GLOBAL ACADEMIC RESEARCH INSTITUTE

COLOMBO, SRI LANKA

GARI International Journal of Multidisciplinary Research

ISSN 2659-2193

Volume: 04 | Issue: 03

On 15th June 2018

http://www.research.lk

Author: Srimurugadas J, Weerasooriya. P

School of Science, BMS, Sri Lanka

GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03

Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)

ISSN 2659-2193 | Edit: GARI Editorial Team

Received: 18.05.2018 | Publish: 15.06.2018

Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018

PLATELET-RICH PLASMA (PRP) INTRA-ARTICULAR KNEE INJECTIONS AS A THERAPEUTIC APPROACH FOR KNEE OSTEOARTHRITIS

[1]Srimurugadas J, [2]Weerasooriya, P

[1,2]BMS School of Science, Sri Lanka

[1]jonakajonathan@yahoo.com, [2]punsisi@bms.edu.lk

ABSTRACT

Knee osteoarthritis is a widely prevalent chronic joint affliction noted worldwide caused by cartilage degeneration. It adversely affects human functionality and lifestyle. Several studies have revealed that 15 % of the world population suffer from Osteoarthritis and the number is on the rise, and by 2020 this is expected to increase exponentially. The significant increase in the occurrence of Osteoarthritis in urbanized and developing countries is rising with an increase in the elderly population. Even though the majority of the data obtained pertains to the western population, the prevalence of knee osteoarthritis appears to be similar to the rural and urban areas in the Eastern world specifically Asia. The poor regeneration and ineffective curative properties of cartilage have led to the exploration of other treatment modalities with enhanced healing aptitude. The novel therapeutic and regenerative treatment with platelet-rich plasma for knee osteoarthritis has been rising in current times in relation to cartilage regeneration. All of the prior clinical research recommend that PRP intraarticular injection is an excellent alternative in the healing of knee osteoarthritis. This process showed superior efficacy in pain reduction, cartilage regeneration, enhanced function and patient contentment compared to contemporary options. Numerous advantages and disadvantages are associated with this therapy, and the efficacy of this therapy is influenced by several factors. Ongoing eminent research on PRP therapy expected to increase its effectiveness, and deliver even more superior results in Knee osteoarthritis therapy in the days to come.PRP- Platelet-rich plasma, KOA- Knee Osteoarthritis,

Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018

INTRODUCTION

Knee Osteoarthritis (KOA) is generating a serious health crisis that affects millions of individuals of all ages, genders, races and racial groups. It is the eighth most nonfatal condition accounting to the worldwide disease burden(Munde, Jha & Malik, 2017). Historically, KOA has been considered a disease predominantly affecting articular cartilage (Fox, Bedi & Rodeo, 2009). This consideration has to be correlated with conditions such as the obesity epidemic, aging population, genetic factors, lower limb malignancy, cartilage defects, joint instability and sedentary lifestyles especially in urbanized parts of the world(Drumpt et al., 2016; Ayhan, Kesmenzacar & Akgun, 2014). Studies have revealed that 15 % of the world population (Figure 01) suffer from this chronic disease and the number of patients affected is on the rise, and by 2020 this figure could possibly see an exponential rise.(Saturveithan et al., 2016).

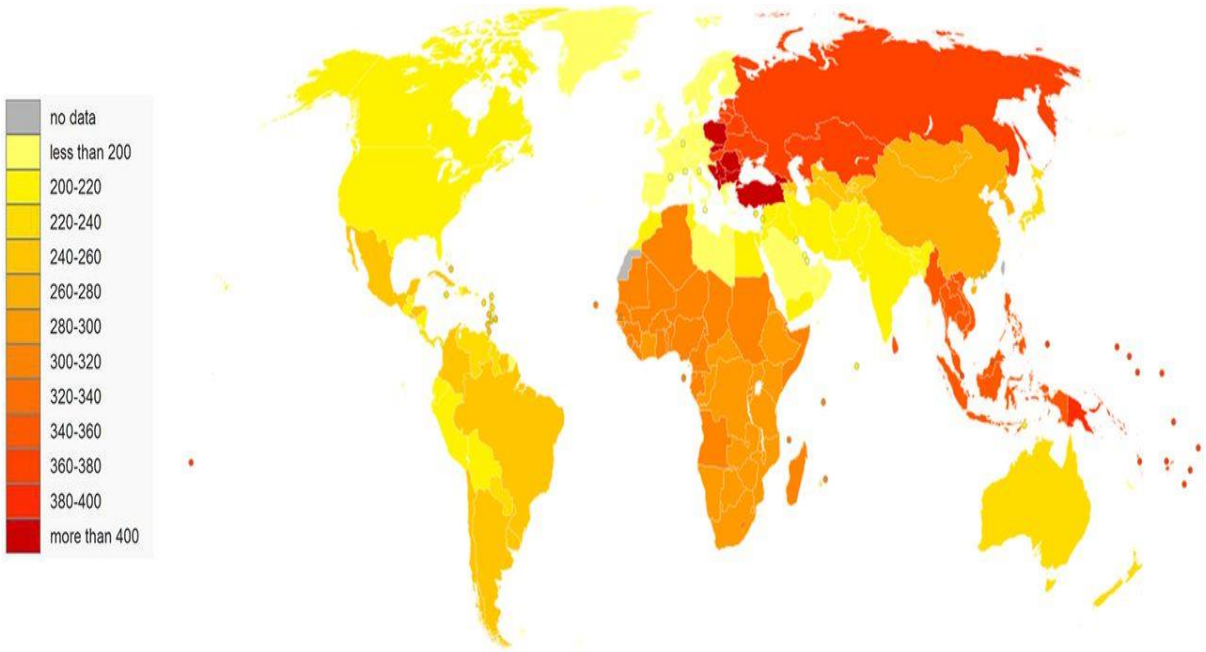


Figure 01: Global Prevalence of Osteoarthritis. Data collected from WHO concerning the precise burden of global OA. OA represents a huge consumer of healthcare resources worldwide with its rising prevalence. Developed and developing countries are screening this increasing burden of KOA especially in the aged population. Among that, Europe is the most affected continent with osteoarthritis (El-Tawil, Arendt & Parker, 2016).

Scanzello et al., 2011 states that there is an increasing affliction of OA in urbanized and developing countries, which will apparently expand with rising elderly population. The majority of the incidence data obtained from the western population, but the incidence of indicative knee OA in the west appears to be similar to the rural and urban areas inside Asia. Figure 02 reveals that knee osteoarthritis (49%) is a most prevalent OA and it's most prevalent among older population (Alhambra et al., 2014).

Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018

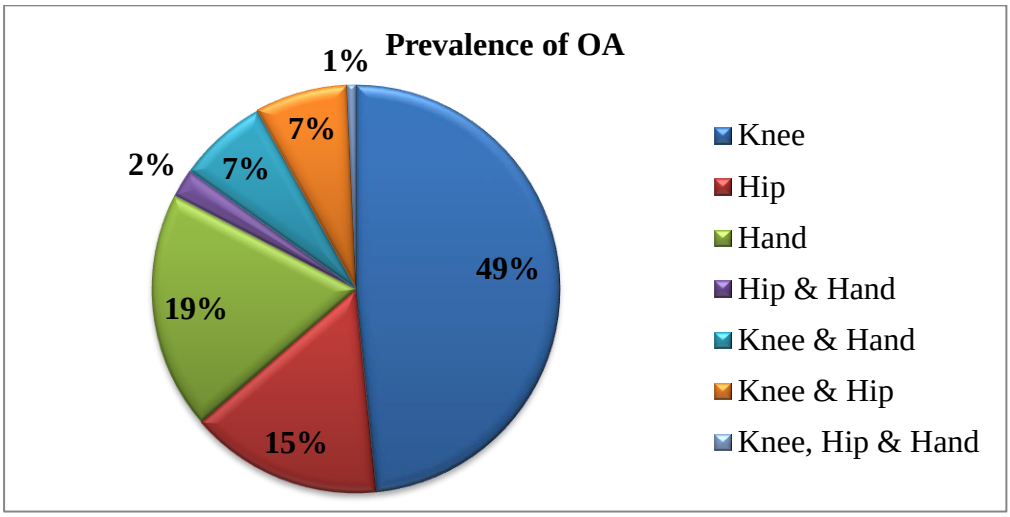


Figure 02: Pie chart representing the types of OA prevalence. Data reveals knee OA- 49%, Hand OA- 19%, Hip OA- 15%, knee and hand OA- 7%, knee and hip – 7%, Hip and Hand OA- 2% and knee, hip and hand – 1%. Adapted from (Alhambra et al., 2014).

Considering this affliction of Knee osteoarthritis in Sri Lanka, based on the Hettihewa et al. research which was carried out in 2017 revealed that evidently increased level of knee osteoarthritis is found in women compared to men, and moreover this KOA burden was higher in older people than younger people. The derived data form that research analysis is shown below.

Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018

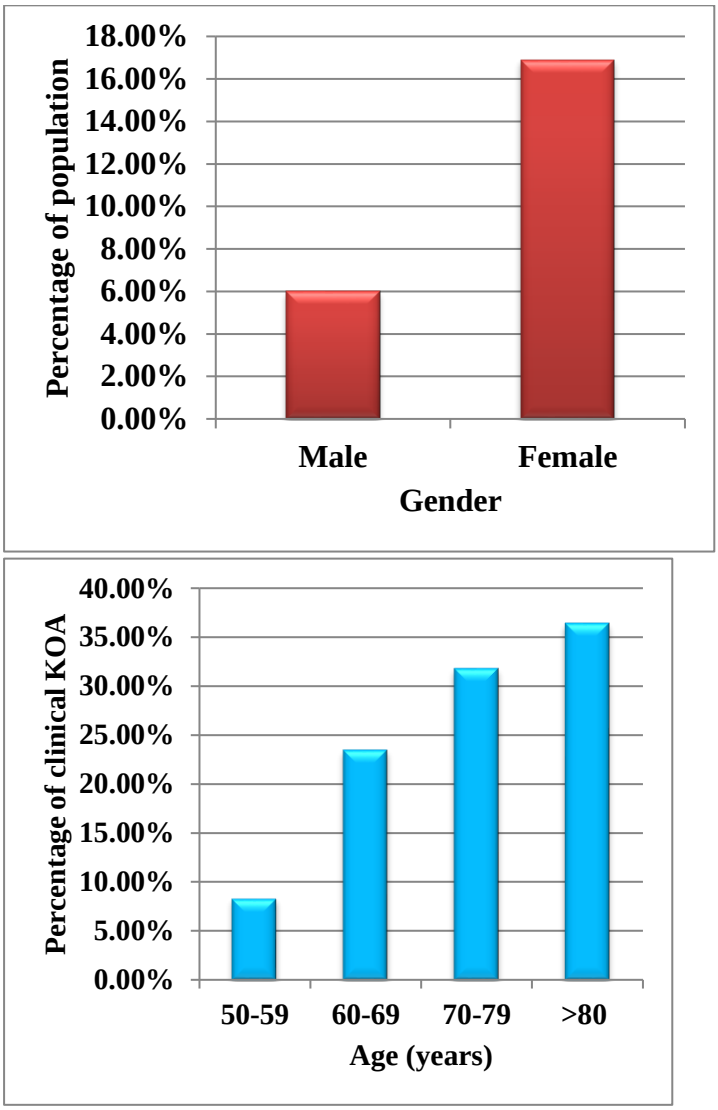


Figure 03: Prevalence of Knee osteoarthritis in Sri Lanka (Hettihewa et al., 2017)

Furthermore, the data derived from the Alhambra et al. (2014) is shown in Figure 03, according to that analysis women are more affected by Knee Osteoarthritis than men.

Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018

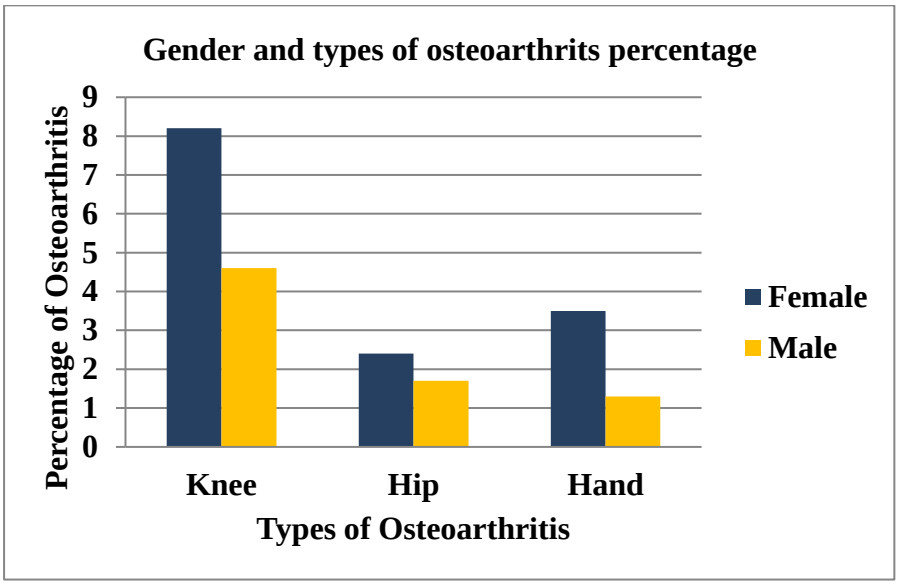


Figure 04: Bar chart representing the prevalence of osteoarthritis types in women and men. Women are mostly afflicted by all types of osteoarthritis. Adapted from (Alhambra et al., 2014).

In view of the above data, Letwic et al., (2013) state that women lose knee articular cartilage at a quicker rate than men; female human articular chondrocytes could function better when estrogen is accessible. Obesity and menopause due to aging are considered contributing factors for higher prevalence of this condition in women. These stated factors lead to initiate the cartilage degeneration process in the knee that consequently leads to knee osteoarthritis (Litwic et al., 2013).

Knee Osteoarthritis and Cartilage

The usual form of this chronic knee osteoarthritis causes severe pain, loss of function, synovial inflammation, disability and affects patients' functionality and lifestyle. The Knee Osteoarthritis is subdivided into five stages according to the Kellgren-Lawerence (KL) grading system. Stage-0 (normal), stage-I (minor), stage-II (mild), stage-III (moderate) and stage-IV (severe). In addition to a physical examination, appropriate diagnostic studies such as an X-ray and an MRI of the affected knee play a vital role in diagnosing the precise stage of osteoarthritis. Knee Osteoarthritis pathogenesis (Figure 04) is correlated with the physical and biochemical changes in the knee joint articular cartilage (Heidari, 2011; Gobbi et al., 2012).

Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018

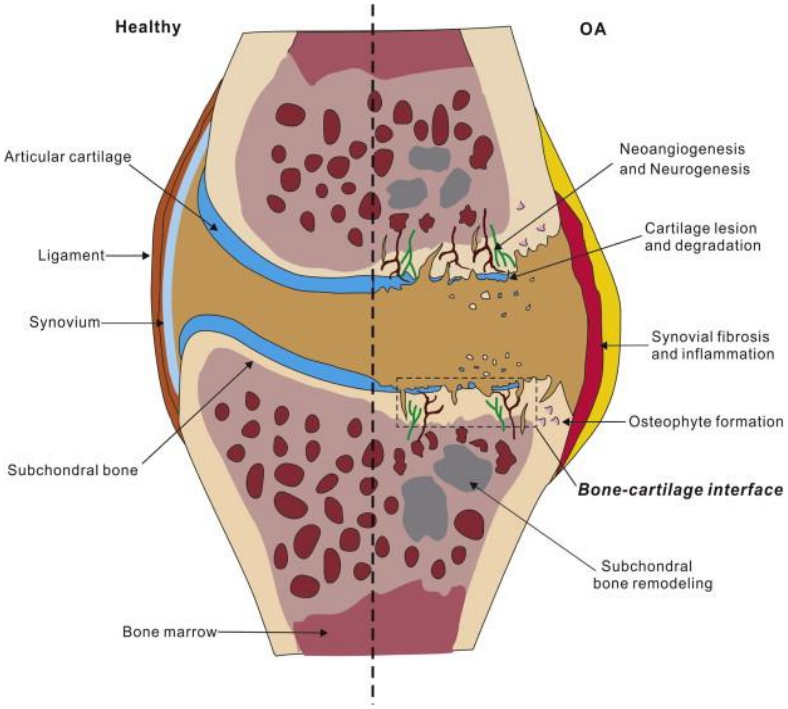


Figure 05: Knee Osteoarthritis pathophysiology: comparison with healthy and diseased knee joint. The healthy knee is not shown with normal cartilage without any fissures nor narrowed joint space. The osteoarthritic knee has fibrillated cartilage, narrowed joint space as well as remodeling of the bone (Yuan et al., 2014).

This articular cartilage is made up of hyaline cartilage which is a vastly specialized connective tissue of diarthrodial joints that provides a smooth surface to enable movement of the joint. Also, it consists of an extracellular matrix with a sparse populace of cells, deficient blood vessels, nerves and lymphatic vessels. In matrix the metabolic activity is low. In healthy adult articular cartilage, there is no cell partition and cell demise, although articular chondrocytes are competent in cell division. Healthy adult articular cartilage is only made up of 1% of chondrocytes. This is the single cell layer present in articular cartilage. Consequently, it is accountable for both the production and the breakdown of the cartilaginous matrix (Fox, Bedi & Rodeo, 2009; Andriachhi & Favre, 2014).

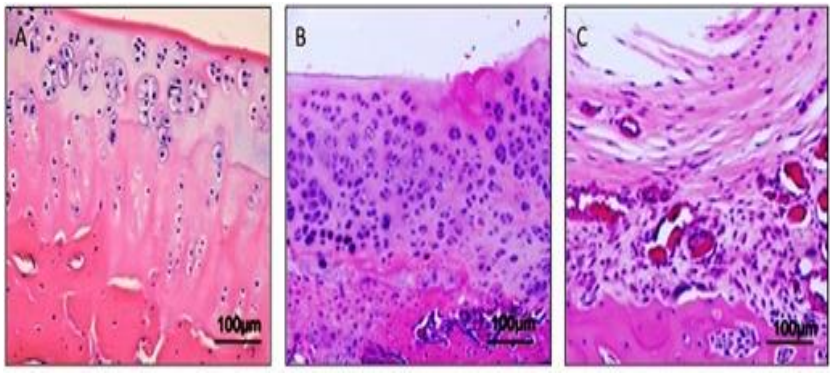


Figure 06: Haematoxylin & Eosin stained knee articular cartilage histology (X100). A-Normal cartilage of knee (No signs of cartilage degradation), B-Moderate KOA

Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018

cartilage (Degenerated cartilage and deteriorated chondrocytes), C-Severe KOA cartilage (Completely deteriorated cartilage, chondrocytes hypertrophy, and chondrocytes apoptosis) (Musumeci et al., 2012)

Knee osteoarthritis results from the inability of chondrocytes to sustain the homeostasis between production and degradation of the extracellular matrix components. As a consequence of this interruption in homeostasis, elevated water content, diminished proteoglycan content of the extracellular matrix and decreased synthesis of type II collagen occurs. Also, the increased pre-existing breakdown of collagen leads to deteriorating the network of collagen. Moreover, the apoptosis of chondrocytes is increased. At most compensatory mechanism, increased matrix molecules synthesis and chondrocytes propagation in the deep layer of cartilage, are capable of keeping up with the reliability of knee articular cartilage. However ultimately loss of chondrocytes and extracellular changes predominate, and osteoarthritic changes expand in knee according to Figure 06 (Houard, Goldring & Berenbaum, 2013; Otsuki et al., 2010).

Based on the previous research studies, in Sri Lanka, the early stage of KOA is the most abundant stage of KOA among the afflicted population which is shown in below Figure 07

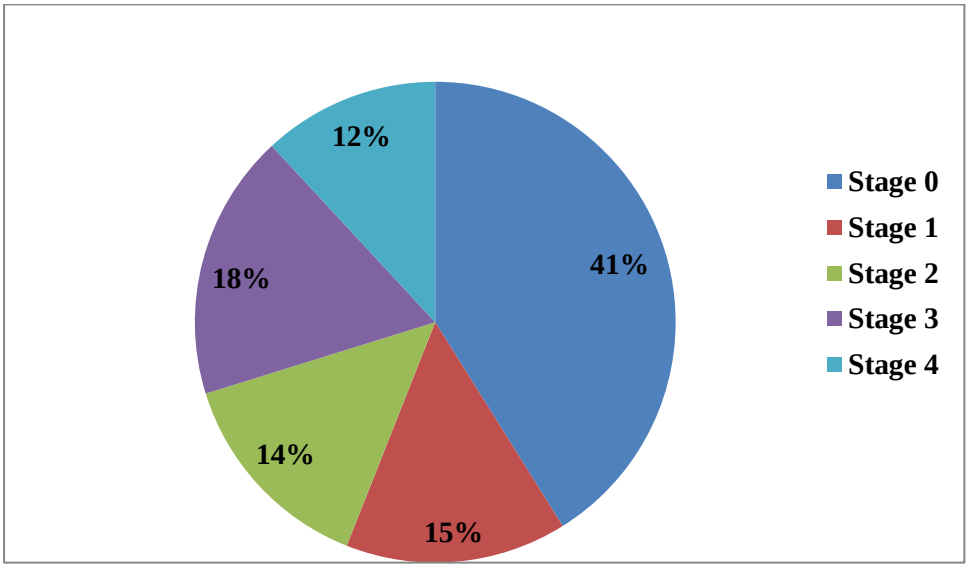


Figure 07: Percentage of Knee Osteoarthritis stages in Sri Lanka (Hettihewa et al., 2017)

Overview of Knee osteoarthritis treatment

Several researchers focused on knee cartilage repair processes throughout the last two decades. General therapies for knee cartilage tissue repair procure relative contentment, but occasionally accomplish a perfect level of functional capability for the patient. Table 01 shows the current treatment options for knee osteoarthritis. (Mendiaa, Cavazos & Rodriguez, 2014)

Table 01: Types of treatments in Knee osteoarthritis (Kennedy & Moran, 2010; Mushtaq,Choudhary & Scanzello, 2011)

