Cold laser, hyaluronic acid, platelet-rich plasma: save the best for last in treating early phases of osteoarthritis

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Optoelectronic devices and techniques are widely, and deeply, involved in natural sciences research, with high achievements in biology, biochemistry, biophysics, medicine, and healthcare. This work deals with particular aspects of optoelectronics and optics as means of healthcare in a particular rheumatic disease - knee osteoarthritis. In the early stages, noninvasive medical aids, e.g., cold laser (low level laser) therapy, drug treatment, and synthetic (hyaluronic acid), or biological (platelet-rich-plasma) intra-articular substances can be used for pain relief. Visible light (650 nm, red) from a 35mW power laser has been used to test the light effect on *ex vivo* damaged pig cartilage samples as such, and on similar ones, which were injected with hyaluronic acid. Samples of both categories had been first injected with silver nanoparticles to enable image enhancement through a confocal microscope, aimed to evidence changes in the morphology of the structure. The light-plasmon interaction is known for its amplification effect. In this work, it brings a wave of novelty in diagnosis, and monitoring, through microscopy, viewing the combination with hyaluronic acid. Also, a comparative study, ran for evaluation from both a functional, and a symptomatic perspective of hyaluronic acid versus platelet-rich plasma administration in human patients with early-stage osteoarthritis, shows that the latter would provide a long-term solution. Cold laser therapy replaces any anti-inflammatory aid.

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1. Introduction

The huge amount of knowledge acquired through exploitation of light-matter interaction has led to the actual progress in diagnosis, monitoring, and cure of painful conditions in living beings, with humans on top. Animal research has strongly supported the discoveries, bearing in mind that comparative medicine is playing an outstanding role in the development of surgery, health care in general, and drug delivery, to cite just a few [1]. Many terrestrial mammals share musculoskeletal impairments with humans, and that explains the enormous amount of literature published on newly evolved techniques for diagnosis and treatment, especially those less, or not at all, invasive [2]. Optoelectronics, with its neighboring fields of advanced materials, nanostructures, plasmonics etc., opens ways to improving quality of life, along with classical treatments. Knee osteoarthritis (OA) is affecting more and more individuals, both humans and animals. Patients are expecting wonder aids to relieve their pain, and enhance their mobility, in order to improve their quality of life. Doctors' options for treatment depend on the stage of OA, predisposing gene, the age of the patient, various comorbidities, the clinical, and radiological findings. One of the often-used classification for OA is the Kellgren- Lawrence system, based on changes observed in X-ray images, and is branched in five grades.

If discovered in early stages, OA can benefit from non-surgical treatments, like anti-inflammatory pills, other painkillers, or physical therapy, including cold laser therapy (CLT), also known as low level laser therapy, low level light therapy, (LLLT) or photo-biomodulation therapy (PBMT) [3-6]. CLT consists in irradiation of a particular body zone with a low power laser, or a system of laser diodes, connected with fibre optics. The power ranges from 1 to 500 mW, and the usual wavelengths belong to the visible (VIS) - 600 to 650 nm, and near infrared (NIR)- 800 to 1000 nm, regions of the electromagnetic spectrum. CLT can be applied to reduce inflammation and support nerve, and tissue, regeneration, including cartilage in OA, and thus relieving pain. In this work we show that besides treatment, CL combined with surface plasmons from silver nanoparticles (AgNPs) can provide a means of diagnostics through confocal microscopy. This is one element of novelty, which we draw to the scientific healthcare attention. The present study on CL-Ag NPs plasmonics has run on *ex vivo* samples. On a future plan, gold NPs (AuNPs) will replace the AgNPs ones, and by then the NPs will be injected in the damaged tissue *in vivo*. That is aimed to co-work with intra-articular injections and CLT.

For early stages of OA, the intra-articular injections are intensely used to date. They act locally, making it safer than the anti-inflammatory pills. One option of intra-articular injection is the platelet-rich plasma (PRP) [7].

The definition of PRP changed in time and now the PRP must contain over 1,000,000 thrombocytes per mL of serum or five times more than the blood level of thrombocytes. Both *in vivo* and *in vitro*, PRP prove to have multiple capacities in reducing the inflammation, enhancing regeneration, and repair of the cartilage [8, 9]. The platelets have alpha granules that contain vascular endothelial growth factor (VEGF), transforming growth factor-b (TGF-b) and platelet derived growth factor (PDGF). PRP decreases the catabolic process and encourages the healthy neighbouring cells in producing more growth factors. All of these will lead to the healing of the chondral defect with the fibrocartilaginous tissue with a high level of collagen type 2 [10-12]. The optimal stage of osteoarthritis that can benefit from PRP and the right number of PRP administrations are still debatable. Several meta-analysis and systematic reviews regarding PRP benefits in OA had controversial results [13-15], because the real stage of the disease had been not properly assessed initially, and hence - the number of intra-articular injections, their profoundness, and the pre-treatment protocol for patients, were not perfectly matched.

