**INTRODUCTION**

Osteoarthritis/Osteoarthrosis is the consequence of mechanical and biological processes leading to imbalance between synthesis and destruction of cartilage and bone under the cartilage. Present treatment is a very costly burden for the individuals as well as for society in general, due to high cost of treatment, the effect not as expected while there might be severe complications. The current treatments are mainly symptomatic, reducing pain and improving motor function of joints, rather than effecting on degenerated articular cartilage which is a major cause of the disease. Furthermore, long-term use of medicines, particularly anti-inflammatory drugs, analgesics lead to side effects such as stomach-duodenal ulcers, gastrointestinal bleeding, hypertension, liver/kidney damages ... including lethal complications.

Thus, a new treatment technique is requied, which impacts towards preserving cartilage in a natural joint, independent or in combination with existing therapies to provide better outcomes, at the same time limiting complications and need for artificial joint replacement. Therapy with autologous Platelet Rich Plasma (PRP) has opened up a new direction for the treatment of osteoarthritis (OA): the most naturally, physically joint conservation therapy. Recently, many studies around the world have evaluated efficacy of this therapy in the treatment of osteoarthritis and provided good results, especially when compared with viscosupplementation treatment and placebo, while the undesirable effects of therapy are usually mild. In Vietnam so far, no systematic studies using autologous platelet rich plasma therapy for the treatment of primary knee osteoarthritis. So we conducted a thesis of "Study the effects of knee intra-articular autologous platelet- rich plasma therapy in treatment of primary knee osteoarthritis" with two objectives:

1. To study the clinical and paraclinical characteristics of primary knee osteoarthritis.
2. To assess the effectiveness and safety of autologous platelet-rich plasma therapy in treament of primary knee osteoarthritis.

\***Urgency of the project**: finding out a new treatment which are safe, effective, natural, contribution to the treatment of knee osteoarthritis, limit potential systemic or local complications in the course of treatment.

\***New contributions of the thesis**: For the first time, a such investigation implementing autologous PRP therapy for treatment of primary knee osteoarthritis (OA) at stages 2-3 in Vietnam. The study outcomes showed efficacy of the PRP therapy: Clinical effect: reduced pain and well improved knee function through VAS and WOMAC scales in both 2 moments of 6 and 12 months after treatment. Paraclinically: partial improvement of articular cartilage thickness assessed by ultrasound and magnetic resonance imaging (MRI). Undesirable effects: pain and arthritis / joint effusion seen at similar rates of treatment with viscosupplementation injection, mild and short duration, usually spontaneous resolved. Also studied in the thesis the clinical characteristics, X-ray, ultrasound and MRI of primary degenerative knee joint of stage 2-3 as well as hematological parameters and concentrations of growth factor TGF-β1 in autologous PRP, derived according Arthrex ACP method.

**THESIS OUTLINE**

This thesis covers 140 pages, including: preamle (2 pages), chapter 1: The Overview (36 pages), chapter 2: Material and method (21 pages), chapter 3: Study outcomes (35 pages), chapter 4: Discussion (43 pages), Conclusions (2 pages), Recommendation (1 page). The thesis consists of 34 tables, 7 charts, 1 diagram, 11 figures. There are 168 references, of which 30 in Vietnamese and 138 in English.

**CHAPTER 1: OVERVIEW**

**1.1. GENERAL ON KNEE OSTEOARTHRITIS**

**1.1.1. Causes, pathology and the role of PRP in the treatment of osteoarthritis**

Osteoarthritis (OA) is a slowly progressive, gradually increasing degenerative lesion of cartilage, caused by a combination of many different factors, such as genetic factors, metabolic, biochemical and bio-mechanical accompanying by secondary inflammatory process. Joints in OA made by an imbalance of degenerating elements: overloading joints, micro-injuries of the joints, chemical intermediates substances of inflammation: IL-1, TNF-α, Il-17, Il-18... with protective elements: growth factors as IGF-1, TGF-β and BMPs, cytokins as Il-4, IL-10, IL-13 and IL-1ra, IL-6. PRP contains growth factors and anti-inflammatory cytokines/anti-catabolic and biosynthetic modulation substrates of articular cartilage matrix such as IL-1ra, IL-4, IL-10, so the PRP therapy is a new approach to the OA treatment: at the same time anti-inflammatory and preserving joint articular cartilage in a natural manner.

**1.1.2. Diagnosis of knee OA**

***1.1.2.1. Diagnostic criteria***

Diagnosis of knee OA according to ACR 1991 criteria, with sensitivity at 94% and specificity of 88%

*1.1.**2.2. Imaging methods*

Typical X-ray of OA includes 5 characteristics: narrow slits, barbed bone, bone surface damage, fibrous bone under cartilage, bone capsules under cartilage. Diagnosis of knee OA level by radiography according to Kellgren-Lawrence divides in 4 stages.

Magnetic resonance imaging (MRI) of knees: MRI not only provides an efficient review of cartilage lesions, which are main lesions in OA, but also evaluation of other injuries of the synovia, bone under cartilage, meniscus, ligaments.

Joint ultrasound provides evaluation of cartilage thickness, synovial membrane inflammation, joint effusion, cyst.

**1.1.3. Treatment of knee OA**

The treatment options consists of non-pharmaceutical treatment, medication treatment (including injection of hyalorunic acid - HA into the knees), and surgery. So far, no medication can stop the progression of joint destruction due to degeneration.

New treatment option such as platelet-rich plasma, gene therapy and stem cell therapy which aim to recovering basic lesions of cartilage, meaning treatment of the cause of disease.

**1.2. AUTOLOGOUS PLATELET-RICH PLASMA THERAPY**

**1.2.1. Platelet-rich plasma**

Platelet-rich plasma (PRP) is a volume of autologous plasma, which contains platelet concentrations much higher than the physiological level in venous blood. Platelets play a role in the healing process, wound repair. Once platelets are activated, α granules in platelet are lysed, releasing many proteins, which have an important role on process of healing wounds or lesions.

**1.2.2. Using autologous platelet-rich plasma therapy in management of knee osteoarthritis**

PRP has many clinical applications with general effect is to accelerate the process of wound healing, shorten treatment duration, reduce post-surgical infection, reduce pain and blood loss. In rheumatology, use of PRP is common for treatment of sport injuries during last 2 decades. During recent 5-7 years, autologous PRP therapy has been studied in treatment of pathological articular cartilage lesions in general and in particular of OA, providing good results with little side effects.