Type of Treatments	Examples	Disadvantages

Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018

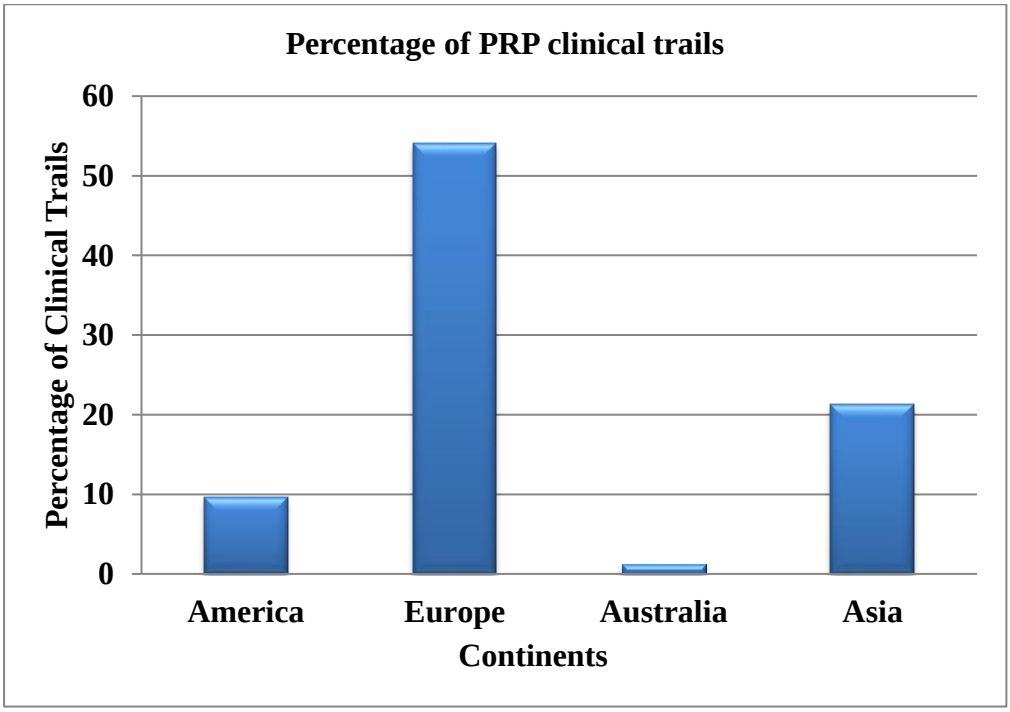
Pain relievers and anti-inflammatory drugs	NSAIDs Acetaminophen Tramadol Opiates Duloxetine Opioids	 •Less effective •Side effects
IA agents	HA Corticosteroids Saline	 •Less effective
Alternative agents	Avacado-soyabean unsaponifiables	•Side effects •Less effective
Topical agents	Capsaicin Lidocaine patches	•Side effects •Less effective
Surgery	Arthroscopy Osteotomy Joint replace Bone Marrow stimulating Techniques Osteochondral Transplantation techniques Autologous Chondrocyte Implantation Minimal Invasive Surgery Arthroscopic Lavage and Debridement	•Mostly not suitable for young people •Not permanent, further surgery may be necessary later on. •Risk and primarily suitable for aged people •Limited hyaline repair tissue •Limited graft and Technical difficulties

Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018

		•Two-stage procedure and the cost of the cell culture •Less effective •Cannot alter the progression of Knee Osteoarthritis

Presently available modalities of treatment for Knee osteoarthritis are mentioned above. These are applied to relieve pain, recover knee function and quality of life. Unfortunately, none of these stated managements are able to halt knee osteoarthritis progression and disintegration of cartilage. (Kennedy & Moran, 2010; Mushtaq, Choudhary & Scanzello, 2011).

Considering the above reasons, treating knee osteoarthritis with a novel therapy of platelet-rich plasma has become a significant remedy in cartilage regeneration. This platelet-rich plasma (PRP) is an emerging biological therapy and has generated attention in articular cartilage repair. PRP is a natural concentrate of autologous blood which was initially utilized in 1987 in open heart surgery. According to the previous studies this therapy has been used in diverse medical fields, ranging from ophthalmology, dermatology, cosmetology, urology and orthopedic surgery in order to improve the tissue regeneration through platelet-derived growth factors and other bioactive molecules (Ficek et al., 2011; Raeissadat et al., 2014).



Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018

Figure 08: Bar chart representing the percentage of PRP administration in KOA patients. Europe- 54.05 %, America – 9.57%, Asia- 21.3 %, Australia - 1.24%. Data analysis reveals Europe has carried out research on PRP therapy. Adapted from (Dai et al., 2017)

Data synthesis (Figure 08) consistently shows that clinical trials in PRP therapy have been performed in many countries. According to the data derived, Europe has carried out many clinical trials on PRP therapy as Europe has more people affected by knee osteoarthritis

Platelet Rich Plasma Therapy (PRP)

PRP is delineated as a quantity of plasma that has a platelet concentration beyond the baseline. Normal platelet count in blood is 150,000µ/l – 350,000µ/l and average about 200,000µ/l.According to prior studies, 100,000µ/l platelet concentration is necessary to increase the renewal of cartilage tissue (Lee et al., 2013; Perez et al., 2014). Smaller concentrations cannot be relied upon to develop regeneration of cartilage tissue, and higher concentrations have not yet been revealed to add additional tissue regeneration. The minimalism of PRP relevance is delineated by three strides which are shown in Figure 07 (Gobbi et al., 2012).

Figure 09: Preparation process of PRP treatment (Perez et al., 2014)

Figure 09 depicts the standardized protocol for PRP treatment which was derived from the previous studies. Whole Blood 150 ml (WB) is primarily compiled in tubes that restrain anticoagulants (21ml of sodium citrate). The primary centrifugation step (1800rpm, 15minutes) is performed at variable speeds to separate RBCs from the residual WB volume. Following the initial spin stride, the WB separates into three layers: an uppermost layer that contains platelets and WBC predominantly, and a middle layer that is recognized as buffy coat and that is affluent in WBCs and a base layer that consists primarily of RBCs. Only the upper layer or the upper layer plus buffy coat are transferred to a blank tube. The next centrifugation step (3500rpm, 10minutes) is then completed. The upper part of the volume that is mainly platelet-poor plasma is separated away to construct the platelet-rich plasma. The concentrations of platelets and WBC in all of the different layers are considered to typify the excellence of PRP. Platelets include considerable quantities of cytokines and growth factors which are competent in invigorating cellular growth, propagation and tissue regeneration (Fortier et al., 2011; Mazzacco et al., 2012; Lee et al., 2013)

Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018

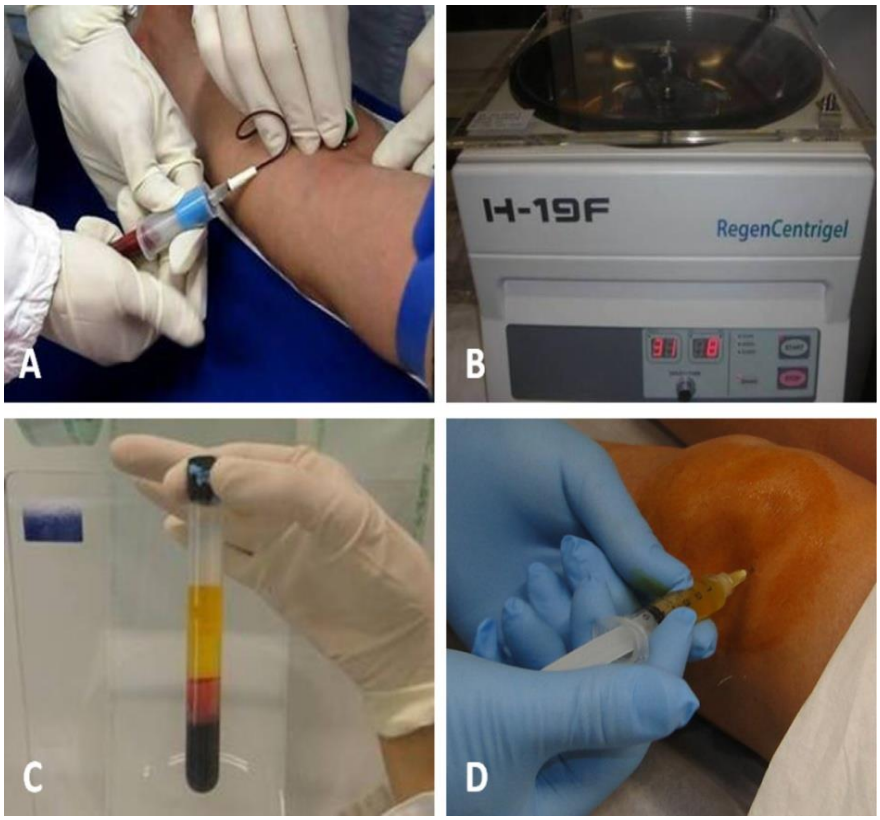


Figure 10: Preparation procedure of PRP (Gobbi et al., 2012)

A- collection of whole blood into the anticoagulant container, B- brief centrifugation C-obtained three layers (RBC, Buffy coat, Platelet Poor Plasma) D-PRP prepared for intra-articular knee injection (Form 20ml blood 2ml PRP prepared only 10%) (Kushida et al., 2015).

PRP's regenerative prospective depends on the levels of released growth factors (GFs). Alpha granules of platelets restrain GFs, which upon activation are dependable for the start and preservation of healing response (Figure 10). PRP is identified to consist of several GFs, and other protein molecules, such as adhesion molecules, chemokines, which interrelate to promote inflammation, cell proliferation, differentiation, and regeneration. These GFs play a chief role in the regeneration of knee cartilage (Kothari et al., 2017)

Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018

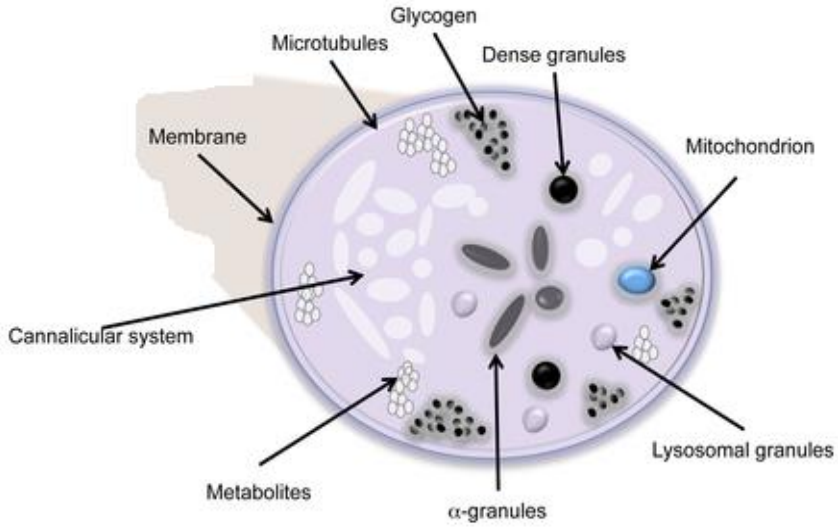


Figure 11: Structure of platelet in the blood. Platelets primarily consist of three types (lysosomal, alpha and dense) granules. α-granules include growth factors, which involves in the regeneration of cartilage tissue (Zapata, Cox & Salyato, 2014).

