Facultad de Ciencias de la Salud

Grado en Fisioterapia

UNIVERSIDAD DE JAÉN

Facultad de Ciencias de la Salud

Trabajo Fin de Grado

Platelet-rich therapy in rotator cuff tears: an evidence based review.

Alumno: Fernández-Fernández, María

Tutor: Prof. D. Delgado-Martínez, Alberto Damián

Dpto: Ciencias de la Salud

Junio, 2016

TABLE OF CONTENTS

“Platelet-rich therapy in rotator cuff tears: an evidence based review”.

1. ABSTRACT

1.1 English Abstract

Objectives. To identify, critically assess, collect and summarize the main possible evidences currently available about the effects of platelet-rich therapies in functional and structural outcomes in patients with rotator cuff tears.

Methods. A research was conducted in PEDro, PubMed and Cochrane for identifying eligible studies. The author selected some studies for inclusion, assessed the methodological quality and extracted data. The risk of bias was measured in each study by using Jadad Scale and “Cochrane risk of bias” tool.

Results. Ten studies (all randomized) met the inclusion criteria; with a total of 576 patients (41 of those were lost at follow-up). It was showed that trials selected held a high methodological quality by the assessment of the risk of bias. The synthesis of the data of the ten studies reveals that there were no statistically significant differences in functional outcomes but structural outcomes in the majority of them showed significant differences regarding to the re-tear rate and the cross-sectional area of supraspinatus muscle.

Conclusion. There is a lack of evidence to prove the effectiveness of platelet-rich therapy in comparison with placebo regarding to functional outcomes in patients with rotator cuff tears. However, it seems that structural outcomes get better before the PRP application.

Keywords. “Platelet-rich therapy”, “PRP” and “rotator cuff”.

1.2 Spanish Abstract

Objetivos. Identificar, evaluar de forma crítica, recopilar y resumir las principales evidencias disponibles actualmente sobre los efectos que produce la utilización de la terapia rica en plaquetas en los resultados funcionales y estructurales en pacientes con desgarro o rotura del maguito rotador**.**

Métodos. Se realizó una búsqueda en PEDro, PubMed y Cochrane para identificar los estudios elegibles. El autor seleccionó los estudios incluidos, evaluó la calidad metodológica y extrajo los datos. El riesgo de sesgos fue medido en cada estudio mediante la utilización de la escala “Jadad” y la “herramienta de Cochrane para el riego de sesgos”.

Resultados. Diez estudios (todos aleatorizados) cumplieron los criterios de inclusión, con un total de 576 pacientes (de los cuales 41 se perdieron durante el seguimiento). Se demostró que los estudios elegidos poseían una alta calidad metodológica mediante la evaluación del riesgo de sesgos. La síntesis de los datos de los diez estudios reveló que no había diferencias estadísticamente significativas en los resultados funcionales, pero, en la mayoría de los estudios, los resultados estructurales si mostraron una diferencia significativa en lo que respecta a la tasa de repetición del desgarro y el área de sección transversal del músculo supraespinoso.

Conclusión. No hay suficiente evidencia para probar la efectividad de la terapia rica plaquetas, en comparación con el uso de placebo, sobre los resultados funcionales en pacientes que presentan desgarro del manguito rotador. Sin embargo, parece ser que los resultados estructurales mejoran tras la aplicación de plasma rico en plaquetas.

Palabras clave. "Plasma rico en plaquetas","PRP" y "manguito rotador".

2. INTRODUCTION

2.1 Why is necessary to do this review?

Since the beginning of PRP researches, numerous researches that yielded optimal results in the application of platelet-rich therapy have been published. Studies, at first, were quite optimistic, but after a long period of controversy, it seems that the effectiveness of this method is being called into question nowadays. While regenerative action of tissues in vitro of the product is clear, there are clinical results shown in agreement and other that are not in harmony to what was observed in these studies. These products were always associated with confusions, mostly related to the lack of consensual terminology.

It has been reported by many authors that the published results of experimental trials are difficult to classify and interpret because they are assorted and controversial. In addition, the relevance of its use is doubtful, considering the literature, the experience feedback and the practical factors (such as the heavy cost of these techniques). The explanation of this unfortunate result is highlighted:

- There are available a large number of diverse techniques for the production of platelet concentrates that lead to different final preparations.
- There was no suitable terminology to sort and describe the many diverse variations of platelet concentrates.
- There is a lot of disorientation concerning to the techniques applied and a lack of precise description of the tested products in most of the trials on the topic [1].

2.2 Objectives

The purpose of this review is to identify, critically assess, collect and summarize the main possible evidences currently available about the functional and structural effect of platelet-rich therapies in rotator cuff tears. In this way, it seeks knowing the benefits of this therapy for the symptoms that cause this disease.

2.3 Platelet-rich therapy.

Platelet-rich therapy consists in the application of a volume of autologous plasma that has a platelet concentration above the baseline. Platelets contain proteins, cytokines, and other bioactive factors that start and regulate basic aspects of tissues healing having a big role in hemostasis. The basic cytokines identified in platelets hold transforming growth factor–β (TGF-β), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I, IGF-II), fibroblast growth factor (FGF), epidermal growth factor, vascular endothelial growth factor (VEGF), and endothelial cell growth factor. These

growth factors are responsible for producing crucial steps in early wounds healing by increasing cell mitosis, increasing collagen production, recruiting other cells to the site of injury, initiating vascular in-growth, and inducing cell differentiation.

The regular range of platelets counted in blood is from 150 000/µL to 350 000/µL. Platelet-rich plasma, with a platelet concentration of at least 1 000 000 platelets/µL in 5 mL of plasma, contains 3- to 5-fold increase in growth factor concentrations. Considering it, increasing the concentration of platelets at a wound may favour a quicker and better healing.[2,3]

The final platelet concentration in PRP depends on the method of preparation and the original platelet concentration in whole blood. There are two techniques for preparing PRP: Apheresis and Centrifugation. Apheresis and automated methods minimize operator errors, have a high repeatability, yield consistently high platelet concentrations, and have a low risk of contamination. While centrifugation systems provide a means of processing PRP with minimal manipulation and a relatively low risk of contamination. However, both of them require expensive specialized equipment, disposable means and the last one can results in inconsistent platelet performance due to an operator error.[4]

It is important to keep in mind that approximately the 70% of the stored growth factors are released within the first ten minutes, and nearly the 100% of the growth factors are released within one hour.[2] However, platelets may continue producing small amounts of growth factors during the rest of its lifespan (8 to 10 days). Delaying the release of growth factors is possible thanks to an alternative system for creating a “platelet-rich fibrin matrix” with only a small amount of thrombin by addition of calcium chloride ($CaCl_2$) which minimized platelet activation. The fibrin matrix may also provide a conductive scaffold for cell migration that contributes to healing process.[3]

2.4 Rotator cuff: Anatomy and pathogenesis.

The humeral head is supported by a tough sheath of the tendons of four muscles, which is call "rotator cuff". These muscles are the subscapularis (that supports the shoulder anteriorly); the supraspinatus (that maintains the superior aspect); the infraspinatus and the teres minor (located on the posterior shoulder).[5]

Trauma, inflammation and instability are pathological conditions that may cause rotator cuff diseases. These conditions can be described as either acute post-traumatic or chronic degenerative. A rotator cuff disease could involve many conditions that may present diverse degrees of pain and weakness.

The prevalence of rotator cuff disease increases with age, as demonstrated by Templehof et al. The MRI scanning revealed partial or complete tears of the rotator cuff in only 4% of patients aged less than 40 years compared with 54% of patients over 60 years. In addition, the ultrasound revealed that the 13% of the population in the fifth decade had an asymptomatic rotator cuff tear; the 20% in the sixth decade, the 31% in the seventh and the 51% in the eighth. More than half of these asymptomatic cuff tears will increase its size and become symptomatic within three years.[6]
The pathogenesis of rotator cuff tears is complex and multifactorial. The rotator cuff tendons are affected by many intrinsic and extrinsic factors that eventually lead to full-thickness rotator cuff tear.[7]

The tendon damage related to age goes worse because repetitive micro traumas results in partial tendon tears. Then, it develop into full rotator cuff tears inducing an inflammatory mediators response which change the local environment [8] and the oxidative stress resulting, induces tenocyte apoptosis bringing about even more rotator cuff tendon degeneration.