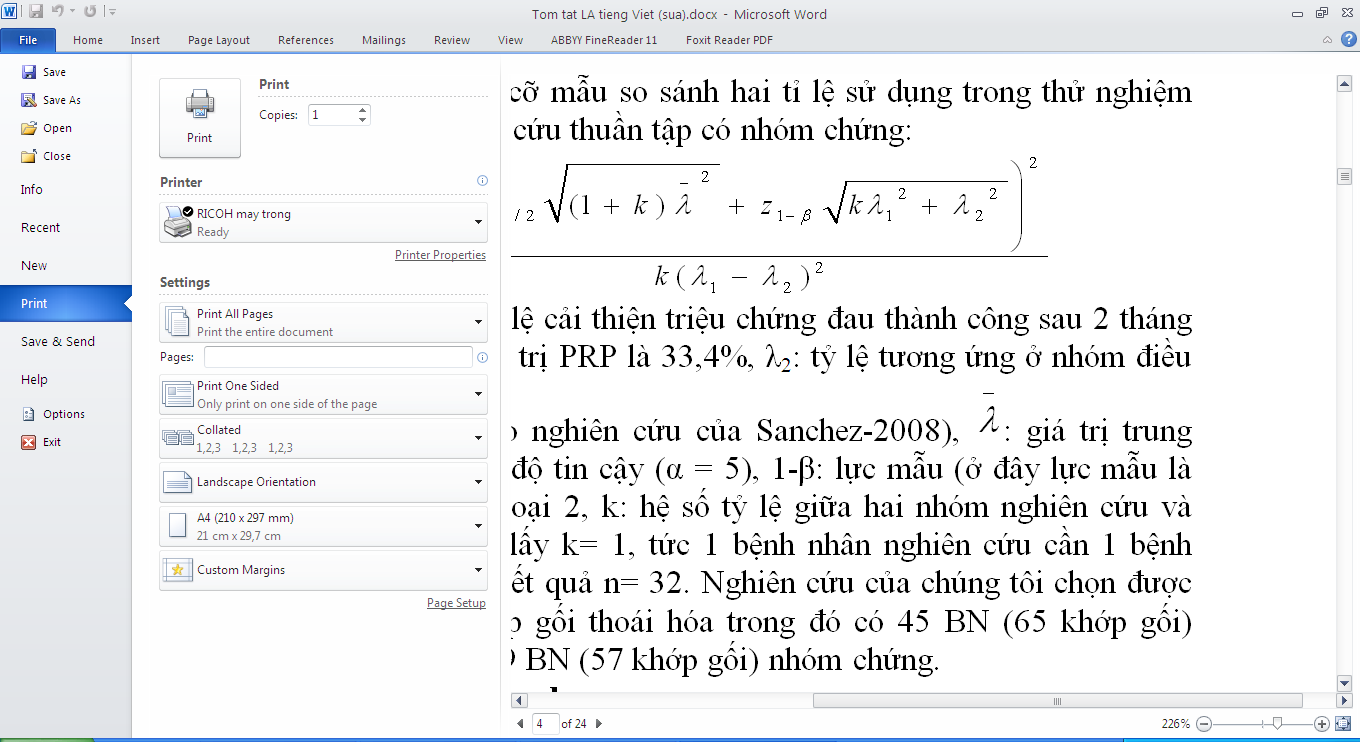
**CHAPTER 2: OBJECTS AND METHOD**

**2.1. MATERIALS**

**2.1.1. Sample size**

Calculation formula of the sample size comparing two groups used in clinical trial for cohort studies with a control group:



In which, λ­1­­ - ratio of improvement of pain symptom after 2 months under treatment, which was 33,4% for the group using PRP; λ­2­: the ratio of the comparable arm with hyalorunic acid (HA) was là 10% according Sanchez study - 2008), : the average value of λ­1 ­and λ­2, α: reliability (α = 5), 1-β: sample power (used here 80%), β is mistake type 2, k: coefficient between the two research groups and the control group, here supposed k= 1, ie 1 study patient requires 1 control patient. As result, n= 32. Our study selected 84 patients with 122 degenerative knees, in which 45 patients (65 knee joints) of intervention group and 39 patients (57 knee joints) of control group.

**2.1.2. Inclusion/Selection criteria**

* Patients over 40 years old.
* Primary knee OA according to ACR 1991 criteria.
* Duration of chronic knee pain lasting more than 3 months.
* The VAS scale assessment > 6/10.
* Uncontrolled pain, although at least 2 following treatments conducted: local injection of steroids, local hyalorunic acid injection, pain relief medications containing paracetamol, anti-inflammatory non-steroidal therapy, physiotherapy, acupuncture, wearing knee aids, changing lifestyles.
* Staging disease: X-ray of knee joints in stage 2 and 3 according to the Kellgren and Lawrence classification.
* Signed written agreement consent form.

**2.1.3. Exclusion criteria**

- Secondary knee OA.

* Other uncontrolled severe systemic diseases.
* Blood Hemoglobin below 110g/l.
* Blood platelets less than 150,000/mm3.
* Pregnancy.
* Corticosteroid/ HA injections into injured knee joints with the latest injection within 6 weeks before the enrolement.
* History of surgery, including laparoscopy of knee joint or degenerative knee infection.
* Stages 1, 4 of OA accroding Kellgren and Lawrence classification.
* Do not agree participation in the research.

**2.2. STUDY METHOD**

* Prospective, interventional, longitudinal research with control group.
* Study location: Rheumatology Department at Bach Mai hospital. The study period: from 8/2011 to 6/2015.

**2.2.1. Study design Quy trình nghiên cứu**

***2.2.1.1. Selection of eligible patients***and divided into 2 groups by a convenient sampling pattern:

Intervention group treated with PRP: 45 patients (pt) with 65 knee joints, PRP injection therapy into the degenerative knee joints.

Control group treated with hyaluronic acid (HA): 39 patients with 57 knee joints having the same characteristics as the intervention group.

***2.2.1.2. All patients received clinical examination, paraclinical tests*** according research criteria:

- Functional, physical symptoms.

- Pain assessment according to VAS (Visual Analog Scales).

- Assessment of mobilisation ability of the knee joint according WOMAC scale.

***- X-ray of knee joints:*** radiography of the injured knees in two positions: anterior-posterior and lateral. Comment on X-ray results by specialists at Diagnostic Imaging department, Bạch Mai hospital, without consulting clinical and paraclinical information of the patients.

**- *Knee ultrasound***was followed the guidance of EULAR, reading results by specialist at Rheumatology Department, Bach Mai hospital, withouts consulting clinical and paraclinical information of the patients.

**- *Knee MRI****:* using magnetic resonance machine with power 1.5 Tesla, reading performed by two specialists at Diagnostic Imaging department of Bach Mai hospital, no clinical status and laboratory data of patients provided. The reading by KOSS scale, measuring the thickness of the articular cartilage according protocol of Bach Mai hospital.

- Blood cells analysis, TGF-β1 measurement in PRP and whole blood (ELISA test).

***2.2.1.3. Therapy intervention***

**PRP group**: collect 15 ml of venous peripheral blood for 1 knee joint (30 ml for 2 joints), separated by ACP technique (Arthrex company). Inject 6ml PRP into the knee joint (the rest volume was for TGF-β1 measurement). PRP injection therapy comprises 3 injections, once a week, interval of 1 week.

**HA (Hyalgan) control group**: 2 ml Hyalgan (Fidia, Italia) contains 20 mg low molecular weight (500-730 kDalton) sodium hyalorunate. HA injection therapy comprises 3 injections, once a week, interval of 1 week.

**For both two groups:** Patients do not take nonsteroidal anti-inflammatory drugs and the long-acting anti-osteoarthritis drugs, such as glucosamine, chondroitin, interleukin-1 inhibitors. Educate lifestyle changes. If patients experience severe pain: use paracetamol (Tylenol) 650mg at dose 1 tab, 1-3 tabs/day. If fluid persist in the knee joint, aspirate the fluid and then carry out PRP or Hyalgan injections.

***2.2.1.4. Monitor, evaluate treatment outcomes***

Clinical examination: at moments of T0, T1, T2, T6, T10, T26, T52.

Ultrasound: T0, T1, T2, T6, T10, T26, T52.

X-ray, MRI: T0, T26, T52.

Satisfaction level: T26, T52.

***2.2.1.5. Review of undesirable effects of PRP and acid hyalorunic therapies***

The safety of these therapies include undesirable effects related to treatment were recorded and management of complications (if occur) at the moment from T0 to T26 and T52, as well as at any time of 1 year follow-up.

The local side effects at the joints: Inflammation of the synovium and/or joint effusion on clinical examination, ultrasound; Pain increases after injection; periarticular soft tissue infections, septic arthritis; Joint bleeding; Systemic symptoms: headache, dizziness, rashes, shock.

Patient withdrawn from studywere assessed at the moment before dropping out of treatment and probed reasons.

