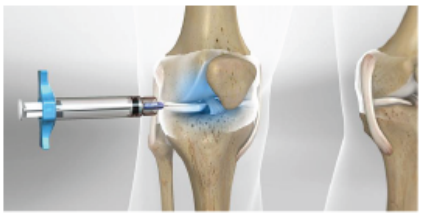
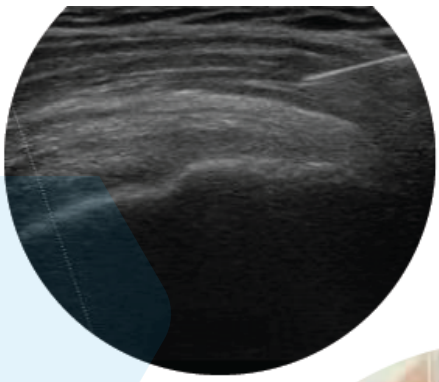
HỘI NGHỊ LIÊN CHI HỘI BỆNH TỰ MIỄN CƠ XƯƠNG KHỚP THÀNH PHỐ HỒ CHÍ MINH
03/2024

VAI TRÒ CỦA HUYẾT TƯƠNG GIÀU TIỂU CẦU TRONG ĐIỀU TRỊ THOÁI HÓA KHỚP

TS. BS. TRẦN ĐẶNG XUÂN TÙNG
Khoa Chấn Thương Chỉnh Hình
Đơn vị Tế Bào Gốc
Bệnh Viện Đa khoa Vạn Hạnh



Dàn bài



- Thoái hóa khớp gối
- Vai trò sinh học của PRP trong THK gối
- Vai trò lâm sàng của PRP trong THK gối
- Cập nhật Phác đồ điều trị và các đồng thuận lâm sàng
- Hướng áp dụng PRP trong THK gối

Chẩn đoán và phân độ THK gối

Knee: Clinical and Radiographic[6]

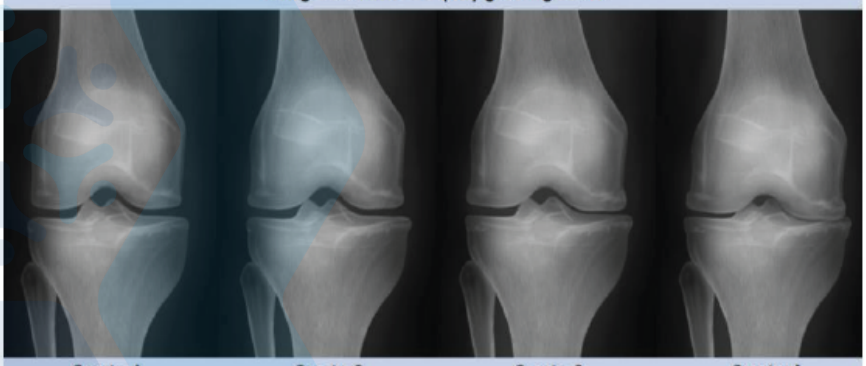
1. Knee pain for most days of prior month
2. Osteophytes at joint margins
3. Synovial fluid typical of osteoarthritis
4. Age ≥40 yr
5. Morning stiffness lasting ≤30 min
6. Crepitus with active joint motion

Chẩn đoán THK gối khi:

1 + 2 hoặc 1 + 3 + 5 hoặc 1 + 4 + 5 + 6

American College of Rheumatology Radiologic and Clinical Criteria for Osteoarthritis