Hyaluronic acid (HA) injections are an option in the nonoperative treatment of OA. They are not a new treatment. It is used since the 1980s, with good results, all over the world [16]. European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) recommends injections with HA as second-line treatment in patients presenting symptomatic OA [17]. The properties of the endogenous HA in the joint are changing due to the OA, affecting the mechanic viscoelastic properties of the synovial fluid. By injecting HA, we aim to reduce the pain and the inflammatory process through restoring the viscoelasticity and the mechanical properties [18]. Different types of HA have been developed, in different concentrations, volume, method of producing, single dose or multidose, etc.

2. Experimental

2.1. Cold laser therapy

We attempted experiments with CL on *ex vivo* pig hind knee cartilage samples (obtained from 2 pigs sacrificed for Christmas by their owner), injected with AgNPs (Sigma-Aldrich, size 20 nm). Four of them were unprepared, and four-injected with hyaluronic acid [19]. The latter ones were aimed to enhance the photo-modulation effect, i.e., the chemical change following light absorption in HA. Optoelectronic sensors for healthcare in orthopaedics have been successfully demonstrated in body alignment, in 3 cases [20]. Our present work signals a new way of monitoring in orthopaedics.

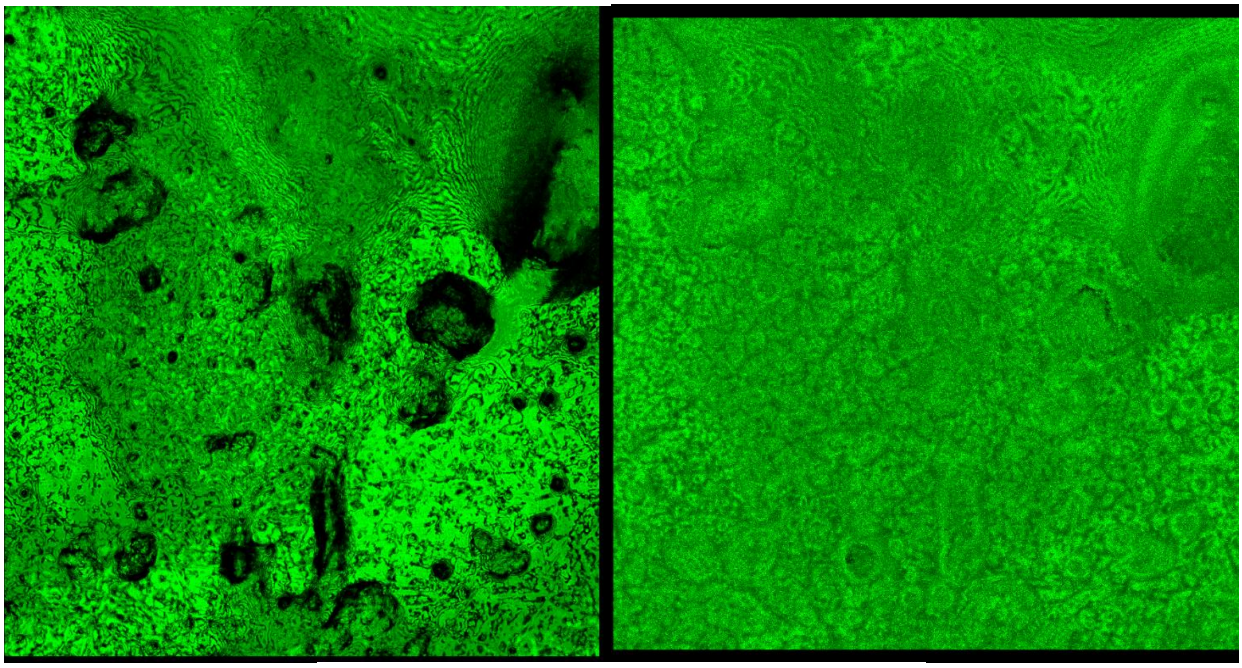
A therapy laser DTL (device for therapy laser, DTL as marked on the front of the instrument Fig. 1, Apel Laser S.R.L., Romania) was employed to irradiate the samples.