**2.3. DATA PROCESSING**

IBM SPSS program 20.0 and STATA 10.0, with biostatistics method.

**CHAPTER 3: RESEARCH OUTCOMES**

**3.1. GENERAL CHARACTERISTIC OF STUDY GROUPS**

***3.1.1 Common anthropometric and clinical features***

**Summary Table 3.1, 3.4, 3.5 and chart 3.1**

84 patients (68 femals, 16 males): 45 pts in PRP group, 39 pts in HA group.

The average age was 59,7±7,16 (46-75) years old in PRP group, 62,5±8,67 (47-82) in HA group, 61,0 ± 7,98 (46-82) in overal group.

There were 122 joints including 65 joints in PRP group (25 pts with 1 joint, 20 pts with 2 joints); 57 joints in HA group (21 pts with 1 joint, 18 pts with 2 joints).

The average disease duration was 40 ± 36,9 (6-168) months in PRP group, 35 ± 29,8 (6-120) months in HA group, 37 ± 33,7 (6-168) months in overal group.

There were 36 joints at 2 stage X-ray, 29 joints at 3 stage X-ray in PRP group, 29 joints at 2 stage X-ray, 28 joints at 3 stage X-ray.

The average VAS score was 6,82 ± 0,89 (6-9) in PRP group, 6,82 ± 0,82 (6-8) in HA group. The overal WOMAC score was 38,3± 10,8 (18- 68) in PRP group, 36,1 ± 11,46 (14- 61) in HA group.

Comments: no statistically significant difference regards anthropometric indices, stages of disease and the VAS, WOMAC scales before treatment between the two groups of PRP and HA injections.

**3.2. CLINICAL, PARACLINICAL SYMPTOMS**

**3.2.1. Clinical symptoms**

***3.2.1.1. Functional symptoms***

Summary Table 3.6

Mechanical type pain 119 joints (97,5%), inflammatory type pain 3 (2,5%); Pain when sleeping 83 (68%); Pain at rest 57 (54,9%); Pain when standing 109 (89,3%); Pain when walking 121 (99,2%): pain after walking a distance 85 (69,7%), pain immediately after walking 36 (29,5%); Pain when climbing stairs 122 (100%); pain when moving up from a standing position no hand rails seats 73 (59,8%); Joint stiffness of out rusty joint pain 92 joints (75,4%).

***3.2.1.2. Physical symptoms***

Summary Table 3.7

Crepitus: 110 joints (90.2%); Click on motion or wood shaving signs 63 (51.6%); Normal skin temperature (99.2%); Bony enlargement 27 (22,1%); Effusion clinically detected 29 (23.8%), Baker cyst 4 (3,3%).

**3.2.2. Paraclinical symptoms**

***3.2.2.1. X-ray of the knee joints***

Summary Table 3.8

Misalignment 66 joints (54,1%): varus (misalignment of O letter) 41 (33,6%); 84 (68.9%) of relatively narrow joint: medial femur-tibial 65 (53.3%), femur-patella 56 (45,9%), lateral femur-tibial 26 (21,3%) narrow; Osteophyte 113 (92,6%): femur-patella 98 (80.3%), medial femur-tibia 97 (79.5%), lateral femur-tibia 71 (58,2%); Subchondral slerosis 106 (86.6%): in medial tray tibia 102 (83.6%), lateral tray tibia 38 (31,1%), medial condyle 18 (14,8%); Subchondral cyst 8 (6,6%): medial tray tibia 4 (3,3%), medial condyle 3 (2,5%); Bony attrition 22 (18,0%): in medial tray tibia 15 (12,3%), patella 9 (7,4%), lateral tray tibia 5 (4,1%), lateral condyle 5 (4,1%).

Comment: most abnormal X-ray features were in medial femur-tibia.

***3.2.2.2. Ultrasound of knee joint***

Summary Table 3.9

Totally, 122 joints performed ultrasound at baseline. *Note: 1 patient of HA group having calcification in joint and cartilage thickness was not measurable.*

22 joints (19,7%) in effusion rate with a majority varying from little to moderate, 1 (0,8%) joint effusion rate was large; 120 (98.4%) of joints having synovium of less 4 mmm (normal), 1 (0,8%) synovial localized thickening, 1 (0,8%) synovial diffused thickening; Osteophyte was 100 joints (82.0%), in which medial femur-tibia was of 96 (78.7%), lateral femur-tibia 76 (62,3%); Baker cyst accounted for 19 (15.6%) of the joints; Dislocated meniscus 4 (3,3%); Calcification in the joint 6 (4,9%).

Cartilage thickness was 1,8±0,52 mm (0,6-3,5, n=121) at medial condyle (M); 2,0 ± 0,63 mm (0,4-4,1, n= 121) at lateral condyle (L); 2,2 ± 0,58 mm (0,2-3,5, n= 121) at intercondylar notch (N).

***3.2.2.3. Features of knee magnetic resonance imaging***

Summary Graphic 3.2

Proportion of knee lesions on MRI (111 knee joints performed before the interventions)

Joint effusion 110 (99.1%), cartilage lesions 109 (98.2%); Osteophyte 108 (97,3%); Bone marrow odema 85 (76.6%); Meniscus lesions 78 (70,3%); Baker cyst 22 (19,8%); Bone cyst 12 (10,9%); Synovitis was least common with 2 joints (1.8%).

***Features of cartilage thickness on MRI***

**Table 3.17: Features of cartilage thickness**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Cartilage thickness** | **PRP/ HA/Study group: M± Std (min, max)** | | | |
| PRP  n= 63 | HA  n=48 | Study  N= 111 | P |
| Lateral condyle (N) (mm) | **1,3 ± 0,31** (0,2-1,9) | **1,5 ± 0,36** (0,3-2,2) | 1,4 ± 0,34 (0,2-2,2) | **<0,05** |
| intercondylar notch (G) (mm) | **1,5 ± 0,46** (0,1-2,6) | **1,7 ± 0,26** (0,8-2,3) | 1,6 ± 0,40 (0,1-2,6) | **<0,05** |
| Medial condyle (T) (mm) | 0,9 ± 0,43 (0,0-2,0) | 1,0 ± 0,56 (0,0-2,1) | 1,0 ± 0,49 (0,0-2,1) | >0,05 |

Comments: cartilage thickness in lateral condyle (N), intercondylar notch (G) of a larger in HA group than PRP group showed a statistically significance at p <0.05 while in no difference in the medial condyle (T).

***3.2.2.4. Features of Platelet Rich Plasma (PRP)***

Summary Table 3.18

Features of PRP in 49 patients (39 pts in PRP group and 10 pts in HA group) were performed.

The average platelet concentration of PRP was 436 ± 100,8 G/l (279-697) in PRP vs 240 ± 70,8 G/l (160-436) in whole blood.

The average white blood cells concentration of PRP was 0,52 ± 0,59 G/l (0,00- 2,60) in PRP vs 7,1 ± 1,61 G/l (4,1-11,38) in whole blood.

The average TGF-β1 concentration was 148,6 ± 106,74 ng/ml (5,6- 400,50) in PRP vs 13,8 ± 14,04 ng/ml (0,6- 62,34) in whole blood.