In addition, two important environmental factors have been described as a potentially source of deterioration of rotator cuff healing response. First, smoking has been shown to be highly correlated with the presence of full-thickness rotator cuff disease.[9] Second, NSAID medication may alter bone-to-tendon healing because it has been suggested that they decrease the healing response of the rotator cuff.[10]

The severity of rotator cuff diseases varies widely. There are many rotator cuff tears classification but all of them are different and do not include all of the factors to be important in classifying rotator cuff tear patterns. This make difficult to get a standard idea of what the kind of lesion the patients have. Two of those are Ellman[12] and Cofield classification[11] that are the most used. Cofield classified complete rotator cuff in four grades:

- Small tears: represent fissuring or an isolated avulsion of the supraspinatus.
- Medium tears: less than 3 cm in the longest diameter.
- Large tears: 3 to 5 cm in diameter.
- Massive tears: greater than 5 cm in diameter.

Ellman classified partial-thickness tears in three grades:

- Grade 1: the lesions are partial tears, with less than 3 mm of depth. They are relatively minor, but definite disruption of then tendinous fibres can be identified.

- Grade 2: lesions with 3-5mm of depth that extend into the substance of the cuff but not exceed one-half of the thickness of the tendon.
- Grade 3: lesions with more than 6 mm of depth that seems as significant disruptions of more than one-half the substance of the cuff.

Generally, Grade I rotator cuff disease consisted of a pre-tear stage characterized by initial tendon weakening. The fascicles disruptions stimulate a healing response from the body causing tendon inflammation and edema by the cell infiltration and vascular proliferation. [13] The continuous aggravation of tendon condition can result in chronic partial or full-thickness tears, classified as grade II and grade III, respectively. In contrast to chronic tears, acute tears result from an incidence of trauma or a specific tendon injury.[14]

2.5 Tendon healing.

Tendon healing generally occurs by two separate mechanisms depending on the source of the regenerative cells: intrinsic (cells from the existing tendon) and extrinsic (cells from Parthenon, periosteum, etc.). Usually both occur simultaneously, although the extrinsic mechanism has a more robust inflammatory response, acts earlier than the intrinsic mechanism, and reacts more vigorously to inflammatory cytokines produced in the initial phase of healing.[11-12] The use of platelet concentrates was designed to augment this natural process.Healing occurs in three overlapping phases [13]:

- "The acute inflammatory phase" that occurs in the first week after the injury and it is characterized by the deposition of fibrin and fibronectin by platelets, which also secrete potent growth factors and chemotactic agents such as insulin like growth factor (IGF-1), platelet-derived growth factor (PDGF), and transforming growth factor beta (TGF-β). These act to recruit fibroblasts and inflammatory cells like macrophages and neutrophils into the wound area to phagocytize necrotic debris and to induce further inflammation. This phase establishes the initial strength necessary to sustain the growing and remodelling matrix that will be soon deposited.
- "The second or fibroblastic phase" that begins at 48 h and can last up to 8 weeks. The primary characteristic of this phase is the deposition of collagen by migrated fibroblasts and intrinsic tenocytes, starting with type III, and eventually shifting to type I collagen. Collagen III is deposited as a temporary structure in random meshwork of uncrosses linked, small-diameter fibrils. Collagen III is also a known constituent of the rotator cuff that plays an important role in the supraspinatus healing.[14]

- "The third or remodelling phase" that is characterized by decreased synthetic activity of fibroblasts with a related increase in collagen orientation and matrix organization. The biomechanical properties of the repaired tissue will always be inferior to that of the uninjured tendon although the result of the repair process is an intact tendon.

2.6 *Rotator Cuff Repair*.

The goal of a repair, even if partial, is to restore force couples and to re-establish the "suspension bridge". Although shoulder strength may not augment after the intervention, function get usually better because of relief from pain caused by mechanical impingement. Furthermore, the partial healing of the cuff, possibly prevents the re-tear although a whole healing of massive tears is not always achievable.[15]

The surgery consists in covering the footprint with the rotator cuff insertion by increasing the area of contact for potential healing and may improving clinical outcomes. The footprint is the insertion site for the supraspinatus from the edge of the humeral articular surface to the lateral edge of the greater tuberosity .[16] Suture anchor repair constructs using a single row of lateral anchors has been shown at best to restore only 67% of the original footprint of the rotator cuff.[17] Double-row suture anchor constructs have been described placing one anchor adjacent to the articular cartilage and one laterally at the edge of the tuberosity.

The biological atmosphere at the rotator cuff footprint and the inherent poor healing potential of the distal rotator cuff tendon create an environment that is not optimal for the tendon to bone healing. The increase of the rotator cuff repair with Platelet-rich plasma could presumably optimize the biologic environment at the repair site, and allow for a more robust healing response at the tendon to bone interface.[18]

Finally, although good symptomatic relief is possible without healing, final functional outcomes have been correlated with repair integrity. Re-tear rates have been shown to increase with tear size in both open and arthroscopic repairs, approaching 55% and 94% in massive tears, respectively. Small and medium-sized tears have been shown to have re-tear rates between 10% and 20% after both open and arthroscopic repairs.[10]

3. METHODS

3.1 Criteria for considering studies for this review:

Types of studies*.* Studies included were randomised controlled trials comparing platelet-rich plasma injection or platelet-rich fibrin matrix with either placebo, saline or dry needling in rotator cuff disease. Non randomized and pilot trials were excluded. A minimum of 1-year follow-up was also required for inclusion. (figure 1)

Types of participant. Only patients with shoulder soft tissue injuries were included, like:

- Chronic tears, partial or full-thickness rotator cuff tears with retraction of less than 3 cm, supraspinatus tendon disease and acute or chronic tendinopathies (tendinitis/tendinosis).

Sonographic examination or MRI diagnosed the injuries before the intervention.

Types of interventions*.* There were considered studies in which the treatment was Platelet-rich plasma or platelet rich fibrin matrix applied by a surgical method (rotator cuff arthroscopy) or by injections guided by ultrasound. Such studies compared intervention (platelet-rich therapy) with no platelet-rich therapy or placebo.

Types of outcome measures.

Primary outcomes:

- Functional assessment (evaluated by subjective questionnaires such as Constant Scale, UCLA, SPADI, SST, etc).
- Pain (assessed by subjective scales such as visual analogue scales (VAS)).
- Re-tear Rate (assessed by MRI study).

Secondary outcomes:

- ROM and muscle strength.
- Cross sectional-area (CSA) of supraspinatus muscle.
- Adverse effects.

3.2 Search methods for identification of studies

A research was conducted in the following databases: PEDro, Cochrane and PubMed (2010 to march 2016) using the search terms: (“PDGF” OR “platelet derived growth factor” OR “platelet”) AND (“tendon” OR “tendinopathy”) AND “rotator cuff”. No language restrictions were applied.

3.3 Data collection and analysis

***Selection of studies*.** The author reviewed titles and abstract of the articles identified in the research. Full texts of all positively relevant studies were gathered. After that, the study selection was performed applying the selection criteria previously mentioned.

Assessment of bias in included studies. The author, using Jadad scale and The Cochrane "Risk of bias" tools appraised the risk of bias of the studies. The following items were assessed: randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting. Each item was rated as "high", "low" or "unclear" risk of bias when using the Cochrane tool. Jadad Scale considers similar items but each study achieve a score from 0 to 5 depending on the number of criteria met. There were consider high-quality studies those that obtain a score from 3 to 5. (tables 1 and 2)

4. RESULTS

4.1 Results of the search.

The search was done in March of 2016. There were consider studies from the following databases: PEDro, Cochrane, and PubMed (136). The search identified a total of sixteen studies for inclusion, for which full-text were obtained. After study selection, ten studies were included (Jo et al.[26] (2015), Jo et al.[25] (2013), Kesikburun et al.[27] (2013), Malavolta et al.[28] (2013), Randelli et al.[29] (2010), Rha et al.[30] (2013), Rodeo et al.[31] (2012), Ruiz Moneo et al.[32] (2013), Wang et al.[33] (2015), Weber et al.[34] (2013)) and five were excluded (Barber et al.[39] (2011), Jo et al.[38] (2011), Zumstein et al. [35] (2014), Carr et al.[36] (2013), Antuña et al.[37] (2013)). More in-depth details of the screening and recruitment process for the inclusion in this review are illustrated in the "Flow chard" figure 1.

4.2 Included studies.

Individual characteristics of the ten studies are described in the table 1. All studies were published in English.

Design. All the studies selected were randomised. Studies were conducted from 2005 to 2014. The randomization protocol was described in the most trials, however in some studies it is unclear (Rodeo et al.[31], Weber et al.[34]).

Some studies failed in the blinding procedure: it is no clear if trials were only single blind or not blinded at all (Jo et al.[25], Jo et al.[26], Wang et al.[33]), as well as some studies did not explain the quantification of the platelet concentration.

Sample sizes. The studies included a total of 576 participants, with 41 participants being lost during follow-up. Any trial had a substantial loss to follow-up.

Participants. Participant characteristics are similar because of the clinical condition covered by these trials. Patients had degenerative conditions like chronic tendinopathies or rotator cuff tears and this is why included population in these trials are middle-age and over. Studies included a higher percentage of women than men did.