Fig. 1. The DTL instrument used to irradiate the ex vivo samples (colour online)

The instrument consists of a control module and 3 fibre optics heads: SL7-650, 7 fibres, wavelength 650 nm, 5 mW each, 35 mW in total; SL1-650, 1 fibre, 650nm, 25 mW; and SL1-808, 1 fibre, 808 nm (IR), 250 mW. The frequency can be adjusted between 1Hz and 10 kHz, in agreement with the particularities of the treatment. In the Fig. 1 there are shown the SL-7 -650, and SL1-650. They can be used either separately, or simultaneously, on different zones of the body.

For the purpose of this work, we used the 7-fibre head at 650 nm (Fig. 1), at a total power of 35mW, and 30cm above the sample, where the beams of the 7 fibres are focused.

Following CL irradiation, the cartilage samples were examined at the confocal microscope (Axio-observer Z1, at PRATIM, Federation Sciences Chimiques Marseille). In the Fig. 2 are shown two examples, one unprepared (a), and one injected with HA (b). Both samples are expected to get a better reorganisation of the collagen matrix after CL treatment. The confocal microscope produces a point source of light and rejects out-of-focus light, thus enabling a high resolution when getting image in the tissue depth (Z-axis). That provides an optical sectioning of the sample (Z-stack) and further permits the 3D reconstruction of the sample. Each of the samples investigated here had 25 optical slices. In the figure below are displayed Z=14 (optical slice) for both samples.



(a) *(b)*

Fig. 2. Confocal microscopy images of ex vivo cartilage samples with injected Ag NPs, following CL irradiation: (a) unprepared; (b) injected with HA (colour online)

2.2. Platelet-rich-plasma and hyaluronic acid

We performed an observational study evaluating the patients who received either PRP, or HA, after being diagnosed with mild OA, looking for a solution for short, or long, term in improving the symptomatology and functionality of the knee. The study involved 32 Romanian patients with symptomatic mild OA. All of them were classified based on plain X-rays of the knees, using the Kellgren and Lawrence system for classification of OA. We considered Grades 1 and 2 as mild OA. Grade 1 is described as doubtful narrowing of joint space, and possible osteophytic lipping [21]. Grade 2 is characterised by definite osteophytes and possible narrowing of the joint space [21]. The patients underwent a three-stage evaluation: initially, at six months, and at one year, using the Lysholm score.

The Lysholm Knee Scale is an 8-item questionnaire, initially designed to evaluate outcomes after ligament reconstruction. However, it is now commonly used to assess knee chondral damage and other knee-related conditions [22].

We excluded the patients that had previous surgical interventions of the knee, or had other knee associated injuries including ligaments, menisci or bone defects. Patients were treated randomly, either with one injection of HA, or 3 doses of PRP injected every 2 weeks. The 2 ml pre-filled syringe of viscoelastic solution (HyalOne, FIDIA Farmaceutici S.P.A. Italy) contains 2% hyaluronic acid and the exact composition is: 40mg of sodium hyaluronate (from bacterial fermentation) and sodium chloride, disodium phosphate, sodium dihydrogen phosphate, water, and 10 mg mannitol. For PRP we used a PRP kit to isolate platelets and growth factors within a plasma layer separated from the red and white blood cells in the blood. A maximum of 16 cm^3 (cc) of blood is drawn from a peripheric vein. The blood was spun at a rate of 1500 rpm for 5 minutes (Hettich Rotofix 32 A, USA). Once the centrifugation was complete, the double syringe was removed from the socket, taking care not to tip or agitate the separated layers. The yellow plasma layer was then removed and injected in the knee. The patients who received PRP were informed to take not anti-inflammatory pills 5 days before infiltration, and one week after.

3. Results

First of all we utilized Shapiro-Wilk test to assess whether the data follows a normal distribution. The "Sig." (p-value) is crucial for interpretation. In general, the PRP group follows a normal distribution for all analyzed variables. The HA group shows deviations from normality at 6 months ($p = 0.048$) and 1 year ($p = 0.024$) (Table 1). Both groups have a similar number of participants, ensuring a balanced comparative analysis**.** The mean age and median are slightly higher in the HA group, but the differences are not significant (Fig. 3, and Table 2). The PRP group shows a greater age dispersion (higher variability).