**3.3. EVALUATION OF EFFICACY, SAFETY OF AUTOLOGOUS PRP THERAPY**

**3.3.1. Evaluation of efficacy, safety of PRP therapy**

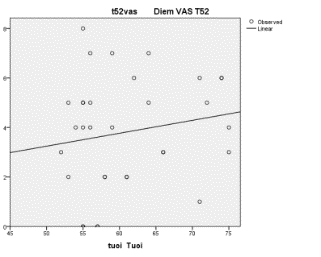
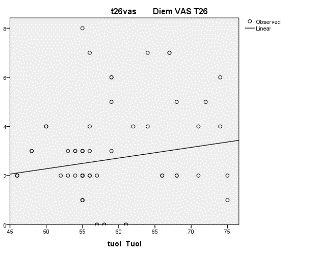
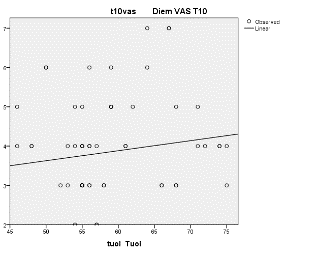
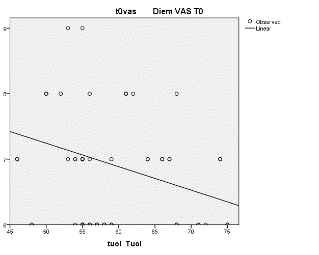
***3.3.1.1. Clinical evaluation***

Among 84 patients (122 joints) at the start of treatment, there were 70 patients (106 joints) after 6 months follow-up: PRP group was of 38 patients (58 joints) - HA group of 32 patients (48 joints); after 12 months: 30 patients (44 joints) in which PRP group was of 22 patients (33 joints) and HA group 8 patients (11 joints).

**Efficacy evaluation according to VAS scale**

**Graphic 3.3: evolution of VAS scale of 2 interventional groups**

Comments: VAS scale was gradually decreased from T0 to T10 in both two groups PRP and HA injection; PRP group showed a continuous decrease from the T10 of VAS scale further to T26, then increase again, while among HA group, VAS scale was ascending from T10, the difference was statistically significant with p <0, 05



VAS t0 VAS t10 VAS t26 VAS t52

**Graphic 3.4: VAS scale changed according ages in PRP group**

Comments: at baseline, VAS scale tends to slightly level in older group; at the moments of 2, 6 and 12 months later, the heaviest VAS scale in elderly patients.

***Table 3.23: Rate of improvement of 30% VAS scores according X-ray stages***

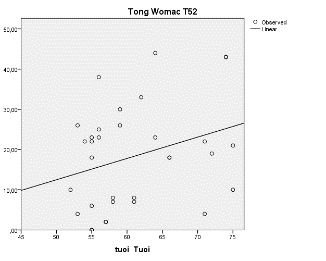
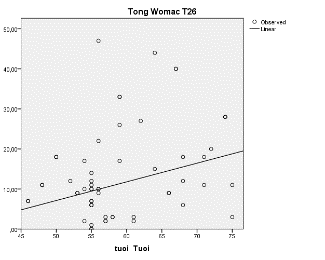
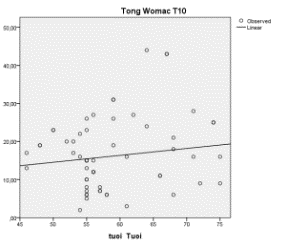
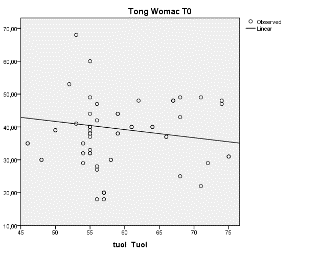
|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Time | T6-T0 (1month) | | T10-T0 (2 months) | | T26-T0 (6 months) | | T52-T0 (12 months) | | p |
| PRP | HA | PRP | HA | PRP | HA | PRP | HA |  |
| Stage 2 | 16/33 *(48,5%)* | 15/26 *(57,7%)* | 27/33 *(81,8 %)* | 26/26 *(100%)* | 29/33 *(87,9%)* | 21/26 *(80,8%)* | 17/23 *(73,9%)* | 2/7 *(28,6%)* | **< 0,05** |
| Stage 3 | 6/25 (*24,0%)* | 6/22 *(27,3%)* | 16/25 *(64,0%)* | 17/22 *(77,3%)* | 19/25 *(76,0%)* | 10/22 *(45,5%)* | 2/10 *(20,0%)* | 0/4 *(0,0%)* |
| Overall rate | 22/58 *(37,9%)* | 21/48 *(43,8%)* | 43/58 *(74,1%)* | 43/48 *(89,6%)* | 48/58 *(82,8%)* | 31/48 *(64,6%)* | 19/33 *(57,6%)* | 2/11 *(18,2%)* |  |
| p | > 0,05 | | **< 0,05** | | **< 0,05** | | **< 0,05** | |  |

Comments: at all times, rates of pain improvement of stage 2 was higher than stage 3 with statistically significant difference p <0.05 for both groups. One month after treatment, there was no difference in pain improvement between the 2 groups, p> 0.05; At 2 months improvement was higher among HA group compared to PRP group with statistical significance; At 6 and 12 months after treatment improvement was higher among injecting PRP compared to HA group, p <0.05.

**Efficacy evaluation according WOMAC scale**

***Graphic 3.6: Efficacy assessment according WOMAC scale***

Comments: at the time of T0 to T10, WOMAC pain, stiffness, function and overal WOMAC scale showed no difference in the two intervention groups; at T26 and T52, WOMAC scores of pain, stiffness, function and overall WOMAC lower in PRP group compared to HA group, which is statistically significant with p <0.05.

Overall WOMAC t0 Overall Wt10 Overall Wt26 Overall Wt52

**Graphic 3.7: overall WOMAC scale depending ages in PRP group**

Comments: at baseline, the overall WOMAC scale tends slight in older group; during follow-up after treatment, especially after 2, 6 and 12 months later, the heaviest overall WOMAC scale was in elderly patients.

***3.3.1.2. Paraclinical evaluation of autologous PRP treatment***

**Ultrasound evaluation of PRP and HA groups**

***Table 3.28: ultrasound evaluation of tretment efficacy on cartilage thickness***

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Before- after cartilarge thickness (mm) | **PRP group** (compare pairs, T- test) | | | | | |
| (T0-T26) n=58 | (T26-T52) n=33 | (T0-T52) n=33 | pt0-t26 | pt26-t52 | pt0-t52 |
| **L** | **-0,17±0,49** | **0,22 ± 0,56** | 0,05±0,54 | **0,011** | **0,034** | 0,563 |
| **M** | **-0,30±0,45** | **0,26 ± 0,54** | -0,05±0,48 | **0,000** | **0,009** | 0,563 |
| **N** | **-0,17±0,51** | 0,08 ± 0,51 | -0,12±0,62 | **0,013** | 0,403 | 0,267 |
|  | **HA group** (compare pairs, T- test) | | | | | |
| (T0-T26) n=47 | (T26-T52) n=7 | (T0-T52) n=8 | pt0-t26 | pt26-t52 | pt0-t52 |
| **L** | 0,34±0,64 | 0,05±0,30 | 0,30±0,55 | 0,001 | 0,571 | 0,087 |
| **M** | 0,16±0,41 | **0,17±0,24** | 0,27±0,37 | 0,012 | **0,036** | 0,027 |
| **N** | 0,13±0,54 | 0,21±0,31 | 0,27±0,44 | 0,093 | 0,039 | 0,06 |

Comments: in PRP group, the 3 positions L, N, M at the time of T26, cartilage thickness were increased (from 0.17 to 0.30 mm) with statistical significance of p <0.05 compared with T0, while at T52 cartilage thickness showed no difference compared to T0; at moment T52 compared to T26, the thickness of cartilage in position L, M decreased with statistically significant difference, but not N position.

In HA group: cartilage thickness of 1 patient was not measured by ultrasound due to large calcification, but assessed well on MRI. Over monitoring time the thickness of cartilage in all 3 positions were reduced (from 0.13 to 0,34mm) in that position L, M showed statistically significant reduction at T26; at T52 cartilage thickness continued decreasing in all 3 positions but statistical difference only seen in the position M (p <0.05).