Conditions and interventions. The main intervention was the application of platelet-rich plasma (PRP) or platelet-rich fibrin matrix (PRFM) to the repair site at the time of, or after, arthroscopic rotator cuff repair (Jo et al.[25], Jo et al.[26], Malavolta et al.[28], Randelli et al.[29], Rodeo et al.[31], Ruiz Moneo et al.[32], Wang et al.[33], Weber et al.[34]) or the application of PRP injection in rotator cuff tendinopathies without intervention (Kesikburun et al.[27]) and comparing it with dry needling (Rha et al.[30]). Five studies included participants with complete supraspinatus or rotator cuff tears (Malavolta et al.[28], Randelli et al.[29], Rodeo et al.[31], Ruiz Moneo et al.[32], and Wang et al.[33]). One study included patients with medium to large (Jo et al.[26]) and another one with large to massive rotator cuff tears (Jo et al.[25]). Two studies included patients with tendinosis or partial thickness tears (Kesikburun et al.[27], Rha et al.[30]). One study did not specify what sort of tear patients had (Weber et al.[34]). Studies mostly assessed rotator cuff tears by MRI or ultrasound exploration before intervention. In six trials, PRP or PRFM was applied into the tendon to bone interface (Jo et al.[26], Jo et al.[25], Malavolta et al.[28], Randelli et al.[29], Rodeo et al.[31], Weber et al.[34]), two were applied in the repair area (Ruiz-Moneo et al.[32], Wang et al.[33]) and the other two were applied the closest as possible to the lesion and around it (Kesikburun et al.[27], Rha et al.[30]).

Outcomes. The primary outcomes listed were mostly reported in the included studies. All the studies assess function or pain using at least one validated instrument. Only two of the ten included studies did not assess the integrity of the rotator cuff after the intervention using MRI (Kesikburun et al.[27], Rha et al.[30]). Strength or range of motion was also evaluated in some of the studies (Jo et al.[25], Jo et al.[26], Randelli et al.[29], Rha et al.[30], Rodeo et al.[31], Weber et al.[34]).

4.3 Excluded studies.

There were excluded two studies due the lack of randomization (Barber et al.[39], Jo et al.[38]) and three pilot trials/study protocol (Zumstein et al.[35], Carr et al.[36], Antuña et al.[37]).

4.4 Risk of bias in included studies.

The author's judgement of the risk of bias for each item listed before, is detailed below and outlined for each trial in figure 2.

Allocation. The selection bias of individual trials was assessed mainly to judge the method of allocation concealment and check the similarity of the treatment groups. Most studies allocated

patients using a randomization sequence created with a statistical software. One study allocated in each group by alternating patients (Weber et al.[34]). All studies demonstrated homogeneity of baseline characteristics between groups.

Blinding. Seven trials reported that participants and follow-up assessors were blinded or partially blinded to the procedure (Kesikburun et al.[27], Malavolta et al.[28], Randelli et al.[29], Rha et al.[30], Rodeo et al.[31], Ruiz-Moneo et al.[32], and Weber et al.[34]). Three studies reported that the participants were not blinded to the procedure, but MRI and follow-up assessors were (Jo et al.[26], Jo et al.[25], and Wang et al.[33]).

Most of the studies reported the same post-intervention care and rehabilitation program in each treatment group that is why they are consider at low risk.

Incomplete outcome data. Most of the studies reported no loss follow-up or small losses that were balanced between groups.

Selective reporting. Six of the included studies did not provide any protocol or trial registration details for the study (Kesikburun et al.[27], Randelli et al.[29], Rha et al.[30], Ruiz-Moneo et al.[32], and Wang et al.[33]); these were judge to be unclear of selective reporting bias.

Additional quality assessment. Another item was assessed: the validation of the platelet-rich concentrate. The information about the platelet quantification after the preparation was not available in five trials (Malavolta et al.[28], Randelli et al.[29], Rha et al.[30], Rodeo et al.[31], and Weber et al.[34]).

4.4 Interventions effects. (table 3)

Function: Functional status was documented at one year follow-up in all the studies researched except two (Rha et al.[30], Wang et al.[33]) which documented it at six and four months respectively. The UCLA (University of California Los Angeles) score was reported in six studies (Jo et al.[25], Jo et al.[26], Malavolta et al.[28], Ruiz-Moneo et al.[32], Weber et al.[34], and Randelli et al.[29]). There was a minimal clinically important difference in favour of Platelet-rich therapies in two studies: Malavolta and Weber showed significantly lower shoulder scores at 12 months after surgery and at follow-up respectively (P=.046). Results based on other scores were the following ones: Constant score was assessed in three studies (Jo et al.[25], Jo et al.[26], Randelli et al.[29]) and there were no statistically significant differences in favour of Platelet-rich therapies except at three months follow-up in Randelli's study (P=.02); SPADI (Shoulder pain and disability index) was assessed in four studies (Jo et al.[25], Jo et al.[26], Rha et al.[30], Randelli et al.[29]). There was only a clinically important difference in Rha's

study which showed that the clinical effects of PRP injections were superior to dry needling at two weeks after second injection, three and six months. SST, reported in four studies (Jo et al.[25], Jo et al.[26], Weber et al.[34], Randelli et al.[29]); ASES, reported in four studies (Jo et al.[25], Jo et al.[26], Rodeo et al.[31], Weber et al.[34]; OSS (Oxford shoulder score), Quick-DASH and SF-12 reported in Wang's Study; L'insalata and WORC (Western Ontario Rotator Cuff Index) assessed in Rodeo's [31] and Kesikburun's [27] studies respectively did not show statistically significant differences. However, the results of these trials were significantly heterogeneous.

Pain: Pain was measured in seven trials (Jo et al.[25], Jo et al.[26], Kesikburun et al.[27], Malavolta et al.[28], Randelli et al.[29], Rha et al.[30], Wang et al.[33]) and although they showed clearly homogeneous results, there were found statistically significant differences in Jo 2015 on VAS scale for worst pain at final follow-up (P=.043) in favour of PRP group. Additionally, Randelli found significantly lower VAS scores in the PRP group at 3,7,14 and 30 days postoperative but no difference at 2,6 and 12 months. The rest of trials did not show significant differences at any follow-up point.

Re-tear rate: Six of the seven studies that assessed re-tear rates (Jo et al.[25], Jo et al.[26], Malavolta et al.[28], Randelli et al.[29], Rodeo et al.[31], Wang et al.[33]) found fewer re-tears in PRP group apart from Weber 2012 in which PRFM group showed higher re-tears rates even though it was not statistically significant. There were found statistically important differences in the two Jo's studies (P=.032 in the recently one, P=.023 in the older one).

Adverse effects: Two trials reported complications: one tendon repair rupture in the control group in Randelli et al.[29] and two cases in Malavolta et al.[28] with postoperative stiffness, one for each group but neither required a second surgical procedure.

Other outcomes:

ROM and muscle strength were measured in six studies (Jo et al.[25], Jo et al.[26], Randelli et al.[29], Rha et al.[30], Rodeo et al.[31], Weber et al.[34]) and there were not found statistically significant differences between the two groups in any of them.

CSA (Cross-sectional area) of supraspinatus muscle was measured in Jo et al.[25] and Jo et al.[26] and a change between one year postoperative and immediately postoperative CSAs was found (P=.047 and P=.014 respectively) which means that CSA of the supraspinatus increased.

4.5 Studies description

Studies included in this review are described below (summary in table 3):

Jo C et al. (2013)[25] compared PRP augmentation with a conventional therapy in a randomized, single blind controlled trial, which enrolled patients with large to massive rotator cuff tears undergoing arthroscopic rotator cuff repair, to assess the efficacy on the speed and quality healing process. Forty-eight patients, who received an arthroscopic double row rotator cuff repair, were randomly allocated into two groups: 24 patients in the PRP group who also received three PRP-augmented gels; 24 patients in the conventional group who only received conventional treatment that included the arthroscopic intervention and the rehabilitation program. Platelet-rich plasma was prepared in the PRP group one day before surgery using plateletpheresis system with leukoreduction set. Platelet counts were adjusted with saline and were added 0,3mL of 10% calcium gluconate to produce 3 mL of PRP gel with $1000x10^3$ platelets/µL. Before de surgical procedure, the rotator cuff tear was carefully evaluated. After the debridement of the footprint of the greater tuberosity, rotator cuff repair was performed covering the original footprint by using 3-5 suture anchors in double row. Three PRP gels were threaded to the suture per patient and it was interposed at the tendon to bone interface. After repair, shoulder was immobilized for 4 to 6 weeks and patients were allowed to further passive, assisted and active ROM exercise after gradual weaning. After 3 months, patients were allowed to practice light sport activities and strengthening exercise. Full return to sports was permitted after 6 to 9 months.

