ULTRASOUND-GUIDED INFILTRATION OF STEROIDS AND HYALURONIC ACID IN THE COMMON TENDON SHEATH OF THE SHORT EXTENSOR POLLICIS BREVIS AND ABDUCTOR POLLICIS LONGUS IN DE QUERVAIN'S SYNDROME

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PURPOSE

To assess the effectiveness of ultrasound (US) guided infiltration of steroids and hyaluronic acid in the common tendon sheath of the extensor pollicis brevis (EPB) and abductor pollicis longus (APL) in the De Quervain's Syndrome in order to obtain a regression of the clinical status with functionality improvement and the regression of pain avoiding surgical intervention.

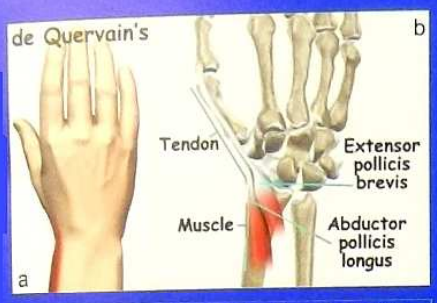

Fig.1 The images show the location of pain (a) and the course of the two tendons near the radial styloid process (b).

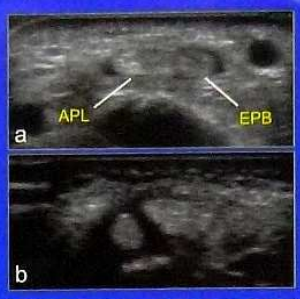

Fig.2 Transverse 7-12 MHz US images obtained over the radial styloid shows EPB and APL tendons (a) and sheath effusion around them (b).

De Quervain's Syndrome is a stenosing tenosynovitis involving inflammation of the tendon sheath of the EPB and APL.

This condition is caused by overuse and usually affects patients who perform repetitive movements of the thumb. Low grade chronic microtrauma at the level of the radial styloid can lead to localized thickening of the extensor retinaculum of the wrist, narrowing of the first compartment of the extensor tendons and subsequent impingement and inflammation of the EPB and APL tendons. The resulting sheath effusion and fibrotic reaction determines the formation of **adhesions between the tendons and sheath**.

Diagnosis is based on the clinical examination (wrist pain, swelling, positive Finkelstein test), but US can help to confirm it. Finkelstein test is performed by applying passive ulnar deviation of the wrist with the thumb maximally flexed. If sharp pain occurs along the distal radius, de Quervain's Syndrome is likely.

Management includes rest, immobilization, anti-inflammatory medication, and, for some patients, surgery.

MATERIALS AND METHODS

24 patients diagnosed with De Quervain's Syndrome were evaluated with US (fig.2) and treated by US-guided infiltration of steroids and hyaluronic acid in the common tendon sheath of EPB and APL. The procedure was performed percutaneously, using a sterile technique, with US guidance and local anesthesia puncturing selectively the common tendon sheath with a 22G needle, respectively for the selective injection of steroids and low molecular weight (750 kDa) hyaluronic acid. US constant monitoring (with 7-12 MHz linear transducer) depicted the correct positioning of the needle tip inside the common tendon sheath and showed its progressive fluid distension. Clinical improvement after treatment was evaluated using a standard ten points visual analogic scale (VAS- and DASH-score), comparing post-procedural score, assessed at 3, 6 and 12 months after treatment, with the pre-procedural value.

Fig.3 Sterile environment, linear ultrasound probe 7-12 MHz, anesthetic, 22G needle, hyaluronic acid, steroids.

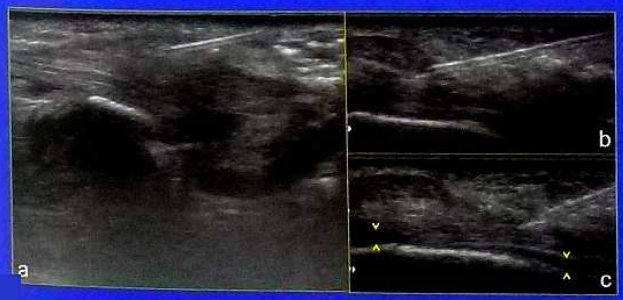

Fig.3 US monitoring during the procedure: immediately after the needle puncture local anhestesia is performed (a), the needle tip is inserted into the common tendon sheath (b), during steroids and hyaluronic acid injection a sheath distension (arrow heads) can be appreciated (c).

RESULTS

3 months after the procedure a reduction of VAS- and DASH-score indexes in 20/24 patients (83,3%) was recorded, while 4 patients (16,7%) did not have regression of clinical symptoms and were retreated (tab.1). At 6 months follow-up 22 patients achieved a significant reduction of scores except for 2 patients that required a new treatment (tab.2). At 12 months follow-up the symptoms reduction was observed in all patients. No complications were observed.

Tab.1

Tab.2

CONCLUSIONS

Our data suggest that the selective infiltration of steroids and hyaluronic acid in the common tendon sheath of the EPB and APL, achieved by US guidance, provides a significative improvement of pain and function in patients affected by De Quervain's Syndrome avoiding a possible surgery. This clinical outcome was related to the biochemical effects of both steroids and hyaluronic acid.