Kellgren-Lawrence (KL) grading scale

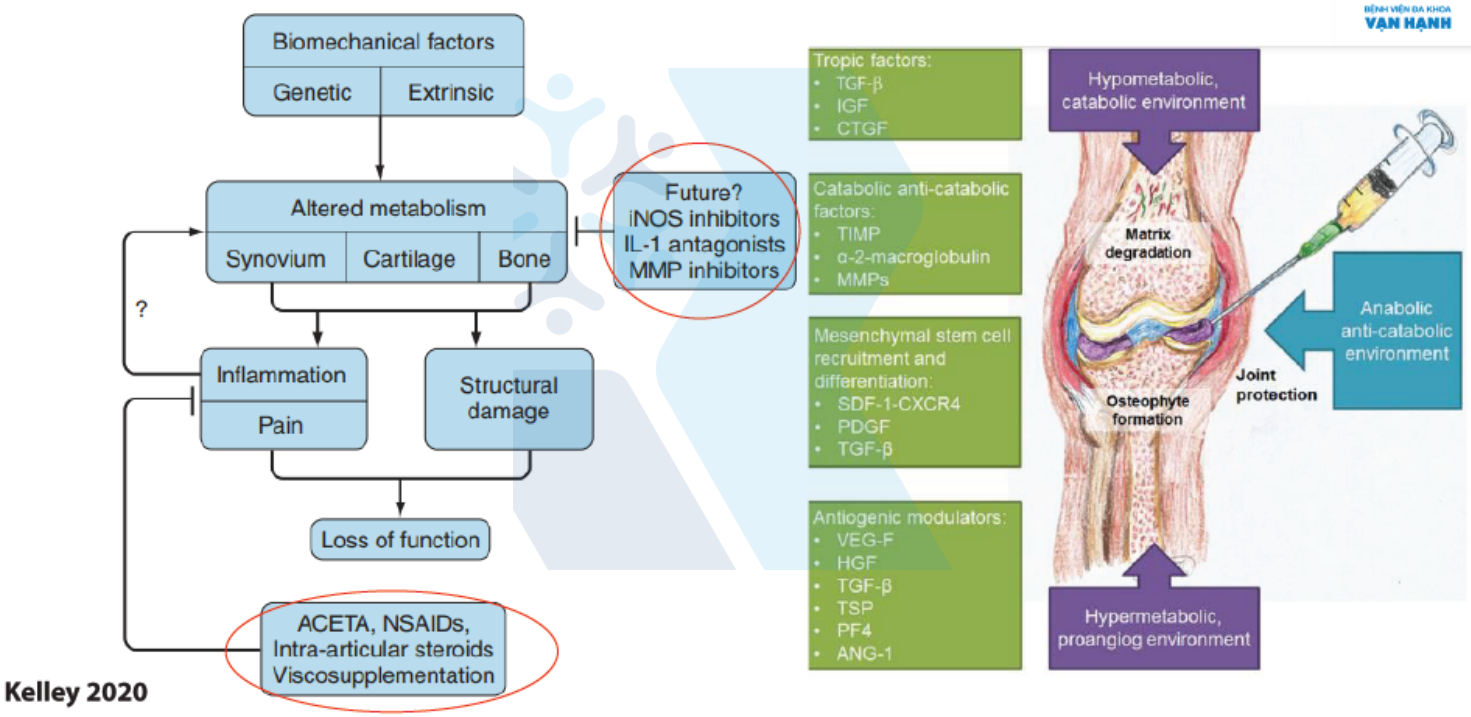


Grade 1 | Grade 2 | Grade 3 | Grade 4

CLASSIFICATION	Normal	Doubtful	Mild	Moderate	Severe
DESCRIPTION	No features of OA	Minute osteophyte: doubtful significance	Definite osteophyte: normal joint space	Moderate joint space reduction	Joint space greatly reduced: subchondral sclerosis

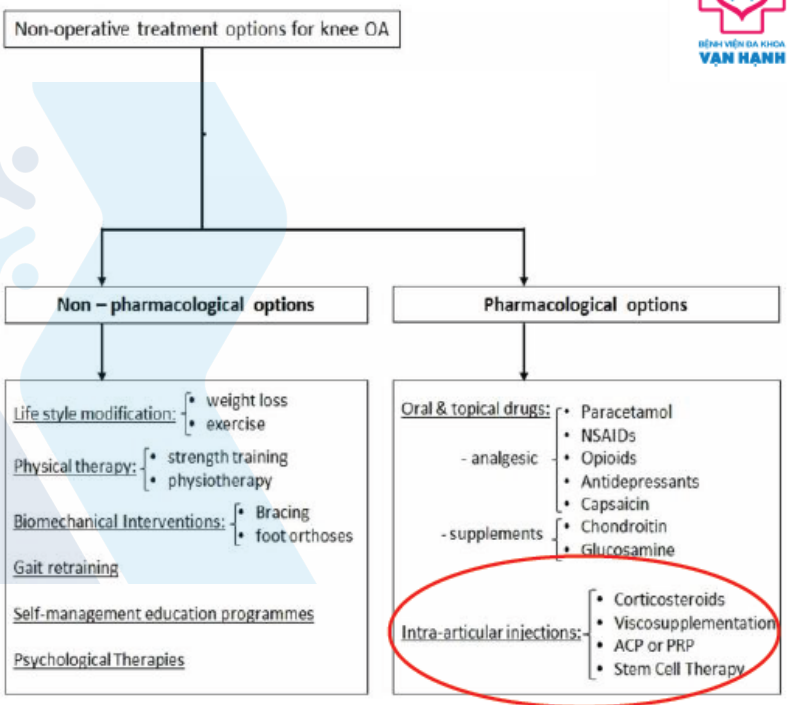
Source: http://www.adamondemand.com/clinical-management-of-osteoarthritis/

Cơ chế bệnh THK gối



Kelley 2020

Điều trị THK gối

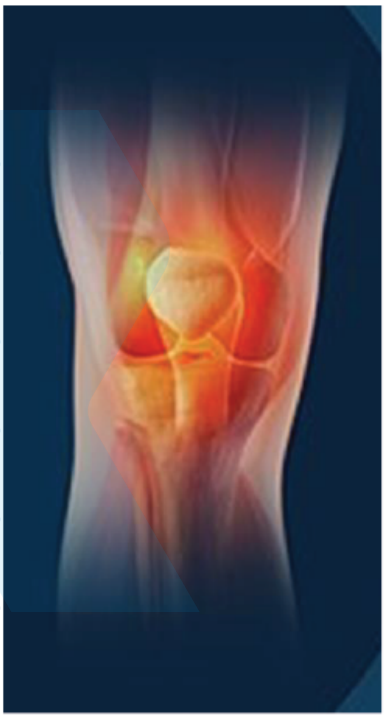


Parker DA, et al. JISAKOS 2018;3:274–281. doi:10.1136/jisakos-2016-000094.

O'Connell, B., Wragg, N. M., & Wilson, S. L. (2019). The use of PRP injections in the management of knee osteoarthritis. Cell and Tissue Research.

Osteoarthritis pain – where does it come from?

- Intra-articular
- Extra-articular
- Intraosseus
- Neuropathic
- Referred
- Some or all of the above



PRP là gì?

- PRP (Platelet-rich plasma): huyết tương giàu tiểu cầu (YT tăng trưởng, YT sinh học khác, một số tế bào khác).
- Trích từ máu toàn phần tự thân.