Outcome assessments was performed at a minimum of nine months after surgery in the case of MRI to measure the re-tear rate. Pain, ROM, muscle strength, CSA and functional outcomes were measured at a minimum of twelve months after surgery. The authors found a lower re-tear rate in the PRP group (P=.023) than that in the conventional group; Clinical outcomes did not show any significant difference between the two groups except for the final overall function (P=.043). They also found a significantly change in 1-year postoperative and immediately postoperative cross-sectional area (CSA) between the two groups (P=.047).

Authors concluded that PRP application improved structural outcomes because of the lower re-tear rate and the increase of the supraspinatus CSA compared with repairs without PRP augmentation.

Jo C et al. (2015)[26] assessed the efficacy on the speed and quality-healing process of PRP augmentation by comparison with a conventional therapy in a randomized, single blind controlled trial, which enrolled patients with medium to large rotator cuff tears undergoing arthroscopic rotator cuff repair. Seventy-four patients, who received an arthroscopic double row rotator cuff repair, were randomly allocated into two groups: 24 patients in the PRP group who also received three PRP-augmented gels; 24 patients in the conventional group who only received conventional

treatment that included the arthroscopic intervention and the rehabilitation program. Platelet-rich plasma preparation, surgical procedures, PRP application and rehabilitation programme were the same as the previous study summarizes.

Refer to outcomes assessment, Constant Score was measured at three months after surgery. Pain, ROM, muscle strength, CSA and functional outcomes were measured at baseline, 3, 6 and 12 months after surgery. The authors found a lower re-tear rate in the PRP group (P=.043) than that in the conventional group; Clinical outcomes did not show any significant difference between the two groups except for the VAS for worst pain (P=.043). They also found a significantly change in 1-year postoperative and immediately postoperative cross-sectional area (CSA) between the two groups (P=.014).

Authors concluded that PRP application improved the quality as evidence because of the lower re-tear rate and the increase of the supraspinatus CSA compared with repairs without PRP augmentation, but not the speed of healing.

Kesikburun et al. (2013)[27] investigated the effect of PRP injections in pain and shoulder functions in patients with rotator cuff tendinopathy in a randomized, double blind, placebo-controlled trial. Forty patients were randomly allocated into two groups: twenty patients in the PRP group who received an ultrasound guided injection with 5 mL of PRP prepared with autologous venous blood; twenty patients in the control group who received an ultrasound guided injection with 5 mL of saline solution. The PRP was prepared by using the GPS III Platelet separation system starting from 54 mL of venous blood from patients mixed with 6 mL of citrate and they obtained 6 mL of PRP, 1 mL was collected to establish the platelet concentration and the remaining 5 mL was infiltrated into the centre of the lesson and 4 sites around the lesion. After injection, all patients received a total of 6 weeks standard rehabilitation programme in which patients were instructed to rest overhead and rotary movement during the first two days. After that, they started in an exercise program supervised by a physical therapist that went on for three weeks. Then, patients moved onto home based program with strengthening and stretching exercise for a further three weeks.

Outcomes measures were assessed at baseline, 3, 6, 12 and 24 weeks and 1 year after the injection. Results revealed no clinically important difference between the groups in WORC, SPADI, ROM and VAS scores at any assessment point in follow up. Authors concluded that Platelet-rich plasma injection effects in functional outcomes were the same as placebo in patients with chronic rotator cuff tendinopathy.

Malavolta EA et al. (2014)[28] investigated if the use of PRP promotes better functional and structural outcomes in arthroscopic rotator cuff repair in a prospective, randomized, double blind controlled trial. Fifty-four patients, who received an arthroscopic single-row rotator cuff repair, were divided into two group with twenty-seven patients each one: PRP group who received also a liquid PRP injection prepared by apheresis with autologous thrombin; Control group who received only conventional surgery. PRP was prepared by apheresis using "the haemonetics MCS+ 9000 blood cell separator and 994-CFE apheresis set" and they obtained two syringes with 10 mL aliquots of PRP, one fraction of 1.5mL of thrombin and 0.8 mL of 10% calcium chloride each one. In the surgical procedure acromioplasty and debridement of the greater tuberosity was performed in all cases. It was a single-row repair with absorbable double-loaded suture anchors and simple stiches. All patients received a rehabilitation programme in which shoulder was immobilized for 6 weeks. After 3 weeks passive exercise was permitted as well as active assisted and active free exercise were permitted after 6 weeks and strengthening exercise was started at week 12.

Outcomes assessment was performed at baseline, 3, 6, 12 and 24 months after surgery to evaluate functional results with UCLA and constant scores, pain with VAS scale and re-tear rate with MRI. The only difference found was in UCLA score at 12 months in favour to PRP group (P=.046) but the rest of outcomes did not showed any important change. Author's conclusion was that PRP prepared by apheresis and applied in liquid state with thrombin did not promote better clinical outcomes at final follow-up.

Randelli et al. (2011)[29] investigated the effect of local application of PRP in tendon healing in patients undergoing arthroscopic rotator cuff repair. Trial was designed as prospective, randomized, controlled and double-blinded. Fifty-three patients, who were subjected to an arthroscopic rotator cuff single-row repair were allocated into two groups: twenty-six in the treatment group who received an intraoperative PRP application with autologous thrombin component; twenty-seven patients in the control group who only received conventional intervention. Autologous platelet-rich plasma preparation was performed by mixing 6 mL of anticoagulant Citrate Dextrose Solution with 54 mL of whole blood and placed in a centrifuge it for 15 minutes at 3200 rpm. Platelet poor plasma was centrifuged again for 2 minutes at 2000 rpm. To obtain the autologous serum, two 9 mL vacuum tubes were centrifuged for 2.5 minutes at 3200 rpm and afterward, a ratio of 1:5 of 10% calcium chloride was added. A final 6 mL PRP was applied in the tendon to bone interface when the surgical procedure was ended. Postoperatively rehabilitation programme included shoulder discharged the

day after the intervention. After 10 days, patients were allowed to start passive assisted exercise and gradually, at minimum of 30 days from operation, start active range of motion exercise. Strengthening exercises were not allowed until 2 months postoperatively. Clinical functional outcomes measurement was performed at baseline, 3, 6, 12 and 24 months after surgery, as well as, pain measurement was performed at 3, 7, 14 and 30 days after surgery and radiological follow-up was performed to assess the rotator cuff integrity. The two groups showed homogeneous results but there were two statistically significant differences: pain scores in treatment group were lower than the control group at the time listed previously and functional outcomes were higher in the treatment group than the control group at 3 months after surgery but not at any other measured point. Authors concluded that autologous PRP reduced pain in the first postoperatively months. In addition, the long- term results of subgroups of grade 1 and 2 tears suggest that PRP positively affected rotator cuff healing.

Rha DW et al. (2012)[30] compared the effects of PRP injections with those of dry needling on shoulder pain and function in patients with rotator cuff disease in a single-centre, prospective, randomized, double-blinded and controlled trial. Thirty-nine patients were randomly grouped: twenty in the PRP group, who received two platelet-rich plasma injection into the lesion, and nineteen in the dry needling group, who received two dry needling procedures. Both interventions were performed under ultrasound guidance and at four weeks intervals. 3 mL of platelet-rich plasma was prepared using “The Prosys PRP concentration system” and they was infiltrated into the lesion (or around the lesion if it was difficult) of the supraspinatus tendon. All the patients received a self-exercise and posture correction protocol and they were recommend relative rest and continue with their usual daily-living activities without overhead and rounded shoulder movements until pain had significantly subsided. Functional scales and passive range of motion were assessed at the six-month follow up. PRP group showed superior clinical effects to the dry needling group from six weeks to six months ($P<.05$). Authors concluded that autologous PRP injections lead to a progressive reduction in pain and disability when compared to dry needling.

Rodeo S et al. (2012)[31] evaluated the effect of platelet-rich fibrin matrix on rotator cuff tendon healing in a prospective, randomized, double-blinded controlled trial. Seventy-nine patients who were subjected to arthroscopic rotator cuff repair were randomized into two groups: forty patients in PRFM group who also received PRFM at tendon to bone interface; thirty-nine patients in the control group who only received standard repair. PRFM was produced using “Cascade Autologous

Platelet System" and it was applied at the tendon to bone interface after the surgical standard techniques. After that, patients carried out a postoperative rehabilitation protocol in which the first 6 weeks consisted of the protection phase but then patients began passive exercises and gradually at 6 weeks, they were allowed to realize active exercise to re-establish motion and finally strengthening exercises were permitted at 12 weeks. Functional outcomes were assessed at baseline, 6 weeks, 3 and 12 months postoperatively and they did not show any statistically significant difference. There were no differences in tendon-to-bone healing neither. However, some analysis demonstrated that PRFM was a significant predictor (P=.037) for a tendon defect at 12 weeks. Authors concluded that PRFM had no demonstrable effect on any clinical outcomes. In fact, analysis suggests that PRFM may have negative effects on healing.