Table 02: Summary of growth factors (GFs) present in platelet-rich plasma. Adapted from (Fortier *et al*., 2011; Parrish & Roides, 2017)

Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health Review | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018

Growth Factors (GFs)	Functions
Transforming growth factor-β (TGF-β)	It promotes angiogenesis and extracellular matrix construction. Stimulates proliferation and demarcation of mesenchymal stem cells and supports the production of collagen type 1 by osteoblasts.
Fibroblast growth factor (FGF)	Motivates and integrate the mitogenesis of mesenchymal stem cells throughout development. Continuation of tissue restoration.
Platelet-derived growth factor a and b (PDGF)	Have frequent positive effects on wound healing counting mitogenesis, angiogenesis, activation of macrophages, re-epithelization and up-regulation of another growth factor.
Epidermal growth factor (EGF)	Mitogenic and chemotactic consequence on epithelial cells. Also, it is an inductor for cell movement and stimulator for the granules construction in tissue.
Vascular endothelial growth factor (VEGF)	Necessary for numerous angiogenic processes counting normal and pathological situation. Activates the chemotaxis and proliferation of endothelial cells to incite the angiogenesis and hyperpermeability of blood vessels, and promote the wound healing.
Connective tissue growth factor (CTGF)	Angiogenetic activity, cartilage regeneration, and fibrosis.
Insulin-like growth factor (ILGF 1 and 2)	Increases the number of osteoblasts and thereby accelerates the configuration of bone. Stimulates the proliferation and induce the protein production.
Platelet factor 4 (PF-4)	It is a chemokine that roles as negative controller of angiogenesis and an important inhibitor of endothelial cell proliferation.
Interleukin 8 (IL-8)	Pro-inflammatory mediator Recruitment of inflammatory cells

Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018

PRP intra-articular injection administered into the joint gap and nearby painful soft tissues distributes a high concentration of these growth factors, (Table 02) which promote regeneration of the cartilage and results in decreased pain. Numerous previous researches have revealed that PRP intraarticular knee injections in Knee osteoarthritis patients are effective in controlling soreness and recuperating mobility (Gobbi et al., 2012).

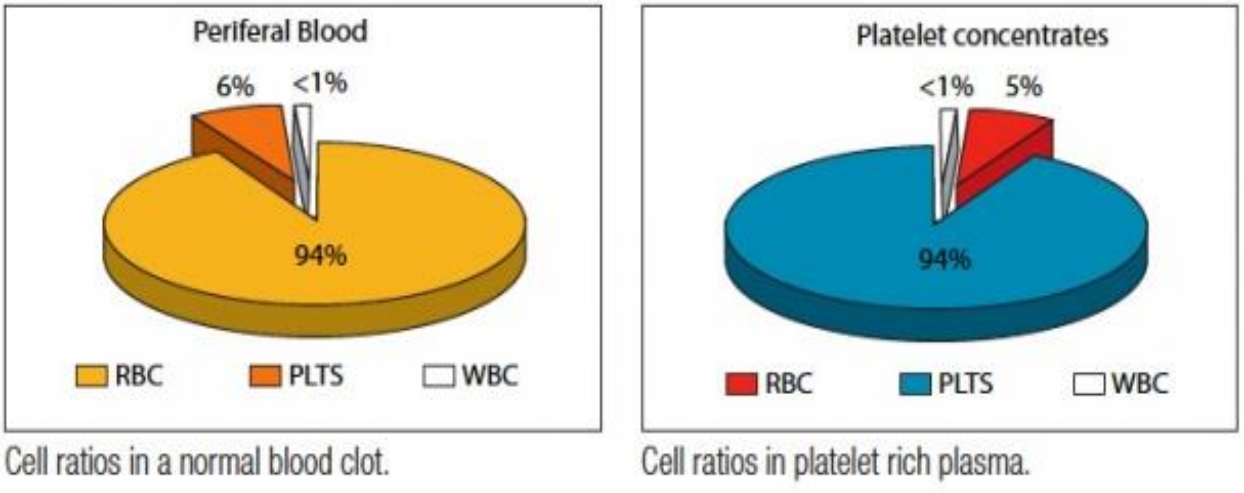


Figure 12: Platelet concentration in Peripheral blood and Platelet-rich plasma. In peripheral blood 6%-Platelets, 1%-White Blood cells and 94%-Red blood cells; In PRP 1%- White Blood cells,5%-Red blood cells and 94%-Platelets(Alderman & Alexander, 2011)

According to Figure 12, the elevated concentration of platelets in the PRP is considered to improve the therapeutic benefit by enhancing and quickening the natural healing cascade. The healing process is schematically delineated in three stages such as inflammation, proliferation, and remodeling. Healing in knee cartilage begins with the release of inflammatory mediators followed by extracellular matrix relocation, collagen production and matrix maturation (Mendia, Cavazos & Rodriguez, 2014).

Different PRP preparation (Table 03) protocols (Centrifugal forces, time and number of spins) may result in different platelet concentrations and thus cause different biologic effects. The platelet count should be one of the key factors to standardize studies investigating the regenerative ability of PRP (Mazzocca et al., 2012).

Table 03: Types of PRP and constituents (Kothari et al., 2017)

Types of PRP	Constituents

Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018

Pure PRP	Low WBC and anti-coagulated liquid
Leukocyte-rich PRP	High WBC, and anti-coagulated liquid
Pure platelet-rich fibrin (PRF)	Low WBC, coagulated fibrin matrix
Leukocyte-rich PRF	High WBC, coagulated fibrin matrix

Recent studies have compared PRP intra-articular injections with other intra-articular injections, including Saline, HA, Ozone and Corticosteroids to explore the effective approach of therapy in the knee osteoarthritis cartilage regeneration (Frizziero et al., 2013; Heredia et al., 2016).

Table 04: Studies carried out to identify the Knee osteoarthritis pain relief by various intra-articular injections.

Research	Year	Results	Authors
48 % of Researches carried out to find the efficacy of PRP	**2010** **2011** **2012** **2011** **2013** **2011** **2012** **2013**	**PRP is effective in cartilage regeneration & pain reduction in Knee OA**	**Kon *et al*** **Kon *et al*** **Napolitano *et al*** **Battaglia *et al*** **Jang, Kim & Cha** **Saegusa *et al*** **Cerza *et al*** **Halpern *et al***

Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018

35 % of Researches carried out to Find the effectiveness of PRP & HA	**2012** **2013** **2015** **2016** **2012** **2013**	**PRP benefits more than HA in Knee OA**	**Sanchez *et al*** **Vaquerizo *et al*** **Raeissadat *et al*** **Dymus *et al*** **Gobbi *et al*** **Say *et al***
18 % of Researches carried out with PRP, Saline & Corticosteroids	**2013** **2015** **2016**	**PRP benefits more than Saline and Corticosteroids in Knee OA**	**Patel *et al*** **Gormeli *et al*** **Smith *et al***

Data synthesis (Table 04) consistently showed that intra-articular PRP injections have significantly reduced knee pain, swelling, and improved physical function, stiffness and physical function scores of Western Ontario and McMaster Universities Arthritis Index (WOMAC), International Knee Documentation Committee (IKDC) and Knee Injury and Osteoarthritis Outcome Score (KOOS) which were evaluated with controls (Martini et al., 2017)

Cole et al., (2016) states, the findings of the prior studies support a considerable improvement in pain and function by PRP in Knee Osteoarthritis. Also, PRP verified a statistically significant improvement over HA in the knee osteoarthritis pain reduction ($p < 0.0001$). Considering this benefit in PRP therapy (Figure 13) such advantage was observed at 3, 6 and 12 months follow up after treatment.

Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018

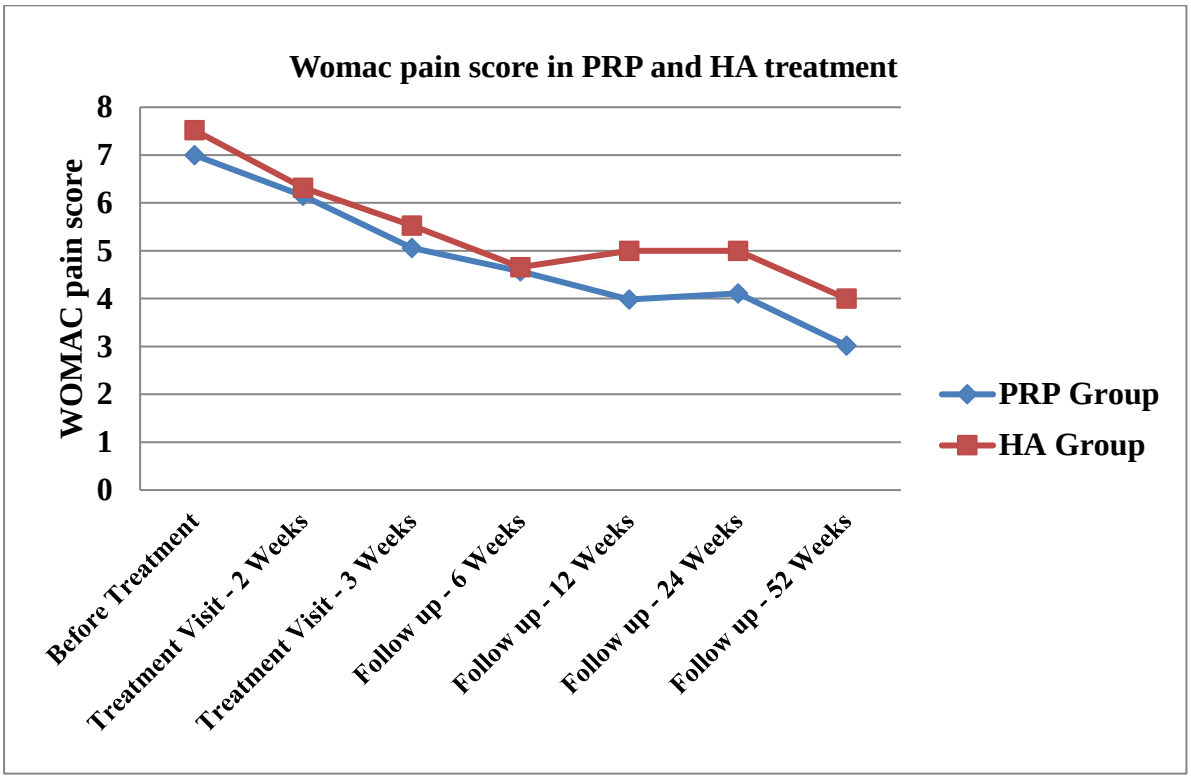
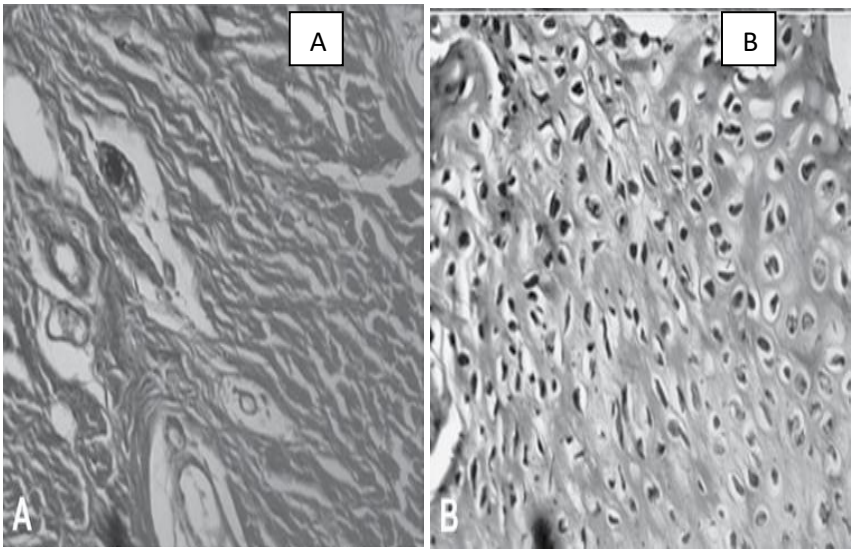


Figure 13: WOMAC pain score in PRP and HA treatments.PRP shows statistically significant improvement in pain score when compared with HA. The pain was drastically reduced in the follow-up month. Adapted from (Cole et al., 2016).