**MRI evaluation of PRP and HA groups**

***Table 3.29: Efficacy evaluation based on cartilage thickness by MR****I*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Before- after cartilarge thickness (mm) | **PRP group (compare pairs, T- test)** | | | | | |
| **(T0-T26) n=48** | **(T26-T52) n=13** | **(T0-T52) n=14** | **p t0-t26** | **pt26-t52** | **p t0-t52** |
| **Lateral (N)** | **-0,13±0,19** | 0,11±0,29 | -0,08±0,22 | **0,000** | 0,189 | 0,212 |
| **Medial (T)** | -0,07±0,33 | -0,08±0,44 | -0,05±0,56 | 0,172 | 0,498 | 0,735 |
| **Inter (G)** | **-0,09±0,28** | 0,05±0,35 | -0,20±0,60 | **0,027** | 0,630 | 0,228 |
|  | **HA group (compare pairs, T- test)** | | | | | |
| (T0-T26) n=15 | (T26-T52) n=5 | (T0-T52) n=6 | p t0-t26 | Pt26-t52 | p t0-t52 |
| **Lateral (N)** | 0,09±0,23 | 0,02±0,04 | 0,22±0,39 | 0,140 | 0,374 | 0,228 |
| **Medial (T)** | **0,18±0,23** | 0,12±0,16 | 0,22±0,26 | **0,009** | 0,178 | 0,093 |
| **Inter (G)** | 0,07±0,13 | 0,04±0,09 | 0,17±0,16 | 0,065 | 0,374 | 0,054 |

Comments: In PRP injection group, cartilage thickness in lateral condyle (N) and intercondylar notch (G) increase (up to 0.13 and 0.09 mm) in T26 compared to T0 with statistical significance at p <0.05, while there was no chage in the medial condyle (T). At other times, change is not statistically significant. Among injecting HA cartilage thickness in the position of (T) decreased in time T26 compared to T0 statistically significant at p <0.05 while the other positions shift are trending down compared to baseline but no statistical significance.

***3.3.2. Safety of autologous PRP therapy***

***3.3.2.1. Complications, undesirable effects of therapy***

***Table 3.30: Complications, undesirable effects of 2 group - PRP and HA***

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Time | T1 | | T2 | | T3 | |
| Group | PRP(65) | HA (57) | PRP (65) | HA (57) | PRP (65) | HA(57) |
| Pain within 6h | 5 (7,7%) | 5 (8,8%) | 1(1,5%) | 4 (7,0%) | 0 (0%) | 0 (0%) |
| Number of joints (analgesic dose) | 1 (2v)  2 (3v) | 2 (1v)  1 (2v) | 1 (3v) | 3 (2v) | 0 | 0 |
| Pain within 12h | 6 (9,2%) | 4(7,0%) | 7(10,8%) | 5 (8,8%) | 1 (1,5%) | 1(1,8%) |
| Number of joints (analgesic dose) | 1 (1v) | 0 | 1 (1v)  1 (3v) | 1 (1v)  1 (2v) | 0 | 0 |
| Pain within 24h | 7(10,8%) | 8(14,0%) | 7(10,8%) | 7(12,3%) | 2 (3,1%) | 5 (8,8%) |
| Number of joints (analgesic dose) | 1 (3v) | 2(2v)  1(3v) | 1 (3v) | 4 (2v) | 1 (1v) | 4 (2v) |
| Pain over 24h | 7(10,8%) | 7(12,3%) | 7(10,8%) | 4 (7,0%) | 3 (4,6%) | 2 (3,5%) |
| Number of joints (analgesic dose) | **3 (2v)**  **1 (3v)** | **6 (3v)** | 1 (2v)  2 (3v) | 2 (2v)  2 (3v) | 1 (1v) | 1 (2v) |
| **Overall pain** | 25 (38,5%) | 24 (41,1%) | 22 (33,8%) | 20 (35,1%) | **6 (0,9%)** | **8 (1,4%)** |
| **Synovitis/New joint effusion** | 11 (16,9%) | 13 (22,8%) | 10 (15,4%) | 15 (26,3%) | 9 (13,8%) | 13 (22,8%) |

Comments: both two intervention groups showed no difference in rates of pain, less frequent using analgesics, low analgesic doses (except at moment after the 1st dosing, analgesics needed among HA group was higher); pain rate after the 3rd injection was lower in both two intervention groups; occurrence of new effusion after injection was higher at HA group compared to PRP group, but the difference was not statistically significant; no complications and severe side effects in both the 2 groups

***3.3.3. Assess the level of satisfaction***

***Table 3.31: Post-therapy assessment of satisfaction level***

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Time** | **After 6 months treament, n=106** | |  | **After 12 months treament, n=44** | |  |
| Level of satisfaction | PRP group (58) | HA group (48) | P(χ2-test) | PRP group (33) | HA group (11) | P(χ2-test) |
| No satisfaction | 5 (8,6%) | 7 (14,6%) | **< 0,001** | 5 (15,2%) | 7 (63,6%) | **< 0,01** |
| Satisfaction | 20 (34,5%) | 33 (68,8%) | 14 (42,4%) | 4 (36,4%) |
| Very satisfaction | 33 (56,9%) | 8 (16,7%) | 14 (42,4%) | 0 (0%) |

Comments: very satisfied rate in the PRP group (56.9%) was higher than in the HA group (16.7%), statistically significant at the moment after 6 months (p <0.001) and 12 months (42.4% versus 0%) (p <0.01).

**CHAPTER 4: DISCUSSION**

**4.1. GENERAL CHARACTERISTICS OF THE STUDY GROUP RESEARCH AND CONTROL GROUP**

There were no statistically significant difference regards anthropometric indices and clinical features before treatment between the two groups of PRP of HA injections, p > 0,05.

**4.2. CLINICAL, PARACLINICAL SYMPTOMS**

***4.2.2.2. Functional symptoms***

In our study 100% of study joints had signs of knee pain. Pain of mechanical manner is the specific type of pain in degenerative joint disease: pain increasing during mobility, decreased with rest. In our study, mechanical type of pain accounted for 97.5%, similar to those of Hong Hoa Dang of 95.2%. Inflammatory pain group accounted for only 2.5% of our painful joint group.

In our study, 68% of joints had pain at night, pain on movement accounted for 45.9% and pain at lying posture accounted for 22.1%. Dang Hong Hoa stated 47.6% of patients with joint pain at night.

99.2% of joints had pain when walking, pain when standing for over 30 minutes was 89.3%, pain when climbing stairs 100%, pain when moving up from a standing position no hand rails seats was 59.8%. Compared with Dang Hong Hoa study (2007) pain when walking accounted for 95.2%, pain when standing for long periods of 30 minutes was 78.6%, pain when up stairs accounting for 59.5%, downstairs accounted for 69,0%, pain when moving up from a chair without hand rails was 61.9%. Nguyen Thi Ai's study (2006) also gave similar results, which were 89.7% pain when walking, 80.2% pain when climbing stairs, pain when moving up from a chair with no hand rails was 80 ,2%.

The statistics of the symptoms in the above studies lead to conclude that pain when movement is one of the characteristic symptoms of knee osteoarthritis. However, 54.9% of joints in our study had pain at rest. Results of Dang Hong Hoa showed 59.5% less painful joints at rest, which means there are 40.5% joint pain still persists, lower than our results.

Signs of rusty joints, stiffness of knee joint usually come in morning after waking up, in osteoarthritis rarely lasting more than 15-30 minutes. However joint stiffness appearing at any time of break is also common, patients must mobilize for a while to return to normal. Our study of 122 knees with 75.4% of knee joints showing signs of rust out. According to Dang Hong Hoa in 42 patients with knee osteoarthritis, 61.9% of patients had signs.