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Single vs Multiple Dose Hyaluronic Asid: Comparison of the Results

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OBJECTIVE

Osteoarthritis (OA) is the most common joint disease in the world. There are various types of treatment used for the knee OA. The purpose of injecting intra-articular HA is to replace HA so that the natural viscosity of synovial fluid is maintained. According to traditional approach, viscosupplementation can be made with the three consecutive intraarticular injections. The purpose of this study was to compare the effectiveness of three consecutive injections of standard HA versus single injection of lightly cross-linking HA in patients with knee OA.

		Single dose lightly cross-linking HA (n=20)	Consecutive three dose standard HA (n=20)	P
Age		57.95±6.97	56.35±5.66	0.431
Sex		16 f / 4 m	17 f / 3 m	0.677
BMI		30.52±4.94	30.83±3.30	0.821
Occupation	housewife	13	13	0.550
	retired	5	4	
	officer	1	3	
	employee	1	-	
Education	primary school	16	15	0.667
	secondary school	1	0	
	highschool	2	3	
	university	1	2	

Table-1. Charactheristics of the groups (no significant difference).

METHODS

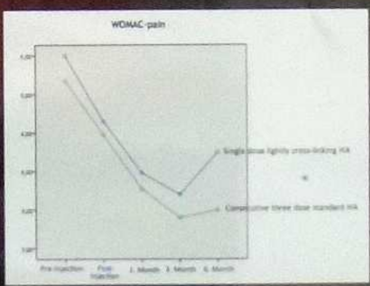
Fourty patients who were diagnosed with knee OA according to American College of Rheumatology criteria and whose X-rays were graded as stage II or III according to Kellgren & Lawrence scale were enrolled to the study. According to the order of presentation to our outpatient clinic, patients were divided subsequently into two groups. In the first group (n=20), 4 ml lightly cross-linking HA (*Monovisc ®, Anika Therapeutics*, Inc.) was injected intraarticularly into knee joint for once. In the second group (n=20), 2 ml standard HA (*Adant ®, Meiji Seika Kaisha, Inc.*) injection was done three times at one-week intervals. WOMAC scores, patient/physician global assessment scores were measured initially and in the first, third, and sixth months.

	Single dose lightly cross-linking HA	Consecutive three dose standard HA	p
WOMAC-pain	5.5000±1.13555	5.1750±1.50678	0.446
WOMAC-physical function	5.0127±1.24641	4.7411±1.58221	0.550
WOMAC-stiffness	2.0000±1.83174	1.5000±1.49561	0.350
WOMAC-total	12.5127±3.32115	11.4661±3.39848	0.331
VAS-activity pain	7.1000 ±1.20961	7.1000± 1.37267	1.000
VAS-rest pain	3.1000 ±1.20961	3.3000± 1.62546	0.661

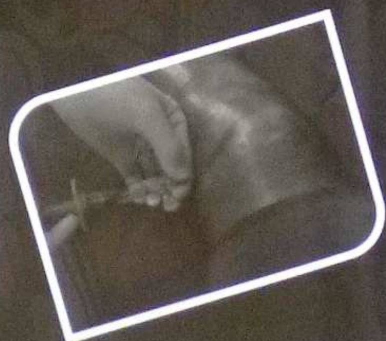
Table 2. Comparison of the groups initially (no significant difference).

RESULTS

There was no significant difference between the groups according to age and body mass index ($p>0.05$) (Table-1).
In within group analysis, VAS-activity pain, VAS- rest pain, WOMAC-pain, WOMAC-physical function, and WOMAC-total scores has been found better after injection(s) in both groups ($p<0.05$). There was no change in WOMAC-stiffness scores in both groups ($p>0.05$) (Table-2). In between group analysis, there was no significant difference between the groups according to all of pre- and post- injection difference of VAS and WOMAC parameters (Graphics).

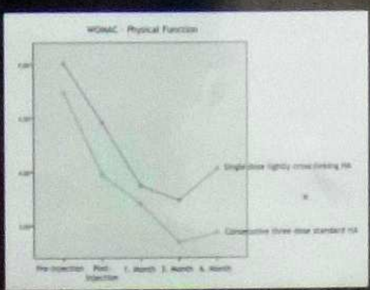


* No significant difference.



CONCLUSION

Single injection of high molecular weight, lightly cross-linking HA seems to be as effective as three injections of standard HA in patients with knee OA, up to six months. Single time injection of HA's advantages are requiring shorter time for application and being more comfortable treatment for the patients. Furthermore, increasing injection number may lead to upward rate of adverse effects.



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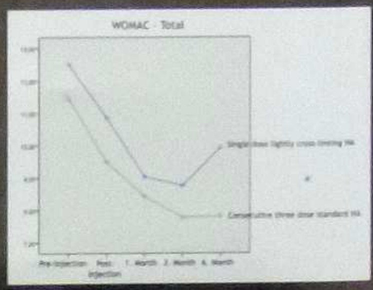

* No significant difference.