Ruiz-Moneo et al. (2013)[32] analysed the functional and structural effects of PRGF in full-thickness rotator cuff tears after arthroscopic repair in a randomized, double-blinded, controlled trial. From sixty-nine patients selected, six were excluded after surgery because their footprint coverage was less than 50%. The remainder patients were allocated into two groups: Thirty-two patients in PRGF group who also received PRGF; Thirty-one patients who only received conventional surgery. During the intervention, the tear and soft tissue was debrided from the footprint area and double-row suture technique was used in all cases. PRGF was prepared using "PRGF System 1, B.T.I Biotechnology Institute, Vitoria-Gasteiz, Spain). This protocol results in platelet concentrations of about 600,000/µL. PRGF was introduced into the repair area and activated with $CaCl_2$ at 10%. The efficacy was measured 1 year after surgery using UCLA score and arthro-MRI to evaluate functional and structural outcomes respectively but no significant differences between PRGF and control groups were observed in any of them. Authors concluded that their trial does not support the use of PRGF because no differences in healing and function were observed.

Wang A et al. (2015)[33] assessed the effects of PRP application in tendon healing and functional recovery after double-row arthroscopic supraspinatus repair in a randomized, not blinded, controlled trial. Sixty patients were randomly allocated into two groups: Thirty in PRP group who also received two ultrasound-guided injection of PRP; Thirty in Control group who received only conventional surgery. Surgical technique was the same as the other ones, with debridement of the bursal tissue and tendon margins and also, they used double-row suture-bridge repair with bio-absorbable anchors. The platelet concentrate was prepared using the "Arthrex Autologous Conditioned Plasma (ACP) system" and they obtained 2-4 mL of PRP with 470,000 platelet/µL

platelets concentration approximately. Two PRP injection were applied on separate occasions at days 7 and 14 after surgery at the tendon repair site under direct visualization with ultrasound and the preparation was activated by the addition of 2 mL of $CaCl_2$. Patients were immobilized for 6 weeks postoperatively and the followed a standard rehabilitation protocol in which only passive exercises was allowed in the first 6 weeks. Active assisted exercises were allowed from 6 weeks and finally strengthening program was allowed from 10 weeks. Clinical effects was measured using Oxford Shoulder Score (OSS), Quick-Dash, VAS, SF-12 at baseline, 6,12 and 16 weeks post-operative; At 16 weeks ROM and strength was assessed and MRI was performed. Any outcome measured showed statistically significant differences between PRP and control group at any time point. Authors concluded that the treatment applied does not improve early rotator cuff healing or functional recovery.

Weber S et al. (2012)[34] assessed the effects of Platelet Rich Fibrin Matrix in rotator cuff surgery in a prospective, double-blinded, randomized, controlled trial. Sixty patients were equally randomly allocated into PRFM or Control group to received PRFM intraoperative during an arthroscopic rotator cuff intervention or not. Surgery was performed as usual using a standard single-row suture anchors technique and all patients underwent an acromioplasty. PRFM was prepared using the "Cascade system" (Musculoskeletal Transplant Foundation, Edison, New Jersey) and calcium was used to initiate the clot which was about 1 cm in size. PRFM was applied under the edge of the rotator cuff tear. Outcome measured were the following ones: SST and ROM assessment performed at 3, 6, 9 and 12 weeks postoperatively; ASES and UCLA shoulder scores were assessed one year later; MRI obtained on patients between 3 and 6 months postoperatively. No differences were observed in any outcome except UCLA shoulder score at final follow-up which was significantly lower in PRFM group than that in control group ($P<.046$). Authors concluded that PRFM did not improve perioperative morbidity, clinical outcomes or structural integrity.

5 DISCUSSION:

The purpose of this review was to identify, critically assess, collect and summarize the main possible evidences currently available about the effect of platelet-rich therapies in functional and structural outcomes in patients with rotator cuff tears.

To this aim, an in-depth analysis of the ten studies selected in a databases (PubMed, PEDro, and Cochrane) research was carried out. The studies selected showed us the effect of the application of

platelet-rich therapy (PRP injection or PRFM) by an ultrasound guided or after an arthroscopic rotator cuff repair in comparison with placebo or dry needling.

Keeping in mind the achieved results, the clinical and structural effects will be summarized to obtain a clear conclusion. On one hand, trials that compare PRP and placebo will be analysed together and on the other hand Rha et al. study will be analysed alone because it compared PRP with dry needling.

As far as clinical outcomes are concerned, only three studies, Malavolta et al.[28] Weber et al.[34] and Randelli et al.[29] showed functional improvement in the PRP group in comparison with the control group but these results were not homogeneous. Malavolta obtained better results in PRP group at 12 months using UCLA shoulder score but not at follow-up what means that PRP effects were higher at the middle portion of tendon healing as well as Weber found significantly lower rates in UCLA shoulder score at final follow up (12 months), with the same meaning. Randelli observed higher subjective scores after the third postoperative month, proving that PRP application produces an accelerated healing process at the early phases.

Regarding to Rha et al.[30] study, PRP injection provided a reduction of SPADI score in comparison with dry needling at six months follow-up. That could be explained because PRP has stronger therapeutic effects or because the plasma has a different therapeutic mechanism than dry needling despite the healing process is thought to be similar.

However, considering that only four of the studies showed these results and not with remarkable differences, it is difficult to say that PRP provided more symptomatic relief and functional improvement than placebo.

In reference to pain assessment only Jo et al.[26] and Randelli et al.[29] found minimal differences between PRP and control group evaluated with Visual Analogue Scale (VAS). Jo et al[26] described a lower score in VAS scale for worst pain in PRP group than that in the conventional group. Whereas Randelli et al.[29] found a significantly lower VAS score in the PRP group after 3, 7, 14 and 30 postoperative days. That fact could be explained by platelet analgesic properties through releasing protease-activated in the receptor of four peptides.[17] But again, there is not enough evidence to claim that platelet-rich therapies decrease the subjective perception of pain.

The re-tears rate was measured by MRI from, at least, 6 months follow-up after the intervention. Six of the trial selected showed a lower re-tear rate in PRP and only one described higher re-tears rates in the PRP group than that in the control group. However, just the two Jo et al.[25,26] studies obtained statistically significant differences. It should be noticed that re-tears considered, were those that occurred in patients whose tears were sorted as IV or V in Sugaya classification.[18] Although Randelli

et al.[29] did not found statistically significant differences, clinical outcomes analysis showed that the repair integrity was associated with age, shape and tear retraction: "The mean age of patients with a torn cuff was higher than those with an intact cuff. Crescent shape tears were more likely to have an intact cuff after repair compared to those with an L, inverted L or U shape tear. Massive tears had the highest chance of re-tears after repair". In addition, there was found a relationship between the risk for re-tear and the grade of tear retraction. However, Weber et al.[34] obtained a higher percentage of re-tears in the PRP group (42.9%) than that in the control group (29.2%) even though MRI scans were obtained at 3-5 months after surgery when the healing process was in the early phases.

Regarding to *ROM and muscle strength*, measurement included in six studies did not showed any difference between the two groups. That could be explained because all patients, regardless of what group they belonged to, received the same rehabilitation protocol, being that the principle responsible of the ROM and muscle strength improvement.

In reference to Cross-sectional area (CSA) of supraspinatus muscle, only two studies assess their results but both obtained important clinical differences. Jo et al.[25,26] found an important change in the CSA between the first postoperative year and immediately after the surgery in favour to the PRP group. A lower decrease in CSA of supraspinatus muscle submits an improvement in structural outcomes 1 year after the repair. Therefore, the application of PRP could be recommended, although it may not provide satisfactory clinical outcomes in the early phases of tendon healing.

With reference to the surgical technique, it is also important to highlight that only Rodeo et al.[31] analysed the relationship between the tendon healing and the type of reconstruction, and they found a significantly higher failure rate in patients treated with PRFM and double row suture in comparison with patients in the control group treated with placebo and a single row suture. These facts suggest that PRFM applied at the tendon to bone interface at the time of surgery may have inhibitory effects on tendon healing.

In any case, the biggest problem for obtaining a real and clear conclusion is the great disparity between the methods and type of interventions performed in each study just like the divergence in the analysing way. There are a great number of types of Platelet-rich therapies as well as methods to obtain it, which obviously could not produce the same clinical effects.

6 CONCLUSION

After the analysis of these studies, it can be concluded that there is a lack of evidence to prove the effectiveness of Platelet-rich therapy in comparison with placebo in rotator cuff tears in functional

outcomes. However, the majority of studies support that PRP reduce the re-tear rate at follow up the same as it improves the cross sectional area of the supraspinatus muscle. Thus, it seems that structural outcomes get better after the PRP application.