In view of the subsequent advantage of PRP intra-articular injection, Sampson et al., (2010) state that it is a superior technique to regenerate the cartilage tissue compared to other techniques. In knee osteoarthritis, PRP induces enhanced manufacturing of hyaluronic acid (HA) which promotes cell proliferation, production of collagen, chondrocytes, and increased new cartilage tissue formation (Figure 14). (Frisbie et al., 2007; Gobbi et al., 2012)



Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018

Figure 14: Benefit of PRP therapy in knee cartilage A- Damaged chondrocytes and degenerated cartilage. B- Regenerated Cartilage with newly synthesized chondrocytes (Carneiro, Barbieri & Neto, 2013)

Bansal et al., (2017) publicized, diagnostic tests like Magnetic Resonance Imaging (MRI) and ultrasound that demonstrated PRP treatment as effective in repairing cartilage (Figure 15).Moreover, ultrasound evaluation has confirmed that cartilage thickness improved by at least 0.2mm in patients after PRP therapy.

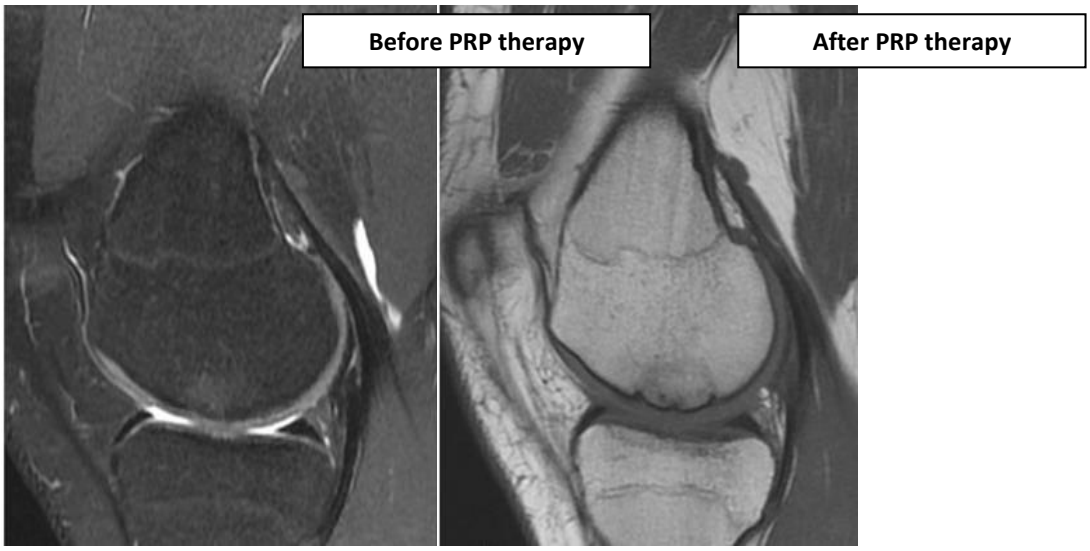


Figure 15: MRI image of Knee cartilage before and after PRP therapy. Before PRP, the cartilage thickness was reduced, but after the PRP therapy significant improvement in the cartilage thickness was observed (Akman et al., 2016)

The advantages of PRP therapy that have been reported from previous studies include its natural healing process, the ease of preparation and administration and relative safety compared to allogeneic or homologous plasma (Foster et al., 2009).

As well, Dan, Mann & Maffulli (2009) states that the manual technique of obtaining PRP used in the present study is cost-effective. While the expenditure of automatic devices and kits to acquire PRP is slightly costly, the cost of the manual technique used to prepare PRP is less expensive, less time consuming and small recovery period compared to other cartilage regeneration techniques in knee osteoarthritis.

PRP rehabilitation seems to be an effective treatment for knee osteoarthritis. Even though it has advantages in treating knee osteoarthritis, it also has several adverse effects including unpretentious pain throughout the intra-articular injection process, dizziness, headache, vomiting and allergic reaction (rashes). Besides, the effectiveness of PRP therapy in knee osteoarthritis could be dominated by several factors such as age, gender, BMI, preparation procedures and the stage of knee osteoarthritis (Filardo et al., 2011; Petel et al., 2013; Shen et al., 2017).

Data analysis reveals that the application of PRP for knee osteoarthritis results is varied outcomes with respect to age, gender and

Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018

stage of OA. Excellent outcome of PRP intra-articular injection was observed in a younger population with less severe OA in the knee (Stage > III) (Kon et al., 2011).

In PRP therapy, the increased numbers of Growth factor receptors (GF) were observed in young platelets compared to old platelets, because in aging people Chondrocytes become less responsive to GFs which leads to further reduction in matrix production and repair. As a result in the young individual, the increased number of GF receptors and higher amounts of GFs could trigger a better cellular response to PRP therapy than the older individuals. This is clearly shown in Figure 16. Therefore the inadequate number of GFs lead to less efficacy of Knee osteoarthritis healing process (Moller et al., 2009; Boesen et al., 2014).

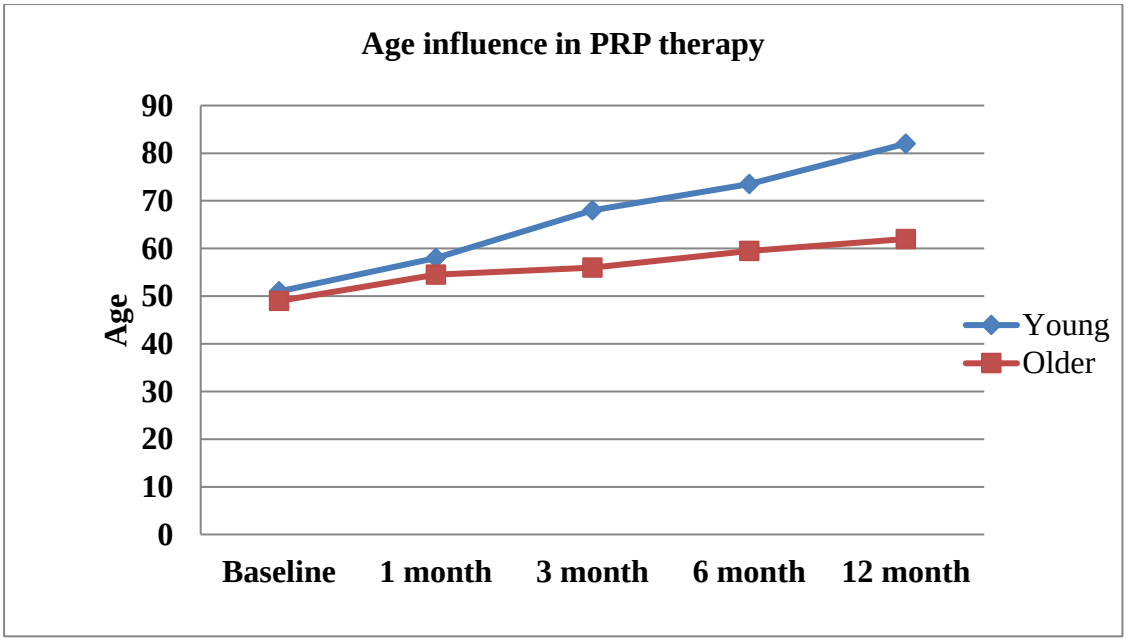


Figure 16: PRP efficacy with Age. PRP efficacy was increased in the follow-up month in the younger population, the efficacy of PRP was reduced in the older population in the follow-up month. Adapted from (Salini et al., 2015)

Gender is another main determinant of PRP effectiveness. According to Figure, 17 women have an elevated level of platelets compared to men after puberty. This is more beneficial to women to increase the efficiency of PRP therapy in knee osteoarthritis and endorse the cartilage regeneration (Balduini & Noris, 2014).

Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018

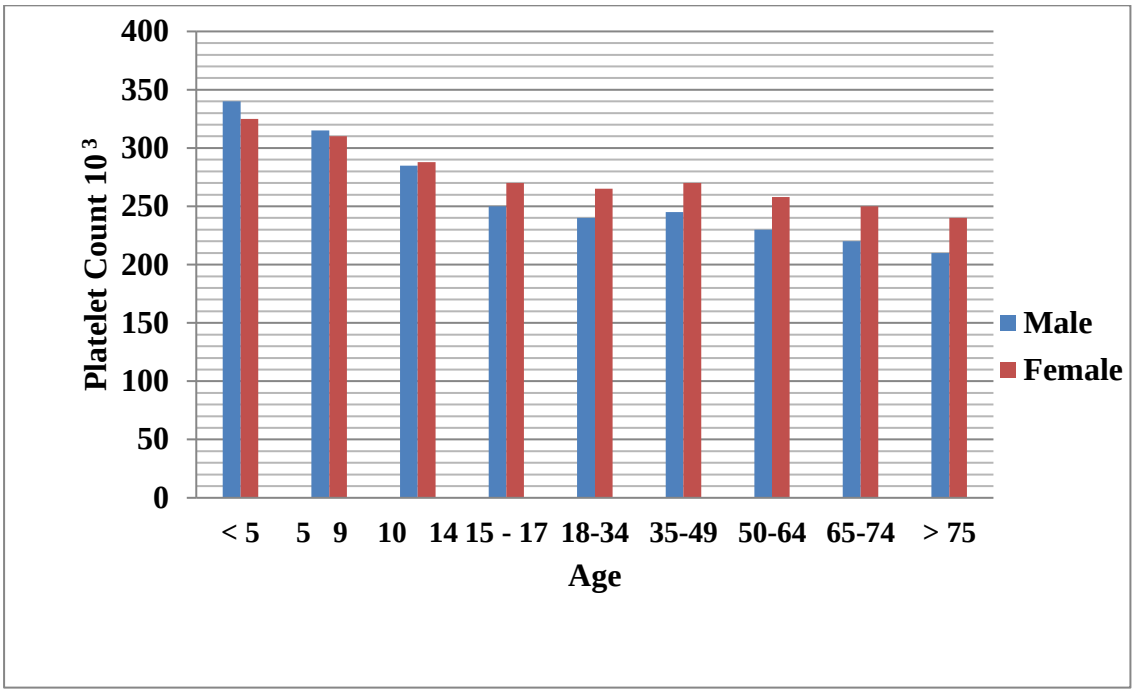


Figure 17: Variation of platelet count in men and women with age. Women have a high amount of platelets compared to men after puberty. Adapted from (Balduini & Noris, 2014)

Prior study reports signify (Figure 15) that sex can manipulate the PRP treatment outcomes due to inherent variations in the biological properties of cartilage in men and women. That impacts their response to PRP treatment differently. According to the current studies, the levels of all GFs were reported to be higher in women than in men. (Kon et al., 2011; Evanson et al., 2014)

Higher BMI (Body Mass Index) correlates with inferior results and is also linked with a trend towards a shorter consequence period, thus signifying that mechanical overload could damage the favorable effect of this treatment. Previous clinical analysis showed a considerably poorer improvements at the 2 month follow-up in patients with elevated BMI (P=0.045), with a comparable propensity at the 6 month follow up (P=0.08) Here P value is required to be < 0.0005, the elevated level of P indicates that the BMI influences the effectiveness of PRP therapy (Munde, Vivek & Maliks, 2017).