***4.2.2.3. Physical symptoms***

Noise during joint examination (crepitus) was seen in 90.2% in our study. This result is similar to findings of Dang Hong Hoa (88.3%) and Nguyen Thi Ai (85.3%).

Wood shavings are signs of femur-patella joint damage in knee osteoarthritis. Signs of wood shavings in our study accounted for 51.6%, lower than 74.1% in the study by Nguyen Thi Ai (2006) or 78.6% of Dang Hong Hoa (1997).

Normal skin temperature of joints in our study was 99.2%. According Dang Hong Hoa, this feature was of 73.8%. According to Altman, percentage of normal skin temperature is 78%. This rate in our study was higher, possibly due patients were in radiographic stage 2-3 according Kellgren and Lawrence, which means average OA, no severe cases.

Bony enlargement accounted for 22.1% in our study. According to Nguyen Thi Ai, these physical symptoms accounted for 51.7%, equivalent to the results of Dang Hong Hoa of 52.4%. According to Altman, Bony enlargement seen in 55%.

In our study, effusion clinically detected in 23.8% of knee joint, equivalent to Dang Hong Hoa’s study of 26.2%. Nguyen Thi Ai’s study with a history of joint swelling amounted to 45.7%, higher than our findings.

The rate of Baker cyst was low, at 3.3% of injured knees, much lower than Dang Hong Hoa was 26.2%.

***4.2.3. Paraclinical symptoms***

***4.2.3.1. X-ray characteristics***

Axis deviation seen in 54.1% of knee joints, main misalignment of O form with 33.6% and X is 20.5%. According to Nguyen Thi Ai, with 37.1% of the joint misalignment, O misalignment was 30.2% O, X was 6.9%. Study results of Dang Hong Hoa showed misalignment the O 38.1%. Thus, percentage of O misalignment is relatively high in OA in Vietnam. According to many studies, bandy/bowlegged phenomenon (misalignment O) with knee axis deviation in strained joints meniscus operation, put the load deflection on femur-tibia board resulting common joint degeneration in this area.

Our study showed that 68.9% had narrow joint space, including 53.3% in the narrow slit of medial femur-tibia and 45.9% femur-patella narrow space. Dang Hong Hoa showed overal narrow space rate was 83.3%, in which 81% medial femur-tibia, femur-patella 81% and 71.4% respectively. Both two studies showed a significantly narrower space in medial tibia-femur compared to the lateral one. This is a characteristic of the OA, when presure primarily fall on medial fumer-tibia cavity.

92.6% of joints in our study showed osteophyte on radiologic images including medial femur-tibia location was 79.5%, 58.2% in lateral one and femur-patella of 80.3%. Similar results seen by Dang Hong Hoa with the 85.7% of osteophyte, in which the ratios of the corresponding positions is 78.6%; 73.8% and 83.3% femoral-tibia. Altman et al showed rate of bone spikes 91%, in that medial femoral-tibia space of 75%, the lateral one of 73% and femur-patella of 89%.

In our study, subchondral slerosis was of 86.9%, which featured in the medial tibial tray at the highest proportion of 83.6%, followed by lateral tibia tray, medial condyle of 31.1% and 14.8%. Subchondral slerosis was the lowest in lateral condyle and patella, were 5,7% and 1,6%. According to Dang Hong Hoa, the percentage of subchondral slerosis was 78.6%, which featured medial femur-tibia cavity was 73.8%. The studies agreed lesions of medial femur-tibia cavity is the most common. This area is also where found the highest ratio of narrow joint space due to the most presure bearing. This conclusion is also consistent with the results of Altman special rate of 80% subchondral slerosis and highest rate was 65% of medial femur-tibia.

Our patients were in everage disease stages, then bone cyst rate was low, 6.6% (8/122 joints. The higher results of Dang Hong Hoa (35,7%) and Altman (38%) would be related to different disease stages.

Bone attrition in the bone adjacent to the cartilage surface area often involves bone severity of knee osteoarthritis. In our study the bone attrition rate was 18.0% in which the most common in medial tibia tray (12.3%), patella (7.4%), medial condyle and lateral tibia tray are of 4.1%. According to Altman, the overall bone attrition rates were 55% in which 42% in medial and 21% in lateral femur- tibia cavity.

***4.2.3.2. Ultrasound charateristics***

The ultrasound lesions include: joint effusion 20.5% at mild-average level of 19.7%, large effusion was of 0.8%; synovium thick 1.6% (2/122 joints); osteophyte (bone spurs) 82.0% (92.6% on X-ray) including osteophyte 78.7% medial femoral-tibia slots (on X-ray 79.5%), lateral femur-tibia slot 62.3% (on X-ray 58.2%); Baker cyst was 15.6%.

According Le Thi Lieu (2009) on 65 patients diagnosed OA showed: ultrasound lesions included: joint effusion (57.7%), synovial proliferation (7.7%), Baker cyst (17.7%), osteophyte (53.8%), thin cartilage (100%) with average thickness of 1,3±0,68 mm.

According to the EULAR (2005) evaluating 600 patients with degenerative knee pain showed effusion of 43.6%, 16.7% having synovial inflammation with average thickness of 2.1 ± 2.5 mm (0- 29mm); however there were 53.7% has no effusion, neither inflammation of synovium; 29.5% effusion only, 14.2% both joint effusion and synovial inflammation at the same time, only 2.7% had synovial inflammation alone.

About the thickness of the articular cartilage on ultrasound, lateral condyle position was 2.0 ± 0.63 mm, medial condyle was 1.8 ± 0.52 mm and intercondylar notch was 2.2 ± 0.58 mm. According Spannow (2010), normal articular cartilage thickness between 2.7- 3.5 mm, thickness of cartilage at the medial condyle is thinner than lateral condyle, and decreases with age. Nguyen Thi Thanh Phuong (2013) showed valuable contribution of ultrasound for knee joint cartilage thickness. The average thickness of the OA patient group lateral condyle was 1.7 ± 0.6 mm, medial was 1.9 ± 0.5 mm and intercondylar notch was 2.0 ± 0.5mm; whereas the corresponding indicators in the control group without OA was 2.0 ± 0.3 mm; 2.0 ± 0.2 mm and 2.4 ± 0.3 mm respectively. According to the author, the articular cartilage thickness of the medial condyle in OA group reduced significantly than that normal group (p <0.01).

***4.2.3.3. MRI characteristics***

In our study, the prevalence of these lesions in OA include: joint effusion 99.1%, 98.2% had cartilage lesions, 97.3% had a bone spur (osteophyte), bone marrow odema 76.6% accordingly, 19.8 % have Baker cyst, bone cysts 10.9%, 1.8% synovitis and 70.3% with meniscal lesions. Nguyen Xuan Thiep (2013) investigated on 32 patients with 54 knee joints by MRI according KOSS scale, showed 100% joint cartilage lesions, 100% had degenerative meniscus, 90.7% joint effusion, bone spurs 74.1%, 70.1% bone marrow odema, 38.9% had a bone cyst under cartilage, Baker cyst 9.3%. According to Link (2003) surveyed 50 knee joints of OA patients showed that 86% (43/50) having knee cartilage lesions, bone marrow edema 60%, bone cysts 44%, 100% bone spur, 76% joint effusion, degenerative meniscal lesions accounted for 10%.