With regards to which type of PRP achieves better results, there is nothing clear and only PRFM was shown to be harmful.

Due to all those reasons, it is concluded that there is necessary to carry out new trials with higher methodological quality and standardized protocols to reach a clear conclusion.

7 TABLES

7.1 Flowchart

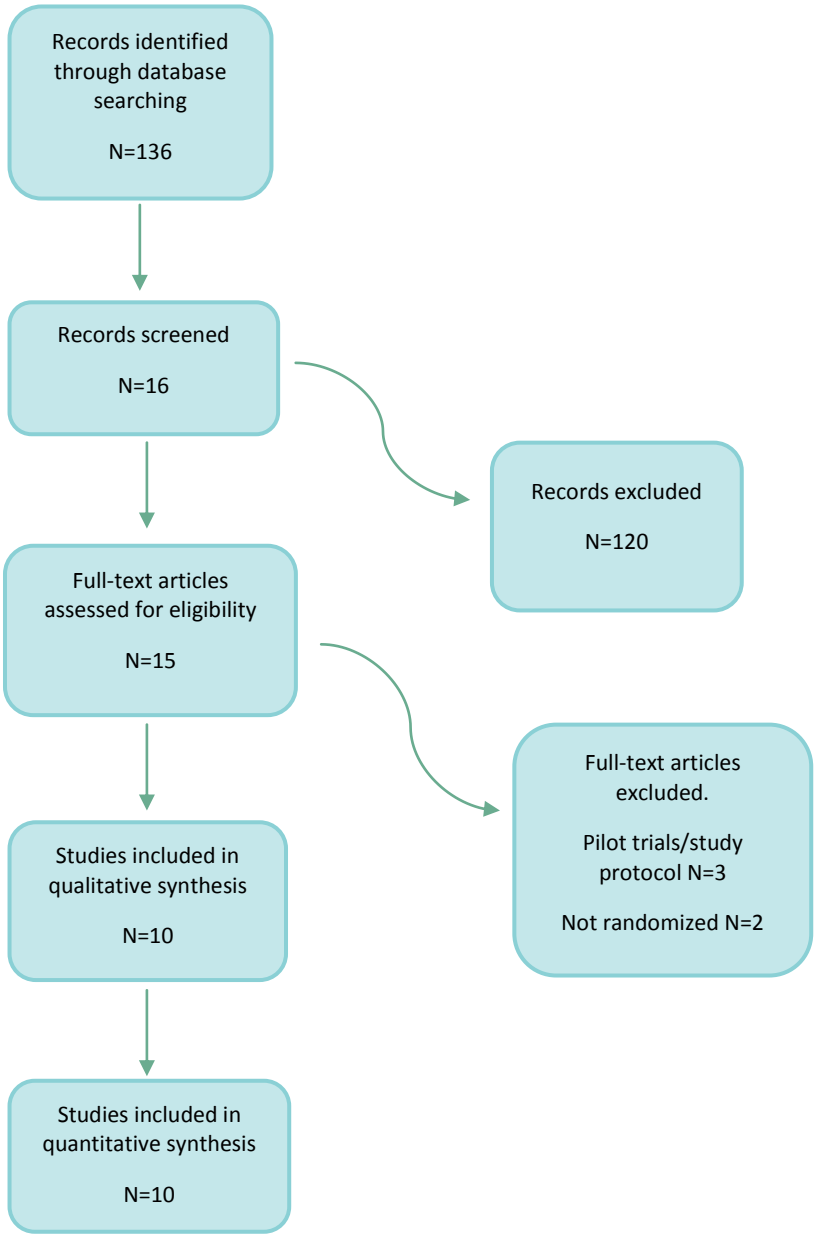

Figure 1: flow-chart

7.2 "Cochrane Risk of bias

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting (reporting Bias)
Jo C, 2013	+	-	-	+	+	+
Jo C, 2015	+	-	-	+	+	+
Kesikburun S, 2013	+	+	+	+	+	?
Malavolta E, 2013	+	+	+	+	+	+
Randelli 2011	+	+	+	+	+	?
Rha D.W 2013	+	+	+	+	+	?
Rodeo 2012	+	+	+	+	+	+
Ruiz Moneo P, 2013	+	+	+	+	+	?
Wang A, 2015	+	-	-	+	+	?
Weber S, 2013	?	+	+	+	+	+

Table 1: Cochrane risk of bias

7.3 Jadad Scale

	Barber Et al.	Rha et al.[30]	Jo et al.	Jo Et al.[25]	Jo Et al.[26]	Kesikburun et al.[27]	Malavolta et al.[28]	Randelli et al.[29]	Ruíz-moneo et al.[32]	Rodeo et al.[31]	Wang et al.[33]	Weber et al.[34]
1. Was the study described as randomised?	0	1	0	1	1	1	1	1	1	1	1	1
2. Was the study described as double blind?	0	1	0	0	0	1	1	1	1	1	0	1
3.Was there a description of withdrawals and drop outs?	0	1	0	1	1	1	1	1	1	1	1	1
Its randomisation is appropriate		1		1	1	1	1	1	1	1	1	1
Its randomisation is inappropriate												
Its blinding is appropriate		1				1	1	1	1	1		1
Its blinding is inappropriate												
Score	0	5	0	3	3	5	5	5	5	5	3	5

Table 2: Jadad scale applied to articles found

AUTHOR-YEAR	PURPOSE	STUDY DESIGN	PATIENTS	PRP INTERVENTION	INTERVENTION	OUTCOMES MEASURES	RESULTS	CONCLUSION
JO C et al.[25] 2013	To assess the efficacy of PRP augmentation in patients undergoing arthroscopic repair for large to massive rotator cuff tears.	It is a randomized, single blind, parallel group, controlled trial.	N=48 Average age: - PRP: 64.21 - Control: 61.92 Patients with large to massive rotator cuff tear.	Patients received three PRP-augmented gels applied at tendon to bone interface. Platelets concentration: 1000x10^{3}platelets/µL PRP was created by Plateletpheresis with leukoreduction set 1 day before surgery.	All the participants received an arthroscopic repair of rotator cuff (double row repair and a postoperative rehabilitation protocol. - PRP group (N=24) who received three PRP-augmented gels. - Conventional group (N=24) who received conventional treatment.	Re-tear rate Pain, ROM, Strength and overall satisfaction ASES Constant shoulder scale UCLA DASH SST SPADI	The re-tear rate of PRP group was significantly lower than conventional group (P=.023) Pain, ROM, Strength and overall satisfaction showed no significant difference between the two groups. There was not statically significant difference in shoulder function scores between PRP and conventional group (ASES (P= .252), Constant (P= .188), UCLA (P= .284), DASH (P= .259), SST (P= .397), SPADI (P=.162)	The application of PRP for large to massive rotator cuff repairs significantly improved structural outcomes, as evidenced by a decreased re-tear rate and increased CSA of the supraspinatus compared with repairs without PRP augmentation. There was no significant difference in clinical outcomes except the overall shoulder function after 1-year follow-up; however, better structural outcomes in the PRP group might suggest improved clinical outcomes at longer term follow-up.
Jo C et al.[26] 2015	To assess the efficacy of PRP augmentation on the speed and quality of healing in patients undergoing arthroscopic repair for medium	It is a randomized, single blind, controlled trial.	N= 74 Range of age: - PRP: 60.08 - Control: 60.92 Patients with a medium to large rotator cuff tear.	Patients received three PRP-augmented gels applied at tendon to bone interface. Platelets concentration: 1000x10^{3}platelets/µL PRP was created by Plateletpheresis with	All the patients received an arthroscopic double row rotator cuff repair and a postoperative rehabilitation program. - PRP group(N=37) who received 3 PRP gels each patients during de intervention	*Primary outcome:* Constant score *Secondary outcomes:* Pain (VAS) ROM Muscle	There was no difference between the two groups in the constant score (P=.545). The two groups had no significant differences in VAS scale, ROM, muscle strength,	The application of PRP for medium to large rotator cuff repairs, reasonably improved the quality, compared with repairs without PRP, by decreased re-tear rate and increased CSA of supraspinatus, but the