Filardo et al., (2012) show that PRP comparison with other types of intra-articular injections in the knee. The tested patients were evaluated with KOOS scores over a period of 12 months. When comparing the patients, regarding the severity of osteoarthritis according to Kellgrene – Lawrence scale, a better response with PRP was noted in milder degree OA (Degree < III) which is shown in Figure 18.

Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018

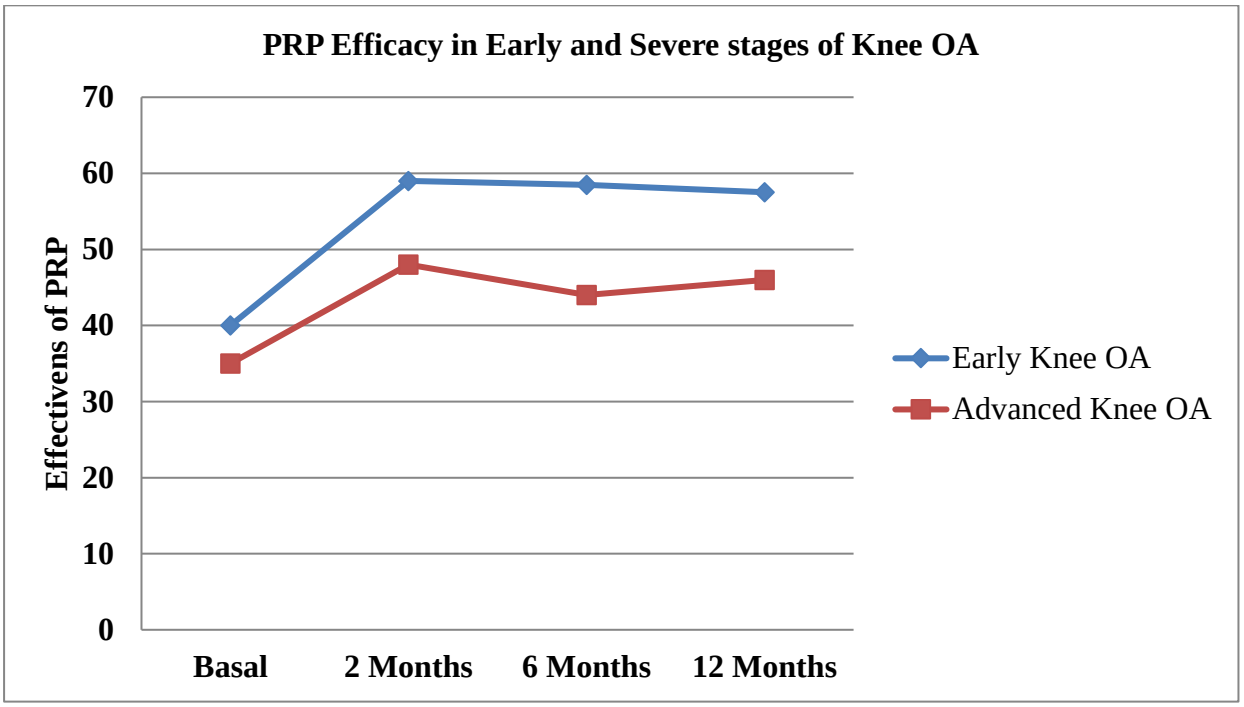


Figure 18: Efficacy of PRP in different stages of knee osteoarthritis. Patients in the early stages of knee OA show statistically significant improvement with PRP therapy though in the advanced stages an insignificant response within the evaluation period was noted. Adapted from, (Kon et al., 2010).

However, in contrast to this opinion, Calis et al., (2015) demonstrated that PRP injection three times a week in patients with grade III and IV knee osteoarthritis obtained results that revealed improved quality of life, diminished pain, and improved cartilage width as measured by ultrasonography on six-month follow-up.

A centrifugation protocol is the next factor influencing the efficacy of PRP therapy. High centrifugation forces and time can cause activation of platelets and consequently reduce platelet function and activity on the cartilage regeneration. In addition, using more advanced centrifugation forces than usual in order to have elevated concentrations of PRP does not necessarily indicate a more effective therapy (Bhatia et al., 2016).

Filardo et al., (2011) state, when the single and double centrifugation procedures are considered, the benefits noted were similar in both methods according to the WOMAC scores. Nevertheless, undesirable proceedings occurred more frequently in the PRP obtained by double centrifugation due to elevated leukocyte concentration formed by this process. Also, Gobbi et al., (2012) show the number of PRP intra-articular injections did not play a role in the efficacy of PRP therapy.

In addition, previous studies have evidently shown the effectiveness of PRP therapy lasts for a maximum of 12-24 months after injection. This implies even though it is the fastest and ideal therapy for cartilage regeneration, it has short lasting results in healing. Therefore reinjection has to be administered to overcome this infirmity (Kon et al., 2010)

Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018

Moreover, several genetic factors and disease conditions related to platelets (thrombocytopenia, Von-Willebrand's disease) significantly affect the effectiveness of PRP therapy and make it ineptitude (Pruna, Til & Artells, 2014).

Ongoing Researches on PRP

Saturveithan et al., (2016) & Lana et al., (2016) state that PRP has been consistently found in several clinical studies to be superior to HA, even though HA with PRP seems to be an evolving future tendency in healing knee osteoarthritis. Research is ongoing to increase the efficiency of this blend of therapy to deliver the ideal curative treatment to the patient. The clinical trials are strongly evocative that combination of PRP and HA is more effective (Figure 19).

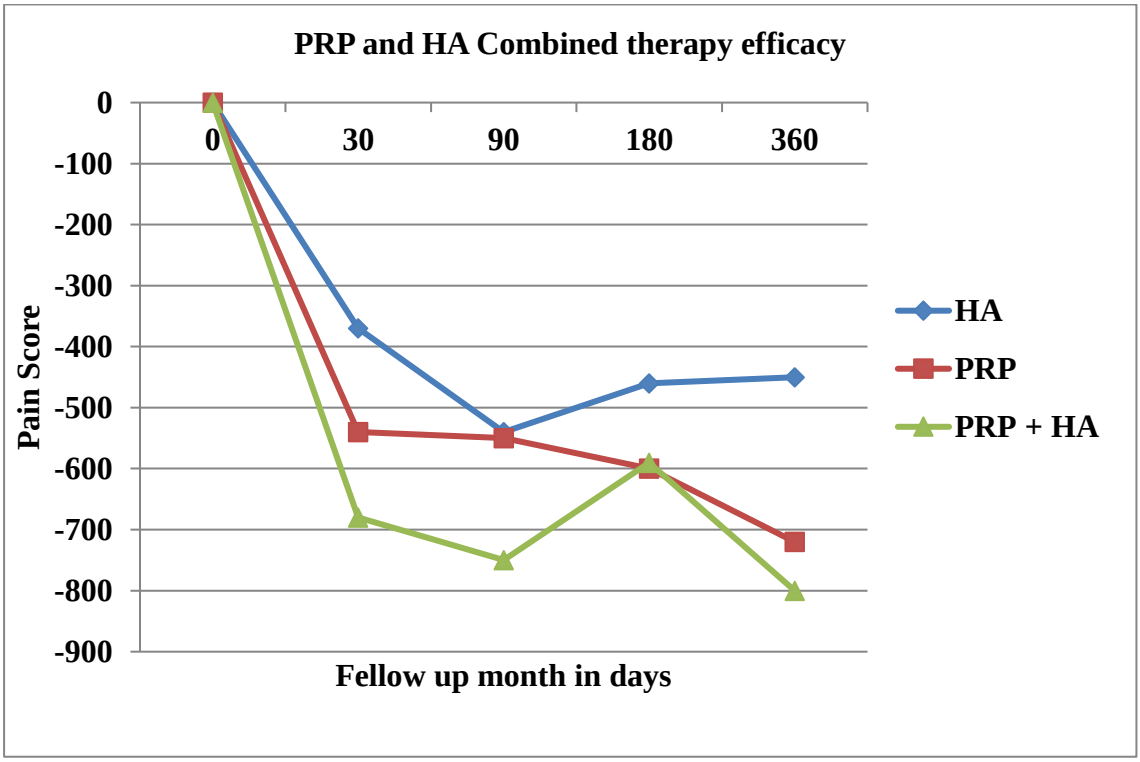


Figure 19: Efficacy of PRP with HA in knee OA Pain reduction. Above data reveals administration of PRP or HA alone is less effective than combined administration. Adapted from (Lana et al., 2016)This is a healing modality in the treatment of grade III and IV KOA in terms of functional outcome and pain control for up to 6 months when surgical treatment is not an alternative. (Correia et al., 2011).

Future techniques on PRP therapy

Future studies are focused on developing an enhanced PRP therapy that results in combining the knee osteoarthritis therapy with different molecules such as gelatine and chitosan. Moreover, the strategies of platelets activators in PRP therapy play a major role in cartilage regeneration process. Calcium, thrombin or collagen essential to activate the release of GFs in different concentration may produce different results. The levels of activator concentration influence the efficacy of this therapy. Precise activator concentration is

required to design this effective PRP therapy. Future studies investigate the consequence of different activation strategies on platelet concentration according to the cartilage damage in order to optimize the in vivo outcome of the released bioactive molecules which in turn increases PRP effectiveness in cartilage regeneration are upcoming(Correia et al., 2011; Cavallo et al., 2016).

LIMITATIONS OF THE STUDIES

Previous studies and analysis have found several restrictions on PRP effectiveness in the KOA healing. Different methodologies in PRP preparation led to high heterogeneity in conducted clinical research. The sample size, in some studies, was too small to get the precise outcomes whereas, in some other studies conducted with a larger sample size, the variations led to differences in the therapeutic efficacy.

SUMMARY

The dramatic improvement in the frequency and prevalence of KOA affects millions of people around the globe. Degeneration of articular cartilage causes the disability mostly amongst the aged population. The conservative management of knee OA with novel PRP therapy is becoming progressively more popular. All of the prior clinical research recommends that PRP intraarticular injection is an excellent alternative in the healing of knee OA. This process showed an advanced extent of efficacy in pain reduction, cartilage regeneration, enhanced functionality and patient contentment compared to contemporary options. Though it has advantages, several complications are affecting the effectiveness of this therapy. However, ongoing eminent research on PRP therapy is expected to overcome these shortcomings and deliver superior results in KOA in the days to come.

ACKNOWLEDGMENT

Apart from the efforts of myself, the success of this scientific literature review depends on the encouragement and guidance of my supervisor Ms. Punsisi Weerasooriya. I take this opportunity to express my gratitude to my supervisor who has been instrumental in the successful completion of this review. I would like to show my highest appreciation and extend my sincere thanks to the Northumbria University of Newcastle, Department of life science, Mr.Nizam, director of BMS and Dr.Sajani for giving this great opportunity to do this literature review.

Thanks again to all who helped me.

REFERENCES

•Akman, B., Guven, M., Bildik, C., Sayli, U., Parnianfard, A. & Rahimli, M. (2016), "MRI Documented Improvement in Patient with Juvenile Osteochondritis Dissecans Treated with Platelet Rich Plasma," *Journal of Prolotherapy*, Vol. 8, pp. 966-970.