- Pure PRP
- LR-PRP
- LP-PRP
- Platelet Rich Fibrin

O'Connell, B., Wragg, N. M., & Wilson, S. L. (2019). *The use of PRP injections in the management of knee osteoarthritis. Cell and Tissue*

PRP cellular contaminants

- **Red blood cells (RBC):** heme toxicity, free radicals, delay healing
  - ➢ **PRP should be free of RBC!**
- **White blood cells (WBC):**

- Granulocytes (Neutrophils) (65%)
Acute inflammation, protease damages to surrounding healthy tissues. Delay healing. Not desired in non-infected tissues.
➢ **Neutrophils are not desired in PRP!**

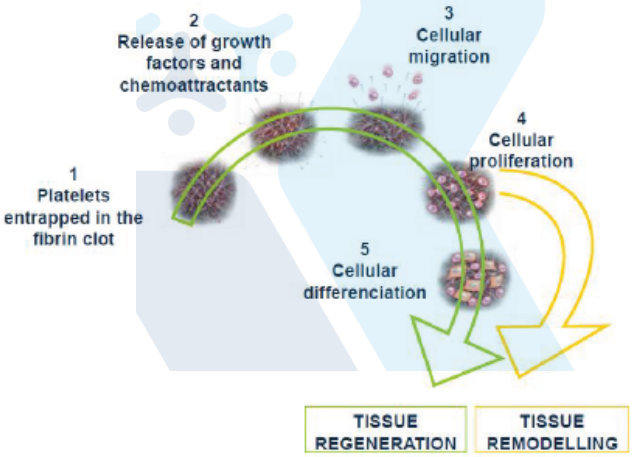
- Lymphocytes (30%) and Monocytes (5%): Support the healing process

Illustration source http://gemharrod.blogspot.ch/2010/05/describe-structure-of-red-blood-cell.html
http://en.wikipedia.org/wiki/White_blood_cell

PRP and tissue regeneration

regenlab

• **PRP** mimics the normal healing process that occurs when a tissue is wounded (blood clot)



Platelets

BỆNH VIỆN ĐA KHOA VẠN HẠNH

More than simple cell fragments !

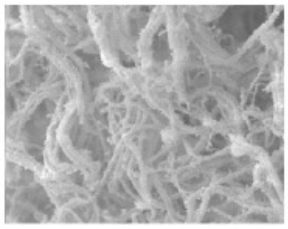
- **Alive and functional entities**
- Can survive **to extreme conditions**
- **Clotting mediators,**
- **Growth Factors (GF)**
- many **other molecules (>300)**
- GF released in a **orchestrated manner** in response to local signals
- Can synthesize new **GF** (stock of mRNA)

Plasma

BỆNH VIỆN ĐA KHOA VẠN HẠNH

- Tissue **hydration**
- **cell nutrients, vitamins, hormones, electrolytes** and growth factors **(IGF, HGF)**
- Contains proteins (albumins, globulins, clotting factors, **fibrinogen**)

Fibrinogen, converted in fibrin **scaffold** for new tissue synthesis



PRP and tissue regeneration

BỆNH VIỆN ĐA KHOA VẠN HẠNH

- **Platelets** give the instructions to the cells
- **Plasma** brings the elements to nourish the cells and for new tissue production

➢ **Both components** of PRP play a **crucial role !**

Name (manufacturer, country)	Approval	System	Circuit	Procedure	Activator	Composition PEF/WBC/RBC	Indications
Peak (Depuy, USA)	FDA	A	C	SS	-	8×/4–6× WBCs/ (1/3) RBCs	Mix with bone graft
PRGF-Endoret (BTI, Spain)	FDA; CE	M	C	SS	$CaCl_2$	2–3×	Oral surgery, dermatology, cosmetic, wound healing, ophthalmology, OA, orthopedics
Pure PRP II (Emcyte, USA)	FDA; CE	M	C	DS	-	6–16×/ 3–7× monocytes/no RBCs	Orthopedics, surgeries
Regenexx-SCP (Regenex, USA)	FDA	M	C	SS	-	20–40×/low WBCs/ low RBCs	Orthopedics, sports med., pain
RegenKit (RegenLab, Switzerland)	FDA; CE	M	SC	SS	-/Ca gluconate	1–2×/1.5×10^3 WBCs/no RBCs	Orthopedics, OA
Res-Q 60 PRP (ThermoGenesis, USA)	FDA	SA	C	SS	-	Equivalent to Pure PRP II	Mix with bone graft, cardiovascular
Selphyl (Cascade Medical, USA)	FDA; CE	M	SC	SS	$CaCl_2$	1–2×	Direct injection; Mix with bone grafts
SmartPReP2 (Harvest/Terumo, Japan)	FDA; CE	SA	SC	DS	-	4–8×/3–4× WBCs/1× RBCs	Orthopedics
TropoCells (Estar Medical, Israel)	FDA; CE	M	O	SS	-	4–5×/ no WBCs/no RBCs	Orthopedics, wound healing, dentistry, ophthalmology.