About the thickness of the articular cartilage on MRI: our research showed that the most thin cartilage was in the medial condyle position (1.0 ± 0.49 mm), followed by lateral condyle (1.4 ± 0.34 mm) and thickest at intercondylar notch (1.6 ± 0.40 mm) (Table 3.17). Similarly, we also find on ultrasound the cartilage was thinnest at medial condyle (1.8 ± 0.52 mm), lateral condyle (2.0 ± 0.63 mm) and intercondylar notch (2.2 ± 0.58 mm). We found a difference in cartilage thickness by ultrasound and MRI with cartilage thickness on MRI was lower than by ultrasound. The reason for the difference is probably due to defferent poisture when measured, as well as different mechanism of working of MRI and ultrasound. But both measurements found the cartilage was thinnest at medial condyle. This is also consistent with analysis showing medial femur-tibia cavity was the most presure bearing hence becoming thinnest, whereas intercondylar notch position is not under pressure so that the greatest thickness

***4.2.4. PRP characteristics according ACP method (Arthrex)***

In our study, platelet concentrations in PRP average was 436 G/L. Platelet concentration in PRP is nearly 2 times more condensed versus physiologic platelet levels in whole blood of 240 G/L. In the study of Mazzocca (2012) separation techniques for Arthrex ACP of platelet number in PRP was 378.300/μL compared to blood platelets of 142,700/μL. Techniques of Arthrex ACP provide platelet concentrations in PRP only about 2 times higher than in whole blood platelets, but for optimal therapeutic effect.

TGF- β1 concentrations in PRP was 148.6 ± 106.7 ng/ml, more than 10 times higher than the concentration in the whole blood was 13.8 ± 14.0 ng/ml. Weibrich study (2002) on 115 healthy volunteers TGF- β1 concentration was 169 ± 84 in PRP ng/ml; Eppley study on 10 healthy volunteers was 120 ± 42 ng/ml. Both two studies provided the same results with our study.

**4.3. EVALUATION OF EFFICACY, SAFETY OF AUTOLOGOUS PRP THERAPY**

***4.3.1. Efficacy of autologous PRP therapy***

***4.3.1.1. Clinical efficacy***

**Efficacy evaluation according VAS, WOMAC scale**

PRP treatment shows effect soon due to anti-inflammatory effects. Our study showed that the treatment group PRP immediately at the time of 1 weeks after injection 1 and 2 with VAS and WOMAC score decreased compared to the baseline with statistical significance, ie an improvement in pain level at fairly early stage. However, this improvement was not evident, similar to the control group (Figure 3.3, 3.6). After 2 months of treatment, the efficacy of treatments with PRP became evident through the significant reduction of both scales: VAS and WOMAC score further reduced at the time of 1,2,6 months after treatment. Meanwhile among injecting HA group, VAS and WOMAC score decreased after 1 and 2 months but increased after 6 months of treatment (the best results happened at 2-month). At 6 months after treatment, VAS and WOMAC score lower in PRP group had statistically significant compared to the HA group with p <0.05. After 1 year of treatment, VAS and WOMAC score in PRP group increased slightly versus in HA group increased much, differences with statistical significance with p <0.05 (Chart 3.3,3.6) showed long efficacy of autologous PRP therapy.

Evaluating the effectiveness of PRP on the VAS scale in our study was similar when compared with treatment using the HA in knee OA, carried out by of other authors like Say (2013), Hassan (2015), Patel (2013), Halpern (2013). Evaluating the effectiveness of PRP on the WOMAC scale was similar to studies of other authors like Cerza (2012), Spakova (2012), Halpern (2013).

In our study, taking moment of pain improvement according VAS scale of 30% compared to baseline, results after 2 months was 37.9% in treated PRP (not different from the HA treatment group was 43.8%) (Table 3:23). After 2 months of treatment, 89.6% among injecting HA has proved effective joint pain relief of at least 30%, higher than the statistical significance compared with 74.1% among injecting PRP. However, after 6 months and 12 months of treatment, this ratio become lower significantly when compared with PRP injection group (64.6% versus 82.8% after 6 months), (18.2% versus 57.6% after 12 months). This proved effective HA injection group quickly in a short time (in our study the best effect reached after 10 weeks of treatment, chart 3.6), but the effect decreased rapidly and usually finished after 6 months of treatment, many other similar results were complied in Database Syst Rev Cochrane Library (2006).

Comparison of treatment effects by age in treated PRP, chart 3.4 (VAS scale) and chart 3.7 (WOMAC scale) shows: baseline (time T0) curvature VAS/ WOMAC scale tend to travel light (downward) by age. After 1 month follow-up VAS/ WOMAC scale tend sideways but after 2, 6 and 12 month follow-up, the curve upward VAS/ WOMAC scale showed high VAS/ WOMAC score (results worse) belongs to the older patients. In other words, the therapeutic effect of autologous PRP injection therapy is better at a young age and decreased with increasing age. This conclusion is also consistent with the study Kon (2010), (2011) and Filardo (2012).

In table 3.23, review criteria 30% improvement of VAS scale in both 2 treatment groups PRP and HA showed stage 2 has a higher improvement rate. Through table 3.24, we found that in patients with low-stage disease (stage 2 on X-ray), the effectiveness of PRP group lower than group HA after 2 months of treatment, but higher with statistical significance in the period from 6 and 12-month follow-up. In the more severe disease group (stage 3) the effectiveness of the 2 groups were similar: PRP treatment group better just at time after 6 months of treatment and for similar effectiveness in the time after 12 months treatment (table 3.24). On the chart 3.5 we see the best effect in the treated PRP stage 2 subgroup, subgroups treatment PRP stage 3 and treatment HA stage 2 for equivalent results, the worst result belongs the HA treatment subgroup stage 3. This result is similar to the conclusions of the authors Kon 2010, 2011 and Filardo 2012.

***4.3.1.2. Efficacy on paraclinical improvement***

**Cartilage thickness assessed by ultrasound**

Our study on thickness articular cartilage by ultrasound showed PRP injection group, at 6 month follow-up, the average thickness of the cartilage covered in femoral trochlear cartilage increased compared to baseline, statistical significance with p <0.05, in position of lateral condyle (L) increased 0.17 ± 0.49 mm, medial condyle (M): 0.30 ± 0.45 mm, intercondylar notch (N): 0.17 ± 0.51. Meanwhile in treatment group with Hyalgan, articular cartilage thickness of the three positions (L), (M), (N) down significantly statistics (Table 3.28). This proved that the cartilage thickness of PRP treatment group at 3 positions are better improved than Hyalgan group. Arcording to Sampson’s study (2010), 6 months after knee injecting PRP, articular thickness increased in some positions: before- after lateral condyle: 2.5mm-2.73 mm, medial condyle: 3.32 mm- 3.38mm.

However, at 12 months after treatment compared to the 6 months after treatment (ie 6 months), the PRP group in our study observed thickness of the cartilage in lateral condyle (L) and medial condyle ( M) tends to decrease as compared with the previous 6 months, this had statistically significant at p <0.05 while intercondylar notch (N) decreased without statistical significance (Table 3.28). Thus cartilage tends to decrease the thickness and medial and lateral condyle may decrease more because it is more pressed than intercondylar notch (N). Thus in the PRP group after 6 months, cartilage thickness achieved greater improvements than after 12 months of follow-up, possibly due to cartilage loss continues to occur with time tracking.

**Cartilage thickness on MRI**

Reviewed cartilage thickness on MRI in the PRP group showed average thickness of before-after 6 months of treatment in the lateral condyle (N) increased by 0.13 ± 0.19 mm and intercondylar notch (G) up 0.09 ± 0.28 mm with statistical significance with p <0.05 while the medial condyle (T) increased by 0.07 ± 0.33 mm without statistical significance. The corresponding indicators dropped in Hyalgan group was 0.09 ± 0.23 mm respectively; 0.07 ± 0.13 mm and 0.18 ± 0.23 mm but medial condyle only had a statistically significant reduction (Table 3.29). This proved that PRP may work to increase the thickness of the cartilage in the positions but the largest rate of loss of cartilage in the medial condyle (due to the largest bearing area of ​​the knee joint).