• Alderman, D. & Alexander, R.W. (2011), "Advances in Regenerative Medicine: High-density Platelet-rich Plasma and Stem cell Prolotherapy for Musculoskeletal Pain."

•Alhambra, D.P., Judge, A., Javaid, K.M., Cooper, C., Perez, A.D. & Arden, N.K. (2014), "Incidence and risk factors for clinically diagnosed Knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis

affecting other joints" *Annals of the Rheumatic Disease*, Vol.73, No. 9, pp. 1659-1664.

•Andia, I., Latorre, P.M., Gomez, M.C., Alonso, N.B., Abate, M. & and Maffulli, N. (2014), "Platelet-rich plasma in the conservative treatment of painful tendinopathy: a systematic review and meta-analysis of controlled studies", *British Medical Bulletin*, Vol. 110, pp. 99 -115.

•Andriacchi, T.P. & Favre, J. (2014), "The Nature of In Vivo Mechanical Signals That Influence Cartilage Health and Progression to Knee Osteoarthritis," *Current Rheumatology Reports*, Vol. 16, No. 11, pp. 463.

•Ayhan, E., Kesmezacar, H. & Akgun, I. (2014), "Intraarticular injections (corticosteroid, hyaluronic acid, platelet rich plasma) for the knee osteoarthritis," *World Journal of Orthopaedics* Vol. 5, No. 3, pp. 351-361.

•Balduini, C.L. & Noris, P. (2014), "Platelet count and aging," *Haematologica*, Vol. 99, No. 6, pp. 953-955.

•Bansal, H., Comella, K., Leon, J., Verma, P., Agrawal, D., Koka., P & Ichim, T. (2017), "Intra-articular injection in the knee of adipose-derived stromal cells (stromal vascular fraction) and platelet-rich plasma for osteoarthritis", *Journal of Translational Medicine*, Vol. 15, No. 1, pp.141.

•Battaglia, M., Guaraldi, F., Vannini, F., Buscia, T.R., Galletti, S. & Giannini, S. (2011), "Platelet-rich plasma intra-articular ultrasound-guided injections as a possible treatment for hip osteoarthritis: a pilot study," *Clinical and Experiment Rheumatology*, Vol. 29, No. 4, pp. 754.

•Bhatia, A., Ramya, B.S., Biligi, D.S. & Prasanna, P.B.K. (2016), "Comparison of different methods of centrifugation for preparation of platelet-rich plasma (PRP)", *Indian Journal of Pathology and Oncology*, Vol. 3, No. 4, pp. 535-539.

•Boesen, A.P., Dideriksen, K., Couppé, C., Magnusson, S. P., Schjerling, P., Boesen, M., Aagaard, P., Kjaer, M. & Langberg, H. (2014), "Effect of growth hormone on aging connective tissue in muscle and tendon: gene expression, morphology, and function following immobilization and rehabilitation", *Journal of Applied Physiology*, Vol. 116, No. 2, pp. 192–203.

•Çalis, H.T., Sutbeyaz, S.T, Guler, E., Halici, C., Sayan, H., Koc, A., Konk, M. & Yazicioglu, J.A. (2015), "Efficacy of intraarticular autologous platelet-rich plasma application in Knee Osteoarthritis", *Archives of Rheumatology*, Vol. 30, pp. 198–205.

•Carneiro, M.O., Barbieri, C.H. & Neto, B. (2013), "Platelet-rich plasma gel promotes regeneration of articular cartilage in knees of sheeps", *Acta Ortopedica Brasileira*, Vol. 21 No. 2, pp. 80-86.

•Cavallo, C., Roffi, A., Grigolo, B., Mariani, E., Pratelli, L., Merli, G., Kon, E.,

Marcacci, M. & Filardo, G. (2016), "Research Article Platelet-Rich Plasma: The Choice of Activation Method Affects the Release of Bioactive Molecules", *BioMed Research International*, No.7.

•Cerza, F., Carni, S., Carcangiu, A., Di Vavo, I., Schiavilla, V., Pecora, A., De Biasi, G. & Ciuffreda, M. (2012), "Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis", *American Journal of Sports*, No.40, pp. 2822-2827.

•Cole, B.J., Karas, V., Hussey, K., Pilz, K. & Fortier, L.A. (2016), "Trial Comparing clinical Outcomes and Effects on Intra-articular Biology for the Treatment of Knee Hyaluronic Acid Versus Platelet-Rich Plasma: A Prospective, Double-Blind Randomized Controlled Osteoarthritis", *The American Journal of Sports Medicine*, Vol. 45, No. 2.

•Correia, C.R., Moreira-Teixeira, L.S., Moroni, L., Reis, R.L., Blitterswijk, C.A.V., Karperien, M. & Mano, J.F. (2011), "Chitosan Scaffolds Containing Hyaluronic Acid for Cartilage Tissue Engineering," *Tissue Engineering Part c Methods*, Vol. 17, No. 7, pp. 17-30.

•Dai, W.L., Zhou, A, G., Zhang, H., & Zang, J. (2017), "Efficacy of Platelet-Rich Plasma in the Treatment of Knee Osteoarthritis: A Meta-analysis of Randomized Controlled Trials", *The Journal of Arthroscopy* and *Related Surgery*, Vol. 33, No. 3, pp. 659-670.

•Dan, O.M., Mann, G. & Maffulli, N. (2009), "Platelet-rich plasma: any substance into it?", *British Journal of Sports Medicine*, Vol. 44, No. 9.

•Drumpt, R.A.M., Weegen, W.V.D., William King, W., Toler, K. & Macenski, M.M. (2016), "Safety and Treatment Effectiveness of a Single Autologous Protein Solution Injection in Patients with Knee Osteoarthritis," *BioResearch Open Access*, Vol. 5, No. 1, pp. 261-268

•Dymus, T.M., Mutlu, S., Dernek, B., Komur, B., Aydogmus, S. & Kesiktas, F.N. (2016), "Choice of intra-articular injection in treatment of Knee osteoarthritis: Platelet-rich plasma, hyaluronic acid or ozone options", *Knee Surgery Sports Traumatology Arthroscopic*, Vol. 25, No. 2, pp. 485-492.

•El-Tawil, S., Arendt, E. & Parker, D. (2016), "Position statement: the epidemiology, pathogenesis and risk factors of osteoarthritis of the Knee," *British Medical Journal*.

•Evanson, J.R., Guyton, K.M, Oliver, D.L., Justin M. Hire, J.M., Topolski, R.L ., Steven D. Zumbrun, S.D., McPherson, J.C. & Bojescul, J.A. (2014), "Gender and Age Differences in Growth Factor Concentrations From Platelet-Rich Plasma in Adults", *MILITARY MEDICINE*, Vol. 179, No. 7, pp. 799-805.

•Ficek, K., Kamiński, T., Wach, E., Cholewiński, J. & Cięszczyk, P. (2011), "Application of Platelet Rich Plasma in Sports Medicine," *Journal of Human Kinetics*, Vol. 30, pp. 85-97.

•Filardo, G., Matteo, D.B., Martino, D.A., Merli, M.L., Cenachhi, A., Fornasari, P., Marcacci, M. & Kon, E. (2011), "Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis", *Knee Surgery, Sports Traumatology, Arthroscopy*, Vol. 19, No. 4, pp. 528-535.

•Filardo, G., Matteo, D.B., Martino, D.A., Merli, M.L., Cenachhi, A., Fornasari, P., Marcacci, M. & Kon, E. (2012), "Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial", *BMC Musculoskeletal disorder*, Vol. 13, pp. 229.

•Fortier, L.A., Barker, J.U., Strauss, E.J., McCarrel, T.M. & Cole, B.J. (2011), "The Role of Growth Factors in Cartilage Repair," *Clinical Orthopaedics and Related Research*, Vol. 469, pp. 2706-2715.

•Foster, T.M., Puskas, B.L., Mandelbaum, B.R., Gerhardt, M.B. & Rodeo, S.A. (2009), "Platelet-Rich Plasma From Basic Science to Clinical Applications," *The American Journal of Sports Medicine*, Vol. 37, No. 11, pp. 2259-2272.

•Fox, A.J.S., Bedi, A. & Rodeo, S.A. (2009), "The Basic Science of Articular Cartilage: Structure, Composition, and Function," *Sports Health*, Vol. 1, No. 6, pp. 461-468.

•Frisbie, D.D., Kawcak, C.E., Werpy, N.M., Park, R.D. & McIlwraith, C.W. (2007), "Clinical, biochemical, and histologic effects of intra-articular administration of autologous conditioned serum in horses with experimentally induced osteoarthritis", *American Journal Veterinary Research*, Vol. 68, No. 3, pp. 290-296.

•Frizziero, A., Giannotti, E., Oliva, F., Masiero, S. & Maffulli, N. (2013), "Autologous conditioned serum for the treatment of osteoarthritis and other possible applications in musculoskeletal disorders," *British Medical Bulletin*, Vol. 105, No. 1, pp. 169-184.

•Gobbi, A., Karnatzikos, G., Mahajan, V. & Malchira, S. (2012), "Platelet-rich plasma treatment in symptomatic patients with knee osteoarthritis: preliminary results in a group of active patients," *Sports Health*, Vol. 4, pp. 162

•Gormeli, G., Gormeli, C.A., Ataoglu, B., Colak, C., Aslanturk, O. & Ertem, K. (2015), "Multiple PRP injections are more effective than single injections and hyaluronic acid in Knees with early osteoarthritis: A randomized, double-blind, placebo-controlled

trial", *Knee Surgery Sports Traumatology Arthroscopy*, Vol. 25, No. 3, pp. 958-965.

•Halpern, B., Chaudhury, S., Rodeo, S.A, Hayter, C., Bonger, E., Potter, H.G. & Nguyen, J. (2013), "Clinical and MRI outcomes after platelet-rich plasma treatment for knee osteoarthritis," *Clinical Journal of Sports Medicine*, Vol. 23, pp. 238-245.

•Heidari, B. (2011), "Knee osteoarthritis diagnosis, treatment and associated factors of progression:part II," *Caspian Journal of Internal Medicine*, Vol. 2, No. 3, pp. 249-255.

•Houard, X., Goldring, M.B. & Berenbaum, F. (2013), "Homeostatic mechanisms in articular cartilage and role of inflammation in osteoarthritis," *Current Rheumatology Reports*, Vol. 15 No. 11, pp. 375.

•Jang, S.J., Kim, J.D. & Cha, S.S. (2013), "Platelet plasma (PRP) injection as an effective treatment for early osteoarthritis," *European Journal* of *Orthopaedic Surgery and Traumatology*, Vol. 23, pp. 573-580.

•Kennedy, S. & Moran, M. (2010), "Pharmacological treatment of osteoarthritis of the hip and knee Bio," *Columbia Medical Journal*, Vol. 52, No. 8, pp. 404-409.

•Kon, E., Filardo, G., Buda, E., Timoncini, A., Di Martino, A., Cenacchi, A., Fornsari, P.M., Giannini, S. & Marcacci, M. (2010), "Platelet-rich plasma: intra-articular knee injections produced favourable results on degenerative cartilage lesions", *Knee Surgery Sports Traumatology Arthroscopy*, Vol. 18, No. 4, pp. 472-481.