	to large rotator cuff tears.			leukoreduction set 1 day before surgery.	- Conventional group (N=37) who received only conventional repair.	strength Overall satisfaction and function Functional scores (ASES, Constant score, UCLA, SST, SPADI, CSA) Re-tear rate (MRI)	overall satisfaction and function and functional scores (P> .05). However, VAS scale for worst pain had at final follow-up shows a significantly lower score in the PRP group than in the conventional group (P= .043). As well as re-tear rate of PRP group was reasonably lower than the conventional group (P= .032). There was shown a lower decrease in CSA of supraspinatus muscle.	healing speed remains the same.
KESIKBURUN S et al .[27] 2013	To investigate the effect of PRP injections on pain and shoulder functions in patients with chronic rotator cuff tendinopathy (RTC).	It is a randomized, double-blind, placebo-controlled trial.	N=40 Average age: - PRP: 45.5 - Placebo: 51.4 Patients with partial tears.	Patients received an injection with 5 mL of PRP prepared from autologous venous blood in four sites around the lesion. Platelets concentration: $1014.9x10^3$platelets/µL.	Forty patients received an ultrasound-guided injection into the sub acromial space, and they were randomized into: - PRP group (N=20) who received a PRP injection. - Placebo group (N=20) who	WORC (Western Ontario Rotator Cuff Index) SPADI VAS	There were no statically significant differences between PRP and Placebo group in any outcome measure (WORC (P=.698), SPADI (P=.565), VAS (P=.068).	At 1-year follow up, a PRP injection was found to be no more effective in improving quality of life, pain, disability and shoulder range of motion than placebo in patients with chronic RTC who were treated with an exercise

					received a 5mL injection of saline solution.			program.
MALAVOLTA E et al.[28] 2014	To determine if the use of PRP promotes better functional and structural results in arthroscopic rotator cuff repair.	It is a prospective, randomized, double-blind controlled trial.	N= 54 Average age: - PRP: 54.07 - Control: 55.30 Patients with complete supraspinatus tears with retraction of less than 3cm.	Patients received an injection with 10mL of PRP combined with autologous thrombin. PRP was created by an apheresis system.	All the patients received an arthroscopic single row rotator cuff repair and a postoperative rehabilitation program - PRP group (N=27). They received a liquid PRP, injection at the end of the surgery. - Control group (N=27). They received only conventional surgery.	Primary outcome: UCLA Secondary outcomes: Constant shoulder scale VAS Re-tear rate (MRI)	There were no statistically significant differences between the two groups in UCLA score except at 12 months (P=.046). Constant and VAS scale did not reveal statistically significant differences at any assessment. MRI did not exhibit statistically significant differences on re-tear rate between the groups at any investigated time point.	PRP prepared by apheresis and applied in the liquid state with thrombin did not promote better clinical results at 24-months follow up.
RANDELLI P et al.[29] 2011	To investigate if local application of PRP improves tendon healing in patients undergoing arthroscopy rotator cuff repair.	It is a prospective, randomized, controlled, double blind trial.	N=53 Average age: - PRP: 61.6 - Control: 59.5 Patients with complete rotator cuff tears.	PRP application was combined with autologous thrombin component. It was created by centrifugation process.	All participants received an arthroscopic rotator cuff repair (single row repair, absorbable anchors) and a postoperative rehabilitation program. - Treatment group (N=26) who	Constant shoulder scale SST UCLA score VAS Strength in external rotation	A significant difference (P< .05) in pain scores was found between the two groups. The VAS score was significantly lower in the PRP group at 3,7,14 and 30 postoperative days	The results of this study showed autologous PRP reduced pain in the first postoperative months. The long-term results of subgroups of grade 1 and 2 tears suggest that PRP positively affected rotator cuff healing.

					received an intraoperative PRP. - Control group (N=27) who received the intervention.	(SER) Rate of re-tear	however no difference was found at 3,6 and 12 months. There was only a statically significant difference between PRP and control groups for all the clinical outcomes (Constant (P=.02), SER (P=.04), UCLA (P=.03), SST (P=.02)) at the three months follow-up, but not at 6, 12 or 24 months. There was not statically significant difference in the re-tear rate (P=.40).	
Rha D.W et al.[30] 2013	To compare the effects (function and shoulder pain) of dry needling with those of PRP in patients with rotator cuff disease.	It is a single centre, prospective, randomized, double-blind controlled trial.	N=39 The average age: - PRP: 52.2 - Dry needling: 53.9 Patients with tendinosis or partial thickness tears less than 1cm.	Patients received two injection with 3mL of PRP with four weeks between each one, into the lesion. PRP was created by a centrifugation system.	- PRP group (N=20). Patients received two PRP injections under ultrasound guidance and self-exercise protocol. - Dry needling group (N=19). Patients received	SPADI Pain Total disability score Improved range of: shoulder internal and external rotation,	Shoulder pain and disability index (SPADI) and pain values shows that the clinical effects of platelet-rich plasma injections was superior to the dry needling ($P< 0.05$) at times 3, 4 and 5. The range of motion	PRP injections provide a pain and disability reduction but not range of motion of the shoulder when compared to dry needling. These findings suggested that treatment with autologous platelet-rich plasma could be safe and

					dry needling under ultrasound guidance twice and self-exercise protocol.	flexion and abduction.	in internal rotation and shoulder flexion was higher too at times 4 and 5 in PRP group (P<0.05).	useful for rotator cuff disease.
Rodeo S et al.[31] 2012	To evaluate the effect of platelet-rich fibrin matrix on rotator cuff tendon healing.	It is a prospective, randomized, double-blind controlled trial.	N=79 Average age: - PRP: 58.9 - Control: 57.21 Patients with rotator cuff tears from 0 to less than 3 cm.	Patients received PRFM down the suture to the bone surface.	All patients received an arthroscopic rotator cuff single and double row surgery. - PRFM group (N=40) who received PRFM at tendon to bone interface. - Control group (N=39) who received standard repair without PRFM.	ASES L'insalata shoulder score Manual muscle testing (MMT)	There were no statistically significant differences between the two groups at any of the time points in any outcome score (P>.05) (ASES, L'insalata, MMT).	Platelet- rich fibrin matrix applied to the tendon-bone interface in arthroscopic rotator cuff repair did not improve tendon healing, muscle strength or clinical outcomes scores. In fact, the analysis suggested that PRFM resulted in lower healing rates may having a negative effect.
Ruiz-Moneo P et al.[32] 2013	To determine whether addition of PRGF improves functional and structural outcomes after arthroscopic repair of full-thickness rotator cuff tears.	It is a randomized, parallel group, double-blind, controlled trial.	N=69 Average age: - PRP: 56 - Control: 55 Patients with full-thickness rotator cuff tears.	Patients received PRGF with platelets concentration about 600000 platelets/µL PRGF was created by a centrifugation system.	All the patients received an arthroscopic double-row rotator cuff repair and a postoperative rehabilitation program. - PRGF group (N=32) who received PRGF after arthroscopy.	UCLA score Arthro-MRI	There were no significant differences in the UCLA score (P=.751) neither in arthro-MRI (40% total healing of tendons, 30% partial healing, 30% lack of healing).	This clinical trial does not support the use of plasma rich in growth factors in the arthroscopic repair of rotator cuff tears because no differences in rotator cuff healing or improvements in function were observed.

					- Control group (N=31) who received only conventional surgery.			It was sponsored.
WANG A et al.[33] 2015	To ascertain whether postoperative and repeated application of PRP to the tendon repair site improves early tendon healing and enhances early functional recovery after double-row arthroscopic supraspinatus repair.	It is a randomized, not blinded, controlled trial.	N=60 Average age: - PRP: 59.8 - Control: 58.4 Full-thickness tear of supraspinatus less than 22 mm.	Patients received two injection with 2-4 mL of PRP at 7 and 14 days after surgery. Platelets concentration: 470000 platelets/µL. PRP was created by a centrifugation system.	All the patients received an arthroscopic double-row supraspinatus repair and a postoperative rehabilitation protocol. - PRP group (N=30) who received two ultrasound-guided injections of PRP to the repair site at postoperative 7 and 14 days. - Control group (N=30) who received only conventional surgery.	MRI at 16 weeks Oxford Shoulder Score (OSS) QuickDASH VAS SF-12	There were no statistically significant differences between the groups on MRI rating at 16 weeks neither in functional scores (OSS, VAS, quickDASH, SF-12), strength and range of motion (P > .05).	After arthroscopic supraspinatus tendon repair, image-guided PRP treatment in two occasions does not improve early tendon-bone healing or functional recovery.
Weber S et al.[34] 2013	To assess the use of platelet-rich fibrin matrix in	It is a prospective, double-	N=60 The average age: - PRFM: 59.67	Patients received PRFM with 1 cm of diameter into the repair site	Sixty patients were randomized to receive PRFM intraoperative	ROM UCLA SST	There were no statistically significant differences between	The application of PRFM in arthroscopic rotator cuff repair did not show

	rotator cuff surgery.	blinded, randomized control trial.	- Control: 64.5		during an arthroscopic single row rotator cuff intervention or not. - PRFM group (N=30) - Control group (N=30)	VAS ASES	the groups on ASES, MRI, ROM, SST and VAS. However, UCLA shoulder scores were statistically significantly lower at follow up (P<.046).	significant differences in pain, functional recovery or structural outcomes.