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Role of high concentrations of mannitol on the stability of hyaluronan in an oxidative stress model induced by xanthine/xanthine oxidase

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Background

Osteoarthritis (OA) is a degenerative joint disease associated with harmful action of reactive oxygen species (ROS).

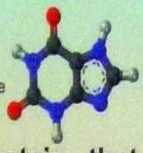
ROS are involved in the degradation of both aggrecan and high-molecular-weight hyaluronan (HMW-HA). The later plays a key-role in the joint lubrication and the visco-elastic and shock absorbing properties of the synovial fluid (SF).

Viscosupplementation consists in injecting intra-articularly exogenous HMW-HA to restore the SF rheological properties, that are dramatically decreased in OA.

However the injected HA is also rapidly degraded by ROS, decreasing its effectiveness and duration of action.

Objective

To evaluate the ability of Mannitol , a powerful oxygen free radical scavenger, to reduce exogenous HMW-HA degradation using a model of oxidative stress induced by xanthine (X) + xanthine oxidase (XOD).



Xanthine

XOD is a flavoprotein that catalyzes oxidation of hypoxanthine to xanthine and then to uric acid generating high levels of superoxide anion.

Methods

Hyaluronan (MW# 0.8mDa) was submitted to an oxidative stress generated by the addition of X + XOD.

Then solution of the same HA + 35g/L of Mannitol in PBS buffer was studied.

Different enzyme concentrations (XOD 109 mUI/mL and 218 mUI/mL) were used and the HA properties were studied after 24 hours of contact at ambient temperature.

Changes of the viscosity of the solution were assessed by rheometry (rheology was determined using a rheometer at 25° C using a cone and plate geometry, steady-state viscosity was determined in Pa.s, as a function of the shear rate).

Rheometer: AR 1000 from TA Instruments

HA MW was also determined by steric exclusion chromatography before and after oxidative stress.

Results

The presence of X/XOD degraded HA in the conditions tested :

- HA viscosity decreased as a function of XOD concentration,
- HA MW decreased dramatically by 36.6%.

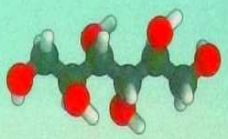
On the opposite, in presence of high concentration of Mannitol:

- HA viscosity was stable,
- HA MW decreased only slightly (-11.9%).

	Initial	+16microl enz.	+32 microL enz.
HA	798000/776000	625600/617300	503800/498900
HA/Mannitol	781200/756600	762200/673300	674000/680300

Conclusion

High concentrations (3.5%) of mannitol protect HA from ROS-mediated degradation.



These in vitro data suggest that **mannitol may increase the intra-articular residence time of HA** and consequently may improve clinical efficacy of viscosupplementation.

Efficacy and safety of viscosupplementation with HANOX-M-XL (HappyCross®) in ankle osteoarthritis. Results of a standardized follow-up

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BACKGROUND

The published data suggest that viscosupplementation may be a safe and effective method in the treatment of ankle OA. However, the limited number of patients with ankle OA enrolled in clinical trials as well as the diversity of the products and dosing regimen are limiting any definitive conclusion about its safety and efficacy.

HANOX-M-XL, HAppyCross® (LABRHA, Lyon, France) is a new viscosupplement, specifically designed to treat middle-sized joint OA. It combines a high molecular weight cross-linked sodium hyaluronate (15.5g/L) of non-animal origin and a high concentration (3.5%) of mannitol, a polyol known for its antioxidant properties by scavenging radical oxygen species (ROS).

OBJECTIVE

To obtain data on both efficacy and safety of HANOX-M-XL, administered through a single injection regimen in patients suffering from symptomatic ankle osteoarthritis (OA).

METHODS

Multicenter standardized follow-up.

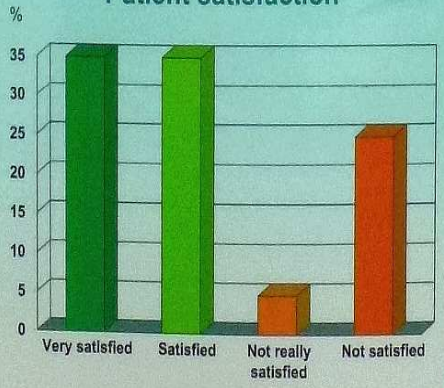
20 consecutive patients treated with a single intra-articular injection of HANOX-M-XL for symptomatic ankle OA, not responding to symptomatic treatments, were included in the survey.

Demographic data, imaging guidance, pain on a 10 point Likert scale (LS), patient's self-evaluation of efficacy, satisfaction with the treatment and tolerability were obtained.

RESULTS

Sex ratio (Male/female) was 15/5. Patients mean age (SD) was 57 (19.4) and average time of follow-up was 11.5 (4.7) weeks.
Viscosupplementation was performed under fluoroscopic guidance in 11 cases, ultrasonography (US) in 4 cases and without imaging guidance in 5 cases.

Patient satisfaction