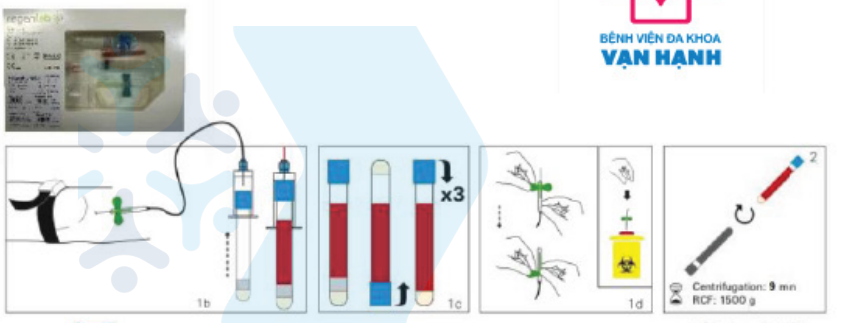
A, automatic; ACP, Autologous Conditioned Plasma; C, closed; CE, European Union CE mark; DS, double spin; F, filtration; FDA, United States Food and Drug Administration; GPS, Gravitational Platelet Separation System; M, manual; NR, not reported; O, open; OA, osteoarthritis; PEF, platelet enrichment factor [(platelets in PRP)/(platelets in whole blood)]; PRP, platelet-rich plasma; RBC, red blood cell; SA, semi-automatic; SC, semi-closed; SS, single spin; WBC, white blood cell.

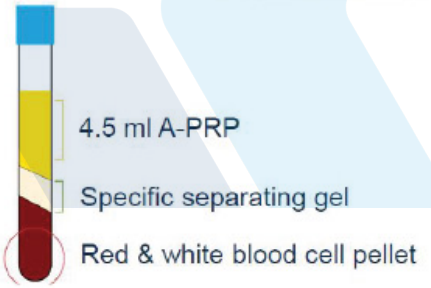
Gato-Calvo, L., et (2019). Platelet-rich plasma in osteoarthritis treatment: review of current evidence. Therapeutic Advances in Chronic Disease, 10, 204062231982556

Simple Procedure

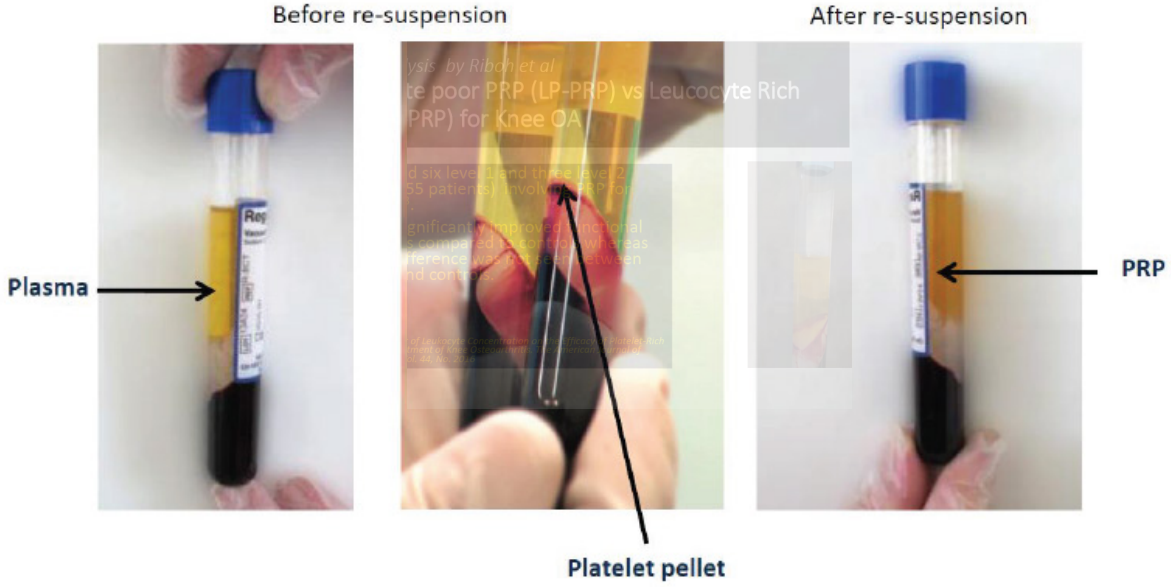
BỆNH VIỆN ĐA KHOA VẠN HẠNH

1- **8 ml** Blood draw
2- **9 min** centrifugation at **1500 x g**
3- PRP ready to use
All steps done in closed circuit





Platelet Re-suspension



Drawbacks of standard plasma devices

No physical separation -> operator dependant, require dexterity

Open manipulations -> infectious risks Work under laminar flow required in Spain for open system like BTI Endoret

When anticoagulant is manually added -> infectious and dosage error risks

ACD-A anticoagulant -> non physiological, acidic pH and hyperosmolar dextrose -> pain

When blood is taken with a syringe -> platelet activation, hemolysis

Either the larger platelets are not collected -> lower growth factor content

Or some of the buffy coat is collected -> highly contaminated PRP

PRP for OA Joints

- Similar for all synovial joints (e.g. Knee, Hip, Ankle)
- Goal:
  - Improve pain/function
  - "hold the line"
  - **Not a cure**
- **Intra-articular. Leucocyte Poor PRP 2 to 3 doses**
- **KIV combine with HA**
- **Extra-articular source of pain?**

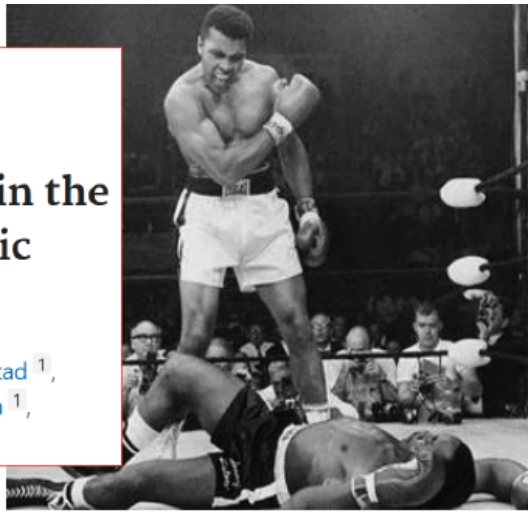
PRP injection for early/mid stage OA Knee... supported by

- Over 40 Meta-analysis – mostly favourable
- **GRIP Consensus (2020)**
- **ESSKA –Orbit Consensus (2022)**

Meta-Analysis > Am J Sports Med. 2022 Sep;50(11):3140-3148.
doi: 10.1177/03635465211029659. Epub 2021 Aug 17.