At 12 months after treatment, cartilage thickness compared to the 6 months after treatment in positions tend to decrease in both 2 PRP and HA groups, but the change is not statistically significant (Table 3.29). When comparing the time after 12 months of treatment with before treatment, the thickness of the cartilage among injecting PRP group tend to increase compared with HA group have decreased but the difference was not statistically significant, which suggests PRP effect on the thickness of the cartilage better than HA but still unclear. Halpern’s study (2013) had 22 patients with OA showed that in 15 patients’knees reviewed by MRI after 1 year treatment: 12/15 (80%) demonstreated no significant worsening of osteoarthritis in their patellofemoral joint; 83,3% was no change in the apperance of OA with lateral femoral and tibial compartment involvement; 73,3% no change in medial one. There was 1 patient (6,7%) showed the improvement in medial femur-tibia compartment. The above results are the authors evaluated as positive given that the annual average 4-6% volume of cartilage loss in patients with degenerative disorder according to a longitudinal study tracking prolonged Raynauld (2004) .

***4.3.2. Safety***

***4.3.2.1. Complications, undesirable effects***

Among 84 pts (122 knees) completed the course of treatment and follow-up period of 1 week after 1 injection (total 3 injections), the group PRP injection observed 38.5% increased knee pain after injection 1; 33.8% and 0.9% increased joint pain after injection 2 and 3. This percentage is lower than injecting Hyalgan with the corresponding ratio in turn is 41.1 %; 35.1% and 1.4% after the injections, the difference was not statistically significant (Table 3.30). In most cases, pain increased slightly within first 1-2 day after injetion. Pain also reduced, solved and last in maximum 3 days (with or without using painkillers).

We consider synovitis and/or new joint effusion are side effect of the disease. By this definition, there are 16.9% of new joint effusion occurs in the treatment group following PRP 1st injection and respectively 15.4% and 13.8% after the 2nd and the 3rd. Hyalgan injection group this side effect is higher with 22.8%; 26.3% and 22.8% but the difference was not statistically significant between the two treatment groups (Table 3.30). In both groups were seen effusion mainly in small quantities and level of mild effusion (mainly detected by ultrasound) and usually resolves. There were no complications like haemorrhage in joint, septic arthritis, septic soft tisue… in our study.

***4.3.2.2. Withdrawn patients***

Each group, we had 7 patients (Total 14 pts, 16 knee joints) dropped out follow-up at different moments: 5 pts immediate after treatment completion (3 pts in PRP, 2 pts in HA group), 6 patients withdrawn after examination at 1month (3 pts in PRP, 3 pts in HA group), 3 pts quitted at 2 month examination (1 pt in PRP, 2 pts in HA group).

We recorded: no patients stopped therapy, 2 patients quit tracking due to increased pain (both treatment group HA); 4 patients (2 patients with 2 joints PRP group, 2 patients with 3 knee HA group) quit track because not palliative, patients taking NSAIDs; 8 patients (5 patients with knee PRP 5, 3 patients with 4 knee HA) may help but leave track for family reasons. Thus, it is possible that although data were still modest, but in treatment group PRP fewer side effects increasing pain compared to group HA.

***4.3.3. Satisfaction level***

We studied 70 patients (106 joints) completed 6-month follow-up period, 30 patients (44 knee) completed 12-month follow-up period. Considering the group completed its own follow-up period: 6 months with 8.6% PRP group unsatisfied 14.6% lower than the rate in the HA group, statistically significant with p <0.001; the corresponding figure at 12 months was 15.2% tracking PRP group was 63.7% lower than the HA group (Table 3.31). However, we classified the patients (in the joint) track give reason not better or increased pain in patients group (joint) are not satisfied with the treatment results, while the proportion dissatisfied with it PRP therapy is (5 + 2)/(58 + 2), with 11.7%; proportion dissatisfied with the HA treatment group (7 + 5)/(48 + 5), by 22.6%. Such ratios are not satisfied with the results of treatment of low PRP treatment group than in the treatment group had statistically significant HA. At the time the group completed 6 months follow-up after treatment of the percentage of very satisfied group was 56.9% PRP treatment is higher than 16.7% of the BP group, p <0.001; after 12 months of follow-up ratio is 42.4% of the PRP group versus 0% in the HA group with p <0.01 (Table 3.31).

**CONCLUSIONS**

By studying 84 patients (122 knee joints) of primary knee osteoarthritis in stages 2-3 from 11/2011 to 6/2015, divided into 2 groups: 45 patients (65 knee joints) received autologous platelet-rich plasma therapy and 39 patients (57 knee joints) treated with hyaluronic acid, we draw the following conclusions:

1. **The clinical and paraclinical characteristics of primary knee osteoarthritis:**

The patients in study had characteristics of knee osteoarrthritis:

* The common functional symptoms: pain when climbing stairs (100%), pain when walking (99.2%), mechanical type pain (97.5%), pain when standing (89.3%), breaking rusty joints (75.6%).
* The common physical symptoms: normal skin temperature (99.2%), crepitus (90.2%), wood shavings signs (51.6%).
* X-ray knee joint features: 92.6% had osteophyte, 86.9% have subchondral slerosis, 68.9% had a narrow joint space.
* Ultrasound features of knee joint: 98.4% joint had normal synovium, 82.0% had osteophyte, 20.5% with joint effusion.
* MRI features of knee joint: 99.1% had at least 1 effusion location, 98.2% had cartilage lesions, 97.3% had osteophyte, bone marrow edema 76.6%, 70.3% have meniscal injuries, only 1.8% had synovitis.
* TG-β1 concentration separated by ACP technique (Arthrex company) in platelet-rich plasma was 106.74 ± 148.6 ng/ml, was 13.8 ± 14.04 ng / ml in whole blood.

1. **Efficacy and safety of therapeutic platelet-rich plasma in the treatment of primary knee osteoarthritis stages 2-3.**

Compared with hyaluronic acid treatment group, patients treated autologous platelet-rich plasma showed the following advantages:

* 1. ***Efficacy***
* Reduce pain and improve function through VAS and WOMAC scale better with p <0.05, achieving the best performance at moment of 6 months after treatment (rates of improvement was 82.8% of VAS scale compared to 64.6% in the group in the glime injection) and remain effective after 12 months of follow-up (57.6% versus 18.2%).
* At stage 2 and younger age, the response to PRP treatment is better than stage 3 and older age.
* Improving on articular cartilage thickness assessed by ultrasound and magnetic resonance, with p <0.05.
  1. ***Safety, complications and undesirable effect of autologous PRP***

The PRP treatment showed the safety similar to the HA treatment: Increased pain (38.5%) and arthritis / knee effusion (16.9%) after the 1st injection of platelet-rich plasma compared with hyaluronic acid injection (41.1% and 22.8%), no statistically significant difference with p> 0.05. The symptoms were mild, short duration and usually resolves; no serious complications leading to abandon treatment.

* 1. ***Satisfaction level***

PRP treatment group had satisfaction levels of 56.9%, statistical significance higher compared with group HA tretment of 16.7% (p <0.05), while the level of unsatisfaction is 11, 7%, lower than in the HA group of 22.6% (p <0.05).

**RECOMMENDATIONS/ PROPOSALS**

With the proven efficiency and safety, autologous platelet-rich plasma therapy can be applied widely in the treatment of primary knee osteoarthritis stages 2-3. Need to conduct implementation for other stages (stage 1 and stage 4) of knee osteoarthritis, as well as extend follow-up period longer to assess comprehensively the effectiveness of therapy.