Table 1. Shapiro-Wilk test analysis of the variables

Tests of Normality				
	Treatment	Shapiro-Wilk		
		Statistic	df	Sig.
	PRP	.970	17	.810
	HA	.965	15	.784
Lysholm initial	PRP	.950	17	.452
	HA	.904	15	.109
Lysholm 6m	PRP	.949	17	.440
	HA	.880	15	.048
Lyshom 1y	PRP	.931	17	.227
	HA	.860	15	.024

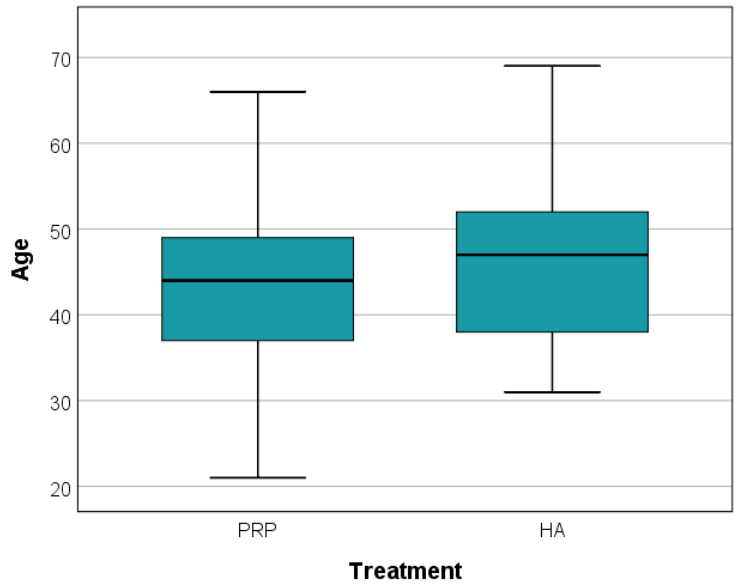


Fig. 3. Age dispersion in HA and PRP groups. Age is expressed in years (colour online)

Table 2. Age statistics per group

		Treatment	
		PRP	HA
N	Valid	17	15
	Missing	0	0
Mean		43.29	45.93
Median		44.00	47.00
Std. Deviation		12.549	10.187
Minimum		21	31
Maximum		66	69

The groups are almost balanced in terms of the number of participants (small difference between PRP and HA). The distribution is approximately equal (PRP: 53.1%, HA: 46.9%) (Table 3), meaning there is no major imbalance between the two treatments. This is ideal for comparing treatment effectiveness, as it reduces the risk that observed differences are due to unequal group allocation rather than the treatments themselves.

Table 3. Participants distribution per group

		Frequency	Percent
Valid	PRP	17	53.1
	HA	15	46.9
	Total	32	100.0

PRP treatment had the Lysholm score improved significantly after 6 months ($p < 0.001$) and continued to improve at 1 year ($p < 0.001$). The improvement between 6 months and 1 year is also significant, but of smaller magnitude (-3.235). HA treatment had the Lysholm score improved significantly after 6 months ($p < 0.001$) and remained stable at 1 year ($p < 0.001$) (Table 4 and Fig. 4), but no significant improvement was observed between 6 months and 1 year ($p = 0.353$) (Table 5). Both treatments (PRP and HA) lead to a significant improvement in the Lysholm score at 6 months and 1 year, compared to baseline. PRP continues to show further improvement between 6 months and 1 year, while HA does not provide significant additional benefits at 1 year compared with 6 months. PRP may have a more sustained long-term effect, whereas HA reaches its peak effectiveness somewhere between 6 months and 1 year.

Table 4. Lysholm mean score and standard deviation

Paired Samples Statistics					
Treatment			Mean	N	Std. Deviation
PRP	Pair 1	Lysholm initial	71.94	17	5.595
		Lysholm 6m	81.53	17	4.823
	Pair 2	Lysholm initial	71.94	17	5.595
		Lyshom 1y	84.76	17	5.426
	Pair 3	Lysholm 6m	81.53	17	4.823
		Lyshom 1y	84.76	17	5.426
HA	Pair 1	Lysholm initial	73.07	15	5.958
		Lysholm 6m	81.73	15	5.637
	Pair 2	Lysholm initial	73.07	15	5.958
		Lyshom 1y	80.60	15	6.843
	Pair 3	Lysholm 6m	81.73	15	5.637
		Lyshom 1y	80.60	15	6.843