Relative Efficacy of Intra-articular Injections in the Treatment of Knee Osteoarthritis: A Systematic Review and Network Meta-analysis

Harsh Singh [1], Derrick M Knapik [1], Evan M Polce [1], Carlo K Eikani [1], Amanda H Bjornstad [1], Safa Gursoy [1], Allison K Perry [1], Jennifer C Westrick [1], Adam B Yanke [1], Nikhil N Verma [1], Brian J Cole [1], Jorge A Chahla [1]



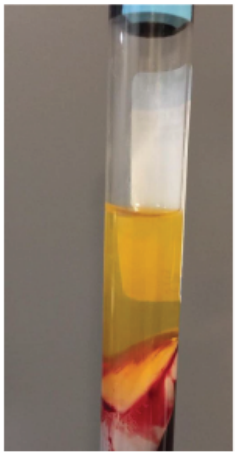
PRP yielded improved outcomes vs. PRGF, HA, CS, placebo at a minimum 6 month follow-up

Meta-Analysis by Riboh et al

Leucocyte poor PRP (LP-PRP) vs Leucocyte Rich PRP (LR-PRP) for Knee OA

- Compared six level 1 and three level 2 trials (1055 patients) involving PRP for Knee OA[3].
- LP-PRP significantly improved functional outcomes compared to controls whereas such a difference was not seen between LR-PRP and controls.

J Riboh et al. Effect of Leukocyte Concentration on the Efficacy of Platelet-Rich Plasma in the Treatment of Knee Osteoarthritis. The American Journal of Sports Medicine, Vol. 44, No. 2016

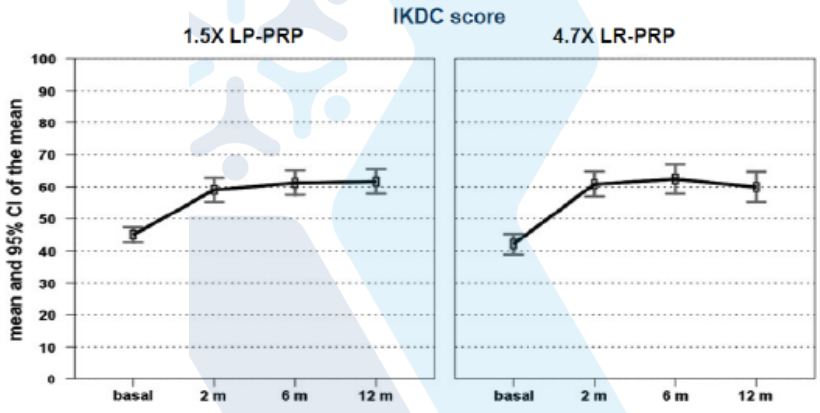


PRP as an IA Injection

- **Accurate intra-articular placement of needle IS crucial**
- Intra-synovial/fat or extra-capsular injections :
  - more painful.. "adverse reaction"
  - Platelets may activate in wrong location
- Intra-articular injections of the knee accurate in 71 to 93 % depending on approach (Jackson DW et al, 2002)
  - more difficult in the osteoarthritic knee, as low as 56% accuracy (Toda Y et al, 2008)
- **Lateral patellar and lateral suprapatellar** shown to be the most accurate for general use in the knee
- **Ultrasound guidance improves accuracy**

1.5 X LP-PRP vs 4.7 X LR-PRP

1.5X leucocyte poor PRP (LP-PRP) is as efficient as 4.7X leucocyte rich PRP (LR-PRP) for intra-articular injections in patients with knee osteoarthritis, **with less adverse reactions** (Filardo G. et al. 2012)

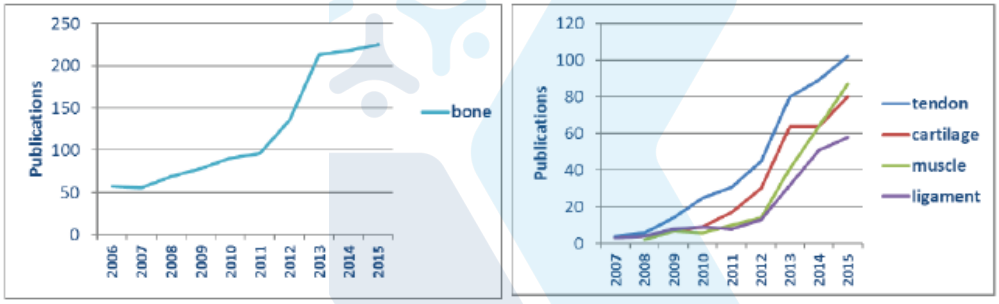


Both treatment groups presented a **statistically significant and similar improvement** in all the scores evaluated at all the follow-up times. However, **4.7X LR-PRP injections produced more pain and swelling reaction** with respect to that produced by 1.5X LP-PRP

Orthopedic use of PRP

BỆNH VIỆN ĐA KHOA VẠN HẠNH

Evolution of the interest for PRP in the scientific literature



Search in PubMed, publications in English up to end of 2015.
Key words: «Platelet rich» and «bone», «tendon », « ligament », « muscle » or « cartilage »

RCT's and Meta-analysis favours PRP+HA over PRP or HA alone

2018

Research Article

International Journal of Clinical Rheumatology

The new treatment approach in knee osteoarthritis: Efficacy of cellular matrix combination of platelet rich plasma with hyaluronic acid versus two different types of hyaluronic acid (HA)

Osteoarthritis pathogenesis is a complex process associated with decreased ability to regenerate cartilage mainly due to lack of physiological vascularization. One of the most commonly affected joints is the knee.

