Clinical efficacy of Plasma Rich in Growth Factor (PRGF) intra-articular infiltrations.

Rationale and Administration Protocols.

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Good morning, first of all on behalf of EA and myself I'd like to thank Omer for inviting us to this specific yet interesting meeting
In this presentation, I would like to discuss 3 questions. What benefits can we get from using PRP in a degenerative process such as the chondropathy? Then, the characteristics of the PRP that we use. And finally, I’m going to show you our administration protocols including the intraosseous infiltrations.
Increasing the tolerable physiological load
Degradation
Extracellular matrix
Adaptation
Chondrocyte
p38 MAPK
NF-κβ
Mεtαbοliс

Mainly chondrocyte, MSCs, and CPCs
- Inhibition of NF-κβ as stress-induced response pathway.
- Suppressing IL-1β and TNFα induced cartilage degradation.

Antiinflammatory cell phenotype modulation
Joint’s pain reduction

Chondroprotective
PRGF
Cited2
SDF-1

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Anitua E, Sánchez A new biological approach to orthopaedic surgery and sports medicine 2011.
This is part of the scientific rationale behind the application of PRGF on Cartilage injuries.
We also performed experimental surgery on animals. We wanted to assess whether we could improve the cartilage regeneration, using other ways of PRP administration. We also wanted to verify the biosafety of the product. We saw that the treatment was safe without any complications or side-effects. We never observed any fibrosis nor synovitis.
Then we injected the joint with PRP stained with methylene blue. We saw that, when we infiltrate it in an intrarticular way, the PRP coagulates into the joint covering all the synovial membrane and stimulating in this way directly the synovioocytes, modulating joint homeostasis.
Heparan Sulfate Domains of Fibrin Matrix

Growth Factors
TGFB, FGFs, HGF, IGF, PDGF, VEGF, CTGF

Cytokines
IL-2, -3, -4, TNF, Interferon

Cell adhesion molecules
L-Selectin, PECAM-1, MAC-1

Chemokines
SDF-1, PF4

PRP and OA clinical studies

Ten years ago, our group published two important papers depicting the application of PRGF-assisted arthroscopic surgery of the knee. We were the first to report the successful application of PRGF-assisted regenerative techniques in the treatment of an articular cartilage avulsion in a 12-yr-old soccer player. With this biological engineering approach, new perspectives in knee surgery were opened (Sanchez et al 2003a). We reattached the fragment with resorbable pins as well as injecting PRP between the bone and cartilage with excellent outcome.

We also published in 2008 a retrospective cohort study comparing the intra-articular injections of hyaluronic acid with administration of an autologous preparation rich in growth factors for the treatment of knee OA.
In 2012 we carried out a multi-center randomized clinical trial, comparing PRGF® Endoret® that is a pure PRP with Hyaluronic Acid. We performed 3 intra-articular infiltrations on a weekly basis.
Randomized Clinical Trial: Level I

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

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Later other studies of level I have been published with encouraging results.
PRP and degenerative joint pathology

✓ Why the use of Growth Factors in joint pathologies
✓ Which PRP to use
✓ How to use it

The next question is which system to use: Which are the characteristics of the ideal PRP for treatment of cartilage degeneration?
Plasma Rich In Growth Factors

*Which system to use?*

*Platelet-Rich plasma, PRPs?, Platelet concentrate?, platelet gel?, PCCs, AGF, PG, PRF, ACP, PRGF....*

*Are we talking about the same biological product??*

*WE CANNOT TAKE ORANGES FOR APPLES IN THE FIELD OF PRPs*

There are more than 50 different systems on the market with different appearance, some of them red or yellow or orange. All of them under the umbrella of PRP, but we should ask if we are talking about only one product, in our opinion the PRPs are different products.
Plasma Rich In Growth Factors (PRGF)

- We DON´T prepare platelet concentrates but platelet-enriched plasma.
- We DON´T include leukocytes in our preparation.
- We DON´T use bovine thrombine to coagulate.

We propose a PRP that does not concentrate a lot of platelets. And it has NOT to contain leukocytes.
Blood  PRGF-ENDORET  L-PRP