•Kon, E., Mandelbaum, B., Buda, R., Filardo, G., Delcogliano, M., Tumoncini, A., Fornasari, P.M., Giannini, S. & Maracacci, M. (2011), "Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementaion as treatments for cartilage pathology: from early degeneration osteoarthritis", *The Journal* of *Arthroscopic and Related Surgery*, Vol. 27, No. 11, pp. 1490-1501.

•Kothari, K. (2017), "Role of platelet-rich plasma: The current trend and evidence," *Indian Journal of Pain*, Vol. 31, No. 1, pp. 1-6.

•Kushida, S., Kakudo, N., Morimoto, N., Mori, Y. & Kusumoto, K. (2015), "Utilization of Platelet-Rich Plasma for a Fistula With Subcutaneous Cavity Following Septic Bursitis: A Case Report-2015", *Plastic Surgery*, Vol. 15, pp. 31.

•Lana, J.F.S.H., Weglein, A., Sampson, S.E., Vicente, E.S.C., . Souza, C.V., Ambach, M.A., Vincent, H., Urban-Paffaro, A., Onodera, C.M.K., Annichino-Bizzacchi, J.M., Santana, H.A. & Belangero, W.D. (2016), "Randomized controlled trial comparing hyaluronic acid, platelet-rich plasma and the combination of both in the treatment of mild and moderate osteoarthritis of the knee", *Journal of Stem Cells and*

Regenerative Medicine, Vol. 12, No. 2, pp. 69-78.

•Lee , J.W., Kwon, O.H., Kim, T.K., Cho Y.K., Choi, K.Y., Chung, H.Y., Cho, C.B., Yang, J.D. & Jun Ho Shin, J.H. (2013), "Platelet-Rich Plasma: Quantitative Assessment of Growth Factor Levels and Comparative Analysis of Activated and Inactivated Groups", *Archives of Plastic Surgery*, Vol. 40. No. 5, pp. 530-535.

•Litwic, A., Edwards, M., Dennison, E. & Cooper, C. (2013), "Epidemiology and Burden of Osteoarthritis," *British Medical Bulletin*, Vol. 105, No. 1, pp. 185-199.

•Martini, L.I., Via, A.G., Fossati, C., Randelli, F., Randelli, P. & Cucchi, D. (2017), "Single Platelet-Rich Plasma Injection for Early Stage of Osteoarthritis of the Knee," *Joints*, Vol. 5, No. 1, pp. 2-6.

•Mazzocca, A.D., McCarthy, M.B.R., Chowaniec, D.M. & Cote, M.P. (2011)," Platelet-Rich Plasma Differs According to Preparation Method and Human Variability," *The Journal of Bone and Joint Surgery*, Vol. 94, No. 4, pp. 308-316.

• Mendía, M.A.S., Cavazos, J.F.V. & Rodríguez, H.G.M. (2014), "Platelet-rich plasma in knee osteoarthritis treatment," *Surgery and Surgeons*, Vol. 83, No. 4, pp. 352-358.

•Moller, N., Vendelbo, M.H., Kampmann, U., Christensen, B., Madsen, M., Norrelund, H., Jorqensen, J.O. (2009), "Growth hormone and protein metabolism," *Clinical Nutrition*, Vol. 36, No. 1, pp. 89-100.

•Munde, S.L., Jha, V. & Malik, J.S. (2017), "Effectiveness of Platelet-Rich Plasma in the Treatment of Moderate Knee Osteoarthritis," *Annals of International Medical and Dental Research*, Vol. 3, No. 4, pp. 42-47.

•Mushtaq, S., Choudhary, R. & Scanzello, C,R. (2011), "Non-surgical treatment of osteoarthritis-related pain in the elderly," *Current Reviews in Musculoskeletal Medicine*, Vol. 4, No. 3, pp. 113-122.

•Musumeci, G., Castrogiovanni, P., Trovato, F.M., Giunta, D.A., Loreto, C. & Castorina, S. (2012), "Microscopic and macroscopic anatomical features in healthy and osteoarthritic knee cartilage," *The Journal of Musculoskeletal Medicine*, Vol. 1, No. 3, pp. 30.

•Napolitano, M., Matera, S., Bossio, M., Crescibene, A., Costabile, E., Almolla, J., Almolla, H., Toqo, F., Giannuzzi, A. & Guido, G. (2012), "Autologus platelet gel for tissue regeneration in degenerative disorders of the Knee", *Blood Transfusion*, Vol. 10, pp. 72-79.

•Otsuki, S., Hanson, S.R., Miyaki, S., Grogan, S.P., Kinoshita, M., Asahara, H., Wong, C.H. & Lotz, M.K. (2010), "Extracellular sulfatases support cartilage homeostasis by regulating BMP and FGF signalling pathways", *Proceedings of the National Academy of Sciences of the United States of*

America, Vol. 107, No. 22, pp. 10202-10207.

•Patel, S., Dhillon, M.S., Aggarwal, S., Marwaha, N. & Jain. (2013), "Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: A prospective, double-blind, randomized trial," *The American Journal of Sports Medicine*, Vol. 41, pp. 356-364.

•Parrish, W.R. & Roides, B. (2017), "Platelet-rich plasma in osteoarthritis: more than a growth factor therapy," *Musculoskeletal Regeneration*, Vol. 3.

•Perez, A.G.M., Lana, J.F.S.D., Rodrigues, A.A., Luzo, A.C.M., Belangero, W.D. & Santana, M.H.A. (2014), "Relevant Aspects of Centrifugation Step in the Preparation of Platelet-Rich Plasma", *International Scholarly Research Notices*, Vol. 8.

•Pruna, R., Til, L. & Artells, R. (2014), "Could single nucleotide polymorphisms influence on the efficacy of platelet-rich plasma in the treatment of sports injuries?", *Muscles Ligaments Tendons Journal*, Vol. 4, No. 1, pp. 63-65.

•Raeissadat, S.A., Rayegani, S.M., Hassanabadi, H., Fathi, M., Ghorbani, E., Babee, M. & Azma, K. (2015) Knee osteoarthritis injection choices; Platelet-rich plasma (PRP) versus hyaluronic acid (a one-year randomized clinical trial', *Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders*, Vol. 8, pp. 1-8.

•Sadabad, H.N., Behzadifar, M., Arasteh, F., Behzadifar, M. & Dehghan, H.R. (2016), "Efficacy of Platelet-Rich Plasma versus Hyaluronic Acid for treatment of Knee Osteoarthritis: A Systematic review and meta-analysis", *Electron Physician*, Vol. 8, No. 3, pp. 2115-2122.

•Sampson, S., Reed, M., Silvers, H., Meng, M. & Mandelbaum, B. (2010), "Injection of platelet-rich plasma in patients with primary and secondary knee osteoarthritis: a pilot study," *American Journal of Physical Medicine Rehabilitation*, Vol. 89, No. 12, pp. 961-969.

•Sanchez, M., Fiz, N., Azofra, J., Usabiaga, J., Recalde, A.E., Gutierrez, A., Albillos, J., Garate, R., Aquirre, J.J., Padlla, S., Orive, G. & Anitua, E. (2012), "A randomized trial evaluating plasma rich in growth fators (PRGF Endoret) versus hyaluronic acid in the short-term treatment of symptomatic Knee osteoarthritis", *The Journal of Arthroscopy and Related Surgery*, Vol. 28, No. 8, pp. 1070-1078.

• Salini, V., Vanni, D., Patalone, A. & Abate, M. (2015), "Platelet-rich Plasma Therapy in Non-insertional Achilles Tendiopathy: The Efficacy is Reduced in 60-years Old People compared to Young and Middle- Age individuals", *Frontiers in Aging Neuroscience*, Vol.7, pp. 228.

•Say, f., Gurler, D., Yener, K., Bulbul, M. & Malkoc, M. (2013), "Platelet-rich plasma injection is more effective than

hyaluronic acid in the treatment of Knee osteoarthritis," *Acta Chirugiae Orthopaedicae Et traumatologiae Cechoslovaca* , Vol. 80, No. 4, pp. 278-283.

•Saturveithan, C., Premganesh, G., Fakhrizzaki, S., Mahathir, M., Karuna, K., Rauf, K., William, H., Akmal, H., Sivapathasundaram, N. & Jaspreet, K. (2016), "Intra-articular Hyaluronic Acid (HA) and Platelet-rich plasma (PRP) injection versus Hyaluronic acid (HA)injection alone in Patients with Grade III and IV Knee Osteoarthritis (OA): A Retrospective Study on Functional Outcome", *Malaysian Orthopaedic Journal*, Vol. 10, No 2, pp. 35-40.

•Scanzello, C.R., McKeon, B., Swaim, B.H., DiCarlo, E., Asomugha, E.U., Kanda, V., Nair,A., Lee, D.M., Richmond, J.C., Katz, J.N., Crow, M.K. & Goldring, S.R. (2011), "Synovial inflammation in patients undergoing arthroscopic meniscectomy: molecular characterization and relationship with symptoms", *Arthritis Rheumatoid*, Vol. 63, No. 2, pp. 391-400.

•Shen, L., Yuan, T., Chen, S., Xie, X. & Zhang, C. (2017), "The temporal effect of platelet-rich plasma on pain and physical function in the treatment of knee osteoarthritis: systematic review and meta-analysis of randomized controlled trials", *Journal of Orthopaedic Surgery and Research*, Vol. 12, No. 16.

•Smith, P.A. (2016), "Intra-articular autologous conditioned plasma injections provide safe and efficacious treatment for Knee osteoarthritis: An FDA-sanctioned, randomized, double-blind, placebo-controlled clinical trial." *The American Journal of Sports Medicine*, Vol. 44, pp. 884-891.

•Saegusa., W.A., Cugat, R., Ares, O., Seijas, R., Cusco, X. & Balletbo, G.M. (2011), "Infiltration of plasma rich in growth factors for osteoarthritis of the knee short-term effects on function and quality of life", *Archives of Orthopaedic and Trauma Surgery*, Vol. 131, No 11-338.

•Vaquerizo,V., Plasencia M.A., Arribas, I., Sejias, R., Padilla, S., Orive, G. & Anitua, E. (2013), "Comparison of intra-articular injections of plasma rich in growth factors (PRGF-Endoret) versus Durolane hyaluronic acid in the treatment of patients with symptomatic osteoarthritis: A randomized controlled trial", *The Journal of Arthroscopic and Related Surgery*, Vol. 29, pp. 1635-1643.

•Yuan, X.L., Meng, Y.C., Wang,J., Peng, Q.Y., Guo, A.Y., Wang, S.B. & Lu, S.B. (2014) Advances in Regenerative Medicine: High-density Platelet-rich Plasma and Stem Cell Prolotherapy For Musculoskeletal Pain, *Osteoarthritis and Cartilage*, 22 (8), 1077-1089.

•Zapata, J.C., Cox, D. & Salvato, M.S. (2014), "The Role of Platelets in the Pathogenesis of Viral Hemorrhagic

Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018

Fevers," *Public Library of Science Neglected Topical Disease*, Vol.8, No. 6.

Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018

Author: - Srimurugadas J, Weerasooriya.P
BMS School of Science, Sri Lanka
GARI Publisher | Health - Knee Osteoarthritis | Volume: 04 | Issue: 03
Article ID: IN/GARI/ICHM/2018/113 | Pages: 57-80 (23)
ISSN 2424-6492 | ISBN 978-955-7153-00-1
Edit: GARI Editorial Team | Received: 18.05.2018 | Publish: 15.06.2018