Purpose: The aim of this study was to compare the efficacy of intra-articular (IA) injections of platelet rich plasma (PRP) combined with hyaluronic acid (HA) prepared with the Cellular Matrix device versus IA injections with two different types of hyaluronic acid for treatment of knee osteoarthritis.

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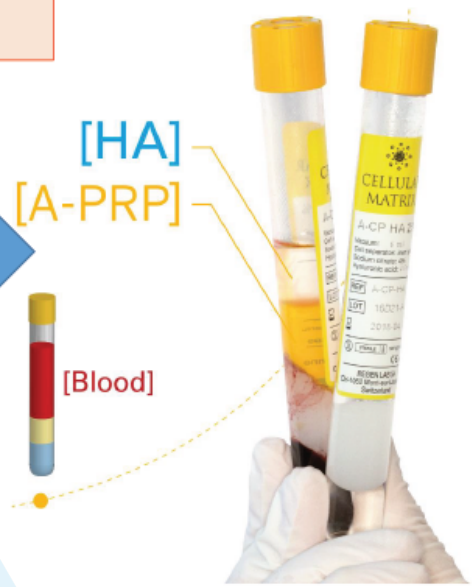


Aw et al, 2021, J Exp Ortho.: ***Meta-analysis: PRP+HA vs. PRP alone***
Karasavvidis et al 2020, Arthroscopy: ***Meta-analysis PRP+HA vs. HA alone***

Seleem, N.A., et al., **Intra-Articular Injections of Platelet-Rich Plasma Combined with Hyaluronic Acid Versus Hyaluronic Acid Alone in Treatment of Knee Osteoarthritis**. ejpmr, 201. 4(4): p. 608-615.

The study involved 100 symptomatic patients with knee cartilage degenerative lesions (Kellgren Lawrence scale grade 0 to III). 50 patients, who had previously unsatisfactory clinical response to HA alone, were treated with IA injections of autologous CM-PRP-HA combination that was repeated 3 times with 3-week interval, while the other 50 patients were treated with IA HA injections.

WOMAC Score (pain) 2 - 6 & 12 months

Pain	HA	CM -PRP -HA	CM -PRP -HA versus HA
Basal	Basal vs 2 mon t-value: 13.7 P < 0.0001	Basal vs 2 mon t-value: 16.8 P < 0.0001	Basal vs Basal t-value: 0.5 P = 0.6307
2 mon	Basal vs 6 mon t-value: 10.9 P < 0.0001	Basal vs 6 mon t-value: 14.5 P < 0.0001	2 mon vs 2 mon t-value: 16.5 P < 0.0001
6 mon	Basal vs 12 mon t-value: 5.4 P < 0.0001	Basal vs 12 mon t-value: 12.1 P < 0.0001	6 mon vs 6 mon t-value: 5.96 P < 0.0001
12 mon	2 mon vs12 mon t-value: 9.99 P < 0.0001	2 mon vs 12 mon t-value: 5.9 P < 0.0001	12 mon vs 12 mon t-value: 4.4 P < 0.0001

Both A-PRP and HA have been extensively used to improve lubrication, modulate inflammation and modify the joint catabolic micro-environment, aiming not only for reducing clinical symptoms, but also interfere with OA progression.

Renevier JL, Marc JF. **Etude Pilote d'un dispositif médical intra-articulaire innovant dans la prise en charge de la gonarthrose symptomatique fémoro-tibiale grade II-III radiologique après échec d'un AH**. Revue du Rhumatisme 2014;81:A202.

CELLULAR MATRIX

A French multicentre prospective study, with patients suffering from knee joint OA, shows that 3 injections of 2ml of A-PRP + 2ml of non-cross-linked HA (CellularMatrix) represent a new medical alternative to knee surgery after failure of HA alone.

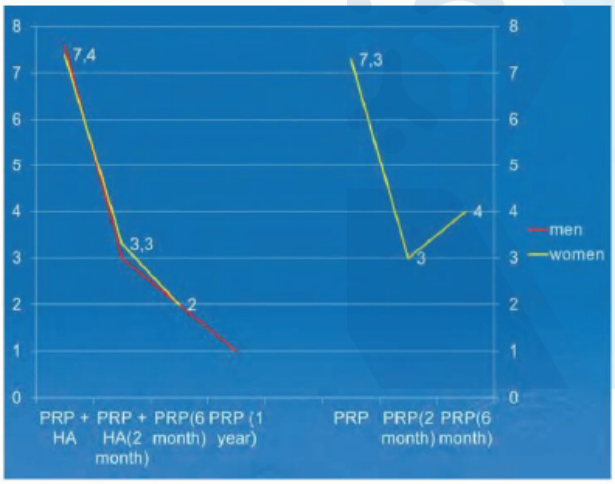
Number of patients: 71

- Average age: 63 (low of 40yrs and high of 84yrs)
- Gender: 37 males (52.1%), 34 females (47.9%)
- Average BMI: 26.83 (low of 20.32 and high of 39.06)
- Kellgren and Lawrence Grading Scale: grade II (46.5%) and grade III (53.5%)

Renevier JL, Marc JF. **Etude Pilote d'un dispositif médical intra-articulaire innovant dans la prise en charge de la gonarthrose symptomatique fémoro-tibiale grade II-III radiologique après échec d'un AH**. Revue du Rhumatisme 2014;81:A202.