Appearances may sometimes be very telling, but only when human eyes can receive the support of technology (Electron microscopy).
Finally, we move to the most important part, in my opinion, of the subject. How should we administer a PRP? Which are the best application protocols?
As we could see in the sheep model we attempt to get the same result by injecting the PRP directly where the MSC are. We treat osteochondral lesions by completely debrading the pathological tissue until we obtain a cancellous bone with a good aspect. We can do microfractures in the lesion. We then infiltrate liquid PRP into the bone. We use a specific instrument for this infiltration. We then infiltrate weekly for 3 weeks with intra-articular injection with 8 cc of PRP.
Sometimes we have to resort to osteochondral grafts in cases of big lesions such as in this case. This is a patient operated on some years ago of an osteochondral lesion performed an osteosynthesis with screws. Later, the patient presented a relapse of this osteochondral lesion as you can see here.
We debrided all the pathological tissue obtaining this bleeding bone. We infiltrated intraosseous liquid plasma and insert a fibrin clot in the defect.
Next, we carved an osteochondral graft from a fresh frozen allograft and placed it into the lesion site. We infiltrated liquid PRGF into the interface between the graft and the condyle, and this is the aspect following surgery.
At 6 weeks, we did a CT scan and you can see the osteochondral allograft incorporation in the medial condyle only 6 weeks later.
we performed an arthro CT scan 16 months later to evaluate the thickness of the cartil...
We use the plasma also in a chondroprotective way. This is the case of a 51 year old woman who, following a fall, suffered a complex fracture of the tibia.
a multifragment fracture of both tibia plateaus with a very poor prognosis and high risk of osteoarthritis
We operated on this patient on July 22, 2008. We performed an osteosynthesis with 2 plates and placed a fresh, frozen bone allograft with PRP leukocytes free. This is the X ray control immediately after surgery.
PRP and osteochondral lesions

This is the x-ray control, 6 weeks later, you can see the fast incorporation of the graft and the excellent bone callus.
PRP and osteochondral lesions

And here you can see her knee 6 weeks after surgery
Since then we have to infiltrate 3 intraarticular injections of PRP every year in order to prevent or slow the osteoarthritis. Here you can see the X ray 6 years later, after removing the plates.
and this is the appearance of her knee with this range of motion and good alignment of the axis. Actually, 6 years later, she continues to climb mountains and ski
Hypothesis for the use of PRP in the treatment of OA

**PRP infiltration in subchondral bone plus into the joint**

We thought that the PRP intraosseus administration could be useful in the treatment of osteoarthritis. The infiltration into the subchondral bone could stimulate the proliferation of MSC and the synthesis of different proteins. On the other hand, the intrarticular infiltration increases the synthesis of hyaluronic acid and other growth factors. We also know the anti-inflammatory effect of the PRP.

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In this slide you can see how after we debraded the pathological tissue, we infiltrated the PRP percutaneously from the medial side of the medial condyle. You can see, once I have aspirated the saline, how the PRP gets to the joint and coagulates in the lesion. As you can see we injected it with a special tool used for the bone biopsies. It might have a mechanical effect as well as a biological effect. We are investigating if the injection in the subchondral bone increases the number of cells in the joint.
IntraOsseus infiltration

1. Mark infiltration sites
2. Prepare surgical site
3. Local anaesthesia
4. Drain off
5. IntraArticular infiltration
   - Positioning the trocar inside the tibia
6. IntraOsseus Infiltration
   - Positioning trocar inside femoral condyle
7. We infiltrate under local anesthesia and sedation:
   - First of all, we drain out the joint effusion and infiltrate 8 cc in an intraarticular way
   - Then, we infiltrate 4 cc of PRP into the tibial plateau under fluoroscopy control
   - Finally we infiltrate 4 cc into the condyle
   - Then, we make two more weekly intrarticular injections of 8 cc of PRP
PRP intraosseus indications:

- Osteoarthritis III or IV grade in young patient or excluded for surgery

- Necrosis of the condyle or tibia plateau

- Osteochondral lesions

Our protocol intraosseus infiltration is especially indicated for:
Osteoarthritis III or IV grade in young patient or excluded for surgery. Also we infiltrate the PRP into the bone in cases of necrosis of the condyle or tibial plateau, as well as in the during surgical treatment of osteochondral lesions.
Patients will be diagnosed of osteoarthritis with a physical examination and imaging techniques, scales such as Ahlbäck or Kellgren. Depending on an osteoarthritis grade, different treatments will be applied:

If the patient presents Ahlbäck grade I or II we propose a classic treatment or intraarticular infiltrations of PRP.

If it is grade III or IV, we apply one intraosseus infiltration and two more intraarticular infiltrations.

If grade V, the patient undergoes a total knee arthroplasty.
A Brief Discussion

- There is still a big confusion with the PRP terminology
- The existing PRPs are different (quality & quantity)
- PRP is not a magic bullet

PRGF acts as a biological system where GFs and other proteins are members of a molecular network

*There is still a big confusion with the PRP terminology*

*PRP is not a magic bullet or silver bullet*
It is impossible to know the future. We can only dream.....and work
We are currently conducting a clinical trial of PRP intraosseus infiltration in patients with osteoarthritis grade 3 and 4 according to Ahlbäck scale. We use as a primary variable the clinical improvement of pain with KOOS scale. Three injections will be applied on a weekly basis. The first infiltration is a combination of intraosseus and intraarticular injection; the next two infiltrations will be intraarticular. Two revisions at 2 and 6 months will be performed.