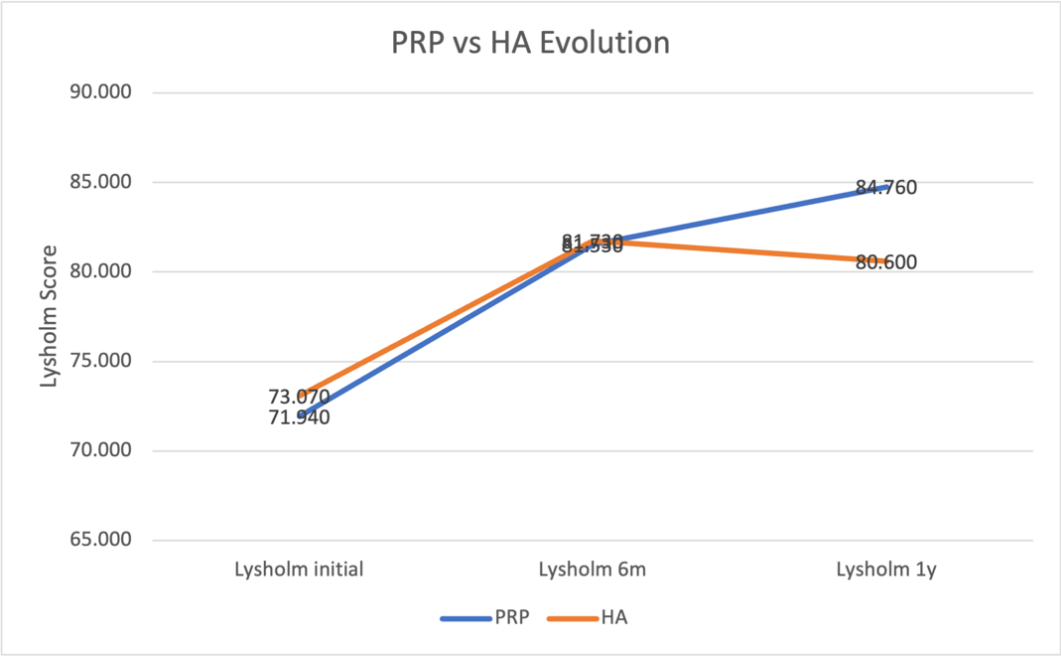


Fig. 4. Lysholm score evolution (colour online)

Table 5. Lysholm score statistical analyses

Paired Samples Test							
Treatment			Paired Differences		t	df	Sig. (2-tailed)
			Mean	Std. Deviation			
PRP	Pair 1	Lysholm initial - Lysholm 6m	-9.588	5.455	-7.247	16	.000
	Pair 2	Lysholm initial - Lyshom 1y	-12.824	5.468	-9.669	16	.000
	Pair 3	Lysholm 6m - Lyshom 1y	-3.235	3.800	-3.510	16	.003
HA	Pair 1	Lysholm initial - Lysholm 6m	-8.667	4.220	-7.954	14	.000
	Pair 2	Lysholm initial - Lyshom 1y	-7.533	4.984	-5.854	14	.000
	Pair 3	Lysholm 6m - Lyshom 1y	1.133	4.565	.962	14	.353

Patients treated with PRP Kellgren and Lawrence grade 2 showed greater improvement, and at 6 months, the difference was close to statistical significance (p = 0.079). For the HA Group, the Kellgren and Lawrence grade did not significantly impact the improvement in Lysholm score (Tables 6, 7).

Table 6. Kellgren-Lawrence grade and Lysholm evolution

Group Statistics					
Treatment		Outerbridge grade	N	Mean	Std. Deviation
PRP	Result improvement (Lysholm score) 6m	1	5	6.00	5.657
		2	12	11.08	4.833
	Result improvement (Lysholm score) 1y	1	5	9.60	6.387
		2	12	14.17	4.687
HA	Result improvement (Lysholm score) 6m	1	5	8.60	5.814
		2	10	8.70	3.561
	Result improvement (Lysholm score) 1y	1	5	9.40	5.983
		2	10	6.60	4.452

Table 7. Kellgren-Lawrence stage and Lysholm score statistical analysis

Independent Samples Test					
Treatment		t-test for Equality of Means			
		t	df	Sig. (2-tailed)	Mean Difference
PRP	Result improvement (Lysholm score) 6m	-1.885	15	.079	-5.083
	Result improvement (Lysholm score) 1y	-1.651	15	.119	-4.567
HA	Result improvement (Lysholm score) 6m	-.042	13	.967	-.100
	Result improvement (Lysholm score) 1y	1.028	13	.323	2.800

Statistical significance (p > 0.05) is absent for both treatments regarding the correlation between age and outcome. This indicates that age does not significantly influence the improvement in the Lysholm score in either group.