CELLULAR MATRIX

- All patients were treated with 3 intra-articular injections of CellularMatrix given at day 0, 2 months and 6 months.

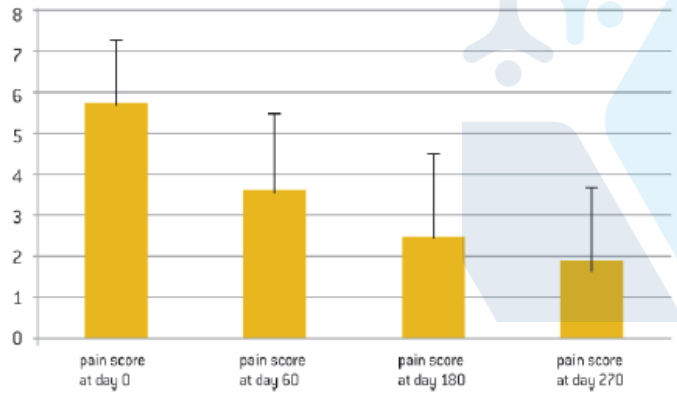


- CellularMatrix treatment was safe and effective: primary efficacy criteria showed a statistically significant decrease of the average WOMAC AI from 5.93 at baseline to 2.03 at 9 m follow-up.

Renevier JL, Marc JF. **Etude Pilote d'un dispositif médical intra-articulaire innovant dans la prise en charge de la gonarthrose symptomatique fémoro-tibiale grade II-III radiologique après échec d'un AH**. Revue du Rhumatisme 2014;81:A202.

CELLULAR MATRIX

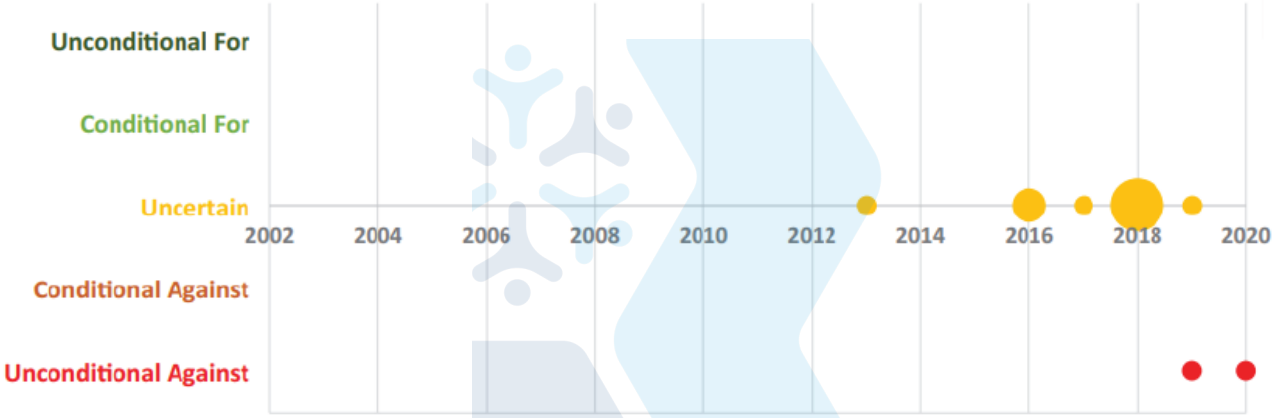
WOMAC A1 Score (pain) at Days 0, 60, 180 and 270



Results:

- 87.3% of patients were responders to treatment with Cellular Matrix based on the OMERACT-OARSI criteria.
- Significant decrease of WOMAC A1 score between day 0 and day 270.
- This study demonstrated that 3 injections CellularMatrix represent a new medical alternative to knee surgery in patients who do not respond to treatment with HA alone.

Các hướng dẫn điều trị PRP



- Các nc đưa vào guideline cần bằng chứng chất lượng cao.
- Các nc về PRP sử dụng các kit PRP không đồng nhất (thiếu ĐN và tiêu chuẩn PRP rõ ràng).
- Shared decision making: hiệu quả, tác dụng phụ, chi phí.

A Systematic Review of Current Clinical Practice Guidelines on Intra-articular Hyaluronic Acid, Corticosteroid, and Platelet-Rich Plasma Injection for Knee Osteoarthritis. The Orthopaedic Journal of Sports Medicine, 9(8), 23259671211030272

Đồng thuận chuyên gia tại Pháp 2020

Knee Surgery, Sports Traumatology, Arthroscopy (2021) 29:3195–3210
https://doi.org/10.1007/s00167-020-06102-5

KNEE

Intra-articular injections of platelet-rich plasma in symptomatic knee osteoarthritis: a consensus statement from French-speaking experts

Florent Eymard[1] · Paul Ornetti[2] · Jérémy Maillet[3] · Éric Noel[4] · Philippe Adam[5] · Virginie Legré-Boyer[6] · Thierry Boyer[7] · Fadoua Allali[8] · Vincent Gremeaux[9] · Jean-François Kaux[10] · Karine Louati[11] · Martin Lamontagne[12] · Fabrice Michel[13] · Pascal Richette[14] · Hervé Bard[15] on behalf of the GRIP (Groupe de Recherche sur les Injections de PRP, PRP Injection Research Group)

Received: 24 March 2020 / Accepted: 11 June 2020 / Published online: 24 June 2020

Chỉ định tiêm PRP khớp gối

Recommendations for action	Expert opinion	Median	Distribution			Level of evidence
			≤3	4-6	≥7	
Intra-articular injections of PRP are an effective symptomatic treatment for early to moderate knee osteoarthritis.	Appropriate with relative agreement	8	0	1	14	1A
Intra-articular injections of PRP may be useful in severe knee osteoarthritis (Kellgren and Lawrence grade IV)	Appropriate with relative agreement	7	0	5	10	2B
Age, weight and physical activity can influence the indication and outcome of intra-articular injections of PRP in knee osteoarthritis	Appropriate with relative agreement	8	0	1	14	4
The topographic pattern of the osteoarthritis influences the outcome of PRP treatment in knee osteoarthritis	Uncertain. Lack of consensus	7	0	4	11	4
PRP treatment should be offered as a second line of treatment, after failure of oral or non-pharmacological treatment for knee osteoarthritis	Appropriate with relative agreement	9	0	1	14	5

Khuyến cáo chung

Recommendations for action	Expert opinion	Median	Distribution			Level of evidence
			≤3	4-6	≥7	
PRP treatment should not be used during a flare-up of knee osteoarthritis	Appropriate with relative agreement	7	0	6	9	5
Intra-articular PRP knee injections should be performed under ultrasound or fluoroscopic guidance	Uncertain. Lack of consensus	8	1	1	13	5
Joint effusion should be systematically drained before PRP injection.	Appropriate with strong agreement	9	0	0	15	5
After injection of PRP, it is recommended to rest the knee for 48 hours	Uncertain. Lack of consensus	9	1	0	14	5
Symptomatic bilateral knee osteoarthritis can be treated at the same time	Uncertain. Lack of consensus	8	2	0	13	5

Khuyến cáo về đặc điểm của PRP

Recommendations for action	Expert opinion	Median	Distribution			Level of evidence
			≤3	4-6	≥7	
The characteristics of the injected PRP influence the result in knee osteoarthritis	Appropriate with relative agreement	8	0	2	13	4
Leucocyte-poor PRP should be preferred in knee osteoarthritis	Appropriate with relative agreement	8	0	1	14	5
The volume of a PRP injection in knee osteoarthritis should be 4 to 8 ml	Appropriate with strong agreement	8	0	0	15	5
The efficacy of PRP in knee osteoarthritis depends on the number of platelets injected	Appropriate with relative agreement	8	0	1	14	4
A PRP treatment sequence in knee osteoarthritis may include 1 to 3 injections	Appropriate with strong agreement	9	0	0	15	1A

Khuyến cáo về chống chỉ định và tương tác của PRP

Recommendations for action	Expert opinion	Median	Distribution			Level of evidence
			≤3	4-6	≥7	
PRP should not be mixed with an anesthetic or intra-articular corticosteroid	Appropriate with relative agreement	9	0	1	14	5
Anti-inflammatory treatment should be avoided in the days before and after PRP treatment	Appropriate with strong agreement	9	0	0	15	5
Treatment of knee osteoarthritis with PRP should be done away from an intra-articular injection of a corticosteroid	Appropriate with relative agreement	8	0	1	14	5
Recent neoplasia (malignant tumors, hematological diseases) may be a contraindication to intra-articular PRP injections	Appropriate with relative agreement	7	0	6	9	5
Antiplatelet aggregation therapy is not a contraindication to PRP injections but may alter its efficacy by preventing platelet activation.	Appropriate with strong agreement	9	0	0	15	5
The presence of radiographic chondrocalcinosis is not a contraindication to intra-articular injections of PRP	Appropriate with strong agreement	8	0	0	15	5

Quy trình tiêm PRP khớp gối

Trước tiêm PRP

- Không đáp ứng với điều trị ban đầu: đt không thuốc, tại chỗ, NSAIDs.
- K-L: độ 2,3 (4)
- Ngưng thuốc NSAIDs, corticoid trước tiêm 1 tuần.
- Bn không có flare up, hút dịch trước tiêm, không tiêm GC IA trước đó

Trong tiêm PRP

- Kit AAA (best)
- Lấy máu: 22 ml (2 gối), 11 ml (1 gối)
- Hệ thống quay li tâm, rút PRP lớp trên cùng (# 10 - 15 phút).
- Tiêm PRP cho mỗi gối dưới hướng dẫn siêu âm.
- Không trộn chung với thuốc gây tê hoặc GC

Sau tiêm PRP

- Sau tiêm: gấp/duỗi thụ động 10 lần, 10 phút nghỉ tại tư thế nằm ngửa. Chườm lạnh (±).
- Nghỉ ngơi gối 48g
- Ngưng thuốc NSAIDs, corticoid uống và IA sau tiêm 1 tuần.
- Lặp lại lần 2 sau ít nhất 2 tuần: 2 tuần, 3 tuần, 4 tuần.

Still pain after Intra-articular PRP?


CÁM ƠN SỰ THEO DÕI CỦA QUÝ ĐỒNG NGHIỆP