-Linked Immunosorbent Assay |
| ESR | | Erythrocyte Sedimentation Rate |
| ESWT | | Extracorporeal shock wave therapy |
| FBS | | Fasting Blood Sugar |
| FGF | | Fibroblast Growth Factors |
| HGF | | Hepatocyte Growth Factor |
| IGF-1 | | Insulin-Like Growth Factor-1 |
| IL | | Interleukin |
| IL-1β | | Interleukin one beta |
| L | | Lumbar |
| L-PRF | | Leukocyte-Rich Platelet-Rich Fibrin |
| L-PRP | | Leukocyte-Rich Platelet Rich Plasma |
| MHz | | Mega Hertiz |
| mm | | millimeter |
| mmHg | | millimeter Mercury |
| MMP | | Matrix Metallo-Proteases |
| MRI | | Magnetic Resonance Imaging |
| MSU | | Diagnostic Musculoskeletal Ultrasound |
| ng/L | | Nanogram per Liter |
| NSAIDs | | Non-steroidal Anti-Inflammatory Drugs |
| OB | | Optical Density |
| PDGF | | Platelet Derived Growth Factor |
| pg/L | | Picogram per Liter |
| P-PRF | | Pure Platelet-Rich Fibrin |
| P-PRP | | Pure Platelet Rich Plasma |
| PRP | | Platelet Rich Plasma |
| RCD | | Rotator Cuff Disease |
| RCT | | Rotator Cuff Tendinopathy |

LIST OF ABBREVIATIONS CON.

| | | |
|---------------------------------|-------|----------------------------------------------|
| RF | | Rheumatoid Factor |
| ROM | | Range of Motion |
| SGOT | | Serum Glutamic Oxaloacetic Transaminase |
| SGPT | | Serum Glutamate Pyruvate Transaminase |
| SLAP | | Superior Labrum Anterior–Posterior |
| T | | Thoracic |
| TGF- β | | Transforming Growth Factor-beta |
| TIMP | | Tissue Inhibitor of Matrix Metalloproteinase |
| TNF- α | | Tumor Necrosis Factor-alpha |
| TNF | | Tumor Necrotic Factor |
| U/S | | Ultrasound |
| VAS | | Visual Analogue Scale |
| VEGF | | Vascular Endothelial Growth Factor |
| WBC | | White Blood Cell |
| WORC | | Western Ontario Rotator Cuff |
| α | | Alpha |
| μm | | micrometer |

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INTRODUCTION

Rotator cuff tendinopathy (RCT) and rotator cuff diseases (RCDs) are leading cause of shoulder pain and a significant source of disability and loss of work (*Kuijpers et al., 2006, Rha et al., 2013 and Whittle & Buchbinder, 2015*).

It is a common disorder; approximately 16% of the general population is believed to have RCD at any given time (*Erstad, 2008*). Its prevalence increases substantial with age and with occupations involving overhead activities. They are affecting more than 50% of population above 60 years (*Seitz et al., 2011*).

In spite of the long standing history and many studies and reviews found in literature concerning RCDs and mechanism of development of tendon tear, the pathophysiology of rotator cuff tendon diseases is still a controversial topic and hasn't been fully understood (*Rha et al., 2013*). The biochemical and molecular events leading to RCD and tear have not yet been defined and still a matter of debate (*Beasley et al., 2000; Dean et al., 2012 and Petterson et al., 2017*).

Disease course pass through 3 stages begin with acute tendinitis then progress to fibrosis and partial tear, end finally in full thickness tear (*Kesikburun et al., 2013*).

Two hypotheses including a combination of extrinsic and intrinsic mechanisms are generally thought to be responsible for the RCD (*Dean et al., 2012*), including biomechanical and anatomic dysfunctional causes. Subacromian impingement, tendon degeneration, alternation in tendon mechanical properties, increase tendon overload and overuse especially with overhead activities are contributing factors in disease progression and development of partial and full thickness tears (*Tytherleigh-Strong et al., 2001, Lewis, 2009 and Seitz et al., 2011*). Although the multiple factor which contribute to develop of RCDs pathophysiology, but the mechanical and biochemical events lead to cuff degeneration and tear need for further investigations and studies (*Voloshin et al., 2005*).

The potential role of inflammatory cytokines, proteases and Angiogenesis-related cytokines (ARC) remain unclear. Recent studies using immune-histochemistry techniques and synovial fluid samples revealed that the hallmark of RCD pathogenesis including proinflammatory, anti-inflammatory_process, an abnormal immune response, angiogenesis and altered variables of vascularity (*Löhr & Uthoff, 2007*). Angiogenesis is a fundamental process and relationship between it and degenerative changes in RCDs is attracting increasing attention (*Folkman, 1995*). Vascular endothelial growth factor (VEGF) found to be highly expressed in degenerated tendon. This cytokine thought to play a pivotal role in

process of tendon degeneration and repair (*Savitskaya et al., 2011*).

As cytokines signal the normal process of inflammation and repair, they play important role in cell chemotaxis, proliferation, matrix synthesis and remodeling. These molecules have the potential to improve RCT healing (*Petersen, 2005 and Savitskaya et al., 2011*). IL-1 β , TNF, IL-6, IL-10, proinflammatory cytokines and matrix metallo-proteases (MPP) are expressed in subacromial bursa in patients with RCD (*Voloshin et al., 2005*).

Accurate and sensitive methods for measuring and detection of cytokines are important for understand cytokine biology and biochemistry for assessment of cytokine involvement in pathophysiology and molecular mechanisms of RCDs (*Bauer, 2008*). The combat between proinflammatory, anti-inflammatory and angiogenic factors that end eventually in a failed healing response, which is considered to play a principle part in pathogenesis of chronic tendon diseases (*Fealy, 2006 and Savitskaya et al., 2011*).

Management of RCD without full thickness tear is mainly conservative (*Andrews, 2005*) with use of physiotherapy, manipulation, NSAID and local steroid injection with high rate of recurrence and persistent pain (*Mantone et al., 2000 and Chou et al., 2010*). Lack of

healing response and limited ability of rotator cuff tendon to regenerate is the main cause of the unsatisfactory results of conservative treatment and considered to play a principal part in the pathogenesis of chronic tendon disease (**Rees *et al.*, 2006**). Therefor growth factors have been suggestive to be used to influence the healing process and promote tendon regeneration during treatment (**Rees *et al.*, 2009 and Wu *et al.*, 2017**).

Despite a growing body of research that has identified numerous cytokines that can positively affect tendon healing, there are significant limitations to single-factor therapy. Healing is a highly complex biological process with precise coordination. Application of a single exogenous factor does not mimic the highly coordinated spatial and temporal expressions of various factors that are required for cell proliferation, differentiation, matrix synthesis and eventual remodeling. This limitation of single factor therapy forms the rationale for the use of Platelet rich plasma (PRP) and related substances to improve healing (**Kaux & Crielaard, 2013**). Because the alpha granules and dense granules in platelets contain several cytokines and other bioactive factors, PRP allows delivery of numerous cytokines in “physiological balance” (**Rodeo *et al.* 2012**).

PRP is obtained by blood centrifugation and contains a higher platelet concentration than whole blood (**Paoloni *et al.*, 2011**). Also it contain cellular component of plasma that settle after centrifugation as well as growth factors.