The CL irradiation of the *ex vivo* samples (Fig. 2 b) shows that HA injection followed by CLT leads to evenness of the cartilage structure, i.e., a concurrent effect of HA and restructuring of the collagen matrix through light absorption.

4. Discussion

The treatment of OA is multidisciplinary, taking multiple factors into account, and being personalised

according to the patient's specific characteristics. Without patient's compliance, the treatment is at risk of failure**.** The primary symptom of OA is pain**,** often accompanied by morning stiffness that is typically brief, worsens with movement, and improves with rest [23]. Additionally, joint damage leads to progressive functional limitations**.** In early stages of OA the treatment is limited to pain-relieving and restoring functionality of the joint. CLT would provide a good replacement of chemical pain killers, associated with intra-articular injections, which are commonly used for OA, allowing direct delivery of therapeutic agents into the joint space. There are several options for intra-articular injections: HA, PRP, and steroids. In recent years, the use of HA and PRP in the treatment of OA has become routine. The patients included in this study received intra-articular injections in accordance with the current therapeutic approach for this condition. The decision to inject either HA, or PRP, was made by the treating physician, based on scientific literature and professional experience, and was not influenced by this study.

The decision to inject HA as a single dose is based on the results of other studies that have demonstrated its effectiveness in this form compared to multiple-dose [24]. In a systematic review, HA demonstrated superior long-term effectiveness (4–26 weeks) compared to corticosteroids that provide greater short-term relief (up to 4 weeks) [25].

PRP injections were administered in three doses, with a two-week interval between each, based on multiple published studies that have demonstrated a significant improvement in pain and knee function compared to patients who received a single dose [26-28]**.** Since anti-inflamatory medication is forbidden before, and after PRP, CLT would make a good means to relieve pain.

The pro-inflammatory cytokines (IL-1β, TNF-α, IL-6, IL-17) and proteases (Matrix Metalloproteinases (MMPs), aggrecanases (ADAMTS-4 and ADAMTS-5), serine proteases (plasmin, cathepsins)), involved in OA, degrade HA, leading to a significant reduction in its molecular weight and the viscoelasticity of synovial fluid. The market offers a wide range of viscoelastic substances for joint fluid supplementation, varying in terms of production method, quantity, composition, etc. Studies provide quite different results regarding both the type of product and the method of administration [29]. Based on published studies and clinical experience, our choice was to inject a single dose of a 2.0% solution of a non-chemically modified, intermediate molecular weight (range 1,000–2,000 kDa) sodium hyaluronate obtained through bacterial biofermentation, combined with 0.5% mannitol (FIDIA Farmaceutica S.P.A. Italy) [17]. The recipe is already given in section 2.2.

5. Conclusions

CLT should be considered as a pain killer before any intra-articular injection, owing to its structuring effect on the cartilage. Given that statistical significance ($p > 0.05$) is absent in all cases, we can conclude that age does not significantly influence the improvement of the Lysholm score in any of the groups. Similarly, gender does not have a significant impact on Lysholm score improvement at 6 months or 1 year, regardless of the treatment received.

Although there are small differences in mean values (e.g., women in the PRP group had a slightly higher score at 1 year), these differences are not statistically significant.

Both treatments, PRP, and HA, lead to a significant improvement in the Lysholm score at 6 months, with no significant differences between PRP and HA at this time point. This suggests that both treatments are equally effective in the short term. However, at 1 year, PRP treatment resulted in a significantly greater improvement in the Lysholm score compared to HA, indicating a stronger long-term effect of PRP.

Thus, PRP may be considered more effective in the long term, whereas for similar short-term results, both treatments appear to be comparable.

A future study is foreseen to investigate the complex treatment of OA of the knee, in the sequence: CLT-PRP-HA, where HA would play the part of a protecting lubricant of the joint following PRP.

To our knowledge, CL-AgNPs - HA concurrent action *via* AgNPs surface plasmons, *ex vivo,* is of absolute novelty and generates the thought of using CL-AuNPs - HA *in vivo* in a forthcoming study.

Patients, who underwent this treatment, were informed about the associated risks and benefits, provided written consent, for both the therapeutic procedures, and for their enrollment in the study.

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https://fr-chimie.univ-amu.fr/pratim/microscopie-confocale/

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