Table 3: Summary of results of articles included in the study

8 REFERENCES:

1. Dohan Ehrenfest David M. Classification of platelet concentrates (Platelet-Rich Plasma-PRP, Platelet-Rich Fibrin-PRF) for topical and infiltrative use in orthopedic and sports medicine: current consensus, clinical implications and perspectives. Muscles, Ligaments and Tendons Journal 2014; 4(1):3-9.
2. Marx RE. Platelet-rich plasma (PRP): what is PRP and what is not PRP? *Implant Dent* 2001; 10(4):225-228.
3. Foster TE, Puskas BL, Mandelbaum BR, Gerhardt MB, Rodeo SA. Platelet-rich plasma: from basic science to clinical applications. The American journal of sports medicine 2009; 37:2259–2272.
4. McLellan J, Plevin S. Does it matter which platelet-rich plasma we use? Equine Vet Educ 2011;23:101–104.
5. Bianchi S, Zamorani MP. US-guided interventional procedures. In: Bianchi S, Martinoli C, editors. Ultrasound of the musculoskeletal system. 1st ed. Berlin: Springer; 2007. p. 246–56.
6. Tempelhof S, Rupp S, Seil R. Age-related prevalence of rotator cuff tears in asymptomatic shoulders. *J Shoulder Elbow Surg* 1999; 8(4):296-299.
7. Vollans S., Ali A. Rotator cuff tears. *Surgery (United Kingdom) 2016;* 34(3): 129-133.
8. Perry SM, McIlhenny SE, Hoffman MC, Soslowsky LJ. Inflammatory and angiogenic mRNA levels are altered in a supraspinatus tendon overuse animal model. *J Shoulder Elbow Surg* 2005;14(1 Suppl S):79S-83S.
9. Baumgarten KM, Gerlach D, Galatz LM, et al. Smoking increases the risk for rotator cuff tears. Paper presented at: Annual Meeting of the American Academy of Orthopaedic Surgeons, Washington, DC, February 2005. Paper 333.
10. Cohen DB, Kawamura S, Ehteshami J, Rodeo SA. Indomethacin and Celecoxib impair rotator cuff tendon-to-bone healing. Am J Sports Med 2006;34:1–8.
11. Khan U, Edwards JC, McGrouther DA. Patterns of cellular activation after tendon injury. J Hand Surg Br 1996;21(6):813–820.
12. Khan U, Kakar S, Akali A, Bentley G, McGrouther DA. Modulation of the formation of adhesions during the healing of injured tendons. J Bone Joint Surg Br 2000; 82(7):1054–1058
13. Beredjiklian PK. Biologic aspects of flexor tendon laceration and repair. J Bone Joint Surg Am 2003;85-A(3):539–550.

14. Blevins FT, Djurasovic M, Flatow EL, Vogel KG. Biology of the rotator cuff tendon. Orthop Clin North Am 1997;28(1):1–16.
15. DeOrio JK, Cofield RH. Results of a second attempt at surgical repair of a failed initial rotator cuff repair. J Bone Joint Surg Am 1984;66:563–567
16. Ellman H Rotator cuff disorders. In: Ellman H, Gartsman GM (eds) Arthroscopic shoulder surgery and related disorders. Lea and Febiger, Philadelphia 1993, p 98–119.
17. Uhthoff HK, Sano H. Pathology of failure of the rotator cuff tendon. Orthop Clin North Am 1997;28(1):31–41.
18. Cofield RH. Rotator cuff disease of the shoulder. J Bone Joint Surg Am 1985; 67(6):974–979.
19. Lädermann A, Denard PJ, Collin P. Massive rotator cuff tears: definition and treatment. Int Orthop 2015;39:2403–14.
20. Gardner MJ, Demetrakopoulos D, Klepchick P, Mooar P. The efficacy of autologous platelet gel in pain control and blood loss in TKR: an analysis of the haemoglobin, narcotic requirement and range of motion. *Int Orthop.* 2007;31:309-313.
21. Garg AK. The use of platelet rich plasma to enhance the success of bone grafts around dental implants. *Dent Implantol Update* 2000;11(3):17-21.
22. Foster TE. From Basic Science to Clinical Applications. Am J Sports Med 2009;37:2259-72.
23. Asfaha S, Cenac N, Houle S, Altier C, Papez MD, Nguyen C, et al. Protease-activated receptor-4: a novel mechanism of inflammatory pain modulation. Br J Pharmacol 2007;150:176-85.
24. Sugaya H, Maeda K, Matsuki K, Moriishi J. Functional and structural outcome after arthroscopic full-thickness rotator cuff repair: Single-row versus dual-row fixation. Arthroscopy. 2005;21:1307–16.
25. Jo CH, Shin JS, Lee YG, et al. Platelet-rich plasma for arthroscopic repair of large to massive rotator cuff tears: a randomized, single- blind, parallel-group trial. Am J Sports Med. 2013;41(10):2240-2248.
26. Jo CH, Shin JS, Lee YG, et al. Platelet-rich plasma for arthroscopic repair of medium to large rotator cuff tears: a randomized controlled trial. Am J Sports Med. 2015; XX(X) XXXX

27. Kesikburun SL, Tan AK, Yilmaz B, Yasxar E, Yaziciog lu K. Platelet-rich plasma injections in the treatment of chronic rotator cuff tendinopathy: a randomized controlled trial with 1-year follow-up. Am J Sports Med. 2013;41(11):2609-2616.
28. Malavolta EA, Gracitelli ME, Ferreira Neto AA, Assuncao JH, Bordalo Rodrigues M, de Camargo OP. Platelet-rich plasma in rotator cuff repair: a prospective randomized study. Am J Sports Med 2014;42(10):2446-2454
29. Randelli P, Arrigoni P, Ragone V, Aliprandi A, Cabitza P. Platelet rich plasma in arthroscopic rotator cuff repair: a prospective RCT study, 2-year follow-up. J Shoulder Elbow Surg 2011;20(4):518-528.
30. Rha DW, Park GY, Kim YK, Kim MT, Lee SC. Comparison of the therapeutic effects of ultrasound-guided platelet-rich plasma injection and dry needling in rotator cuff disease: a randomized controlled trial. Clinical Rehabilitation 2012;27(2):113 –122.
31. Rodeo SA, Delos D, Williams RJ, Adler RS, Pearle A, Warren RF. The effect of platelet-rich fibrin matrix on rotator cuff tendon healing: a prospective, randomized clinical study. Am J Sports Med 2012;40(6):1234-1241.
32. Ruiz-Moneo P, Molano-Muñoz J, Prieto E, Algorta J. Plasma rich in growth factors in arthroscopic rotator cuff repair: a randomized, double-blind, controlled clinical trial. Arthroscopy 2013;29(1):2-9.
33. Wang A, McCann P, Coliver J, Koh E, Ackland T, Joss B, Zheng M, Breidahl B. Do Postoperative Platelet-Rich Plasma Injections Accelerate Early Tendon Healing and Functional Recovery After Arthroscopic Supraspinatus Repair?: A Randomized Controlled Trial. Am J Sports Med 2015;43(6): 1430-1437
34. Weber SC, Kauffman JI, Parise C, Weber SJ, Katz SD. Platelet-rich fibrin matrix in the management of arthroscopic repair of the rotator cuff: a prospective, randomized, double-blinded study. Am J Sports Med 2013;41(2):263-270.
35. Zumstein MA, Rumian A, Lesbats V, Schaer M, Boileau P. Increased vascularization during early healing after biologic augmentation in repair of chronic rotator cuff tears using autologous leukocyteand platelet-rich fibrin (L-PRF): a prospective randomized controlled pilot trial. J Shoulder Elbow Surg 2014;23(1):3–12.
36. Carr A, Cooper C, Murphy R, et al. PARot – assessing platelet-rich plasma plus arthroscopic subacromial decompression in the treatment of rotator cuff tendinopathy: study protocol for a randomized controlled trial. *Trials*. 2013;14:167.

37. Antuna S, Barco R, Martinez Diez JM, Sanchez Marquez JM. Platelet-rich fibrin in arthroscopic repair of massive rotator cuff tears: a prospective randomized pilot clinical trial. Acta Orthop Belg 2013;79: 25–30 .
38. Jo CH, Kim JE, Yoon KS, Lee JH, Kang SB, et al. Does platelet-rich plasma accelerate recovery after rotator cuff repair? A prospective cohort study. Am J Sports Med 2011;39: 2082–2090 .
39. Barber FA, Hrnack SA, Snyder SJ, Hapa O. Rotator cuff repair healing influenced by platelet-rich plasma construct augmentation. Arthroscopy 2011; 27: 1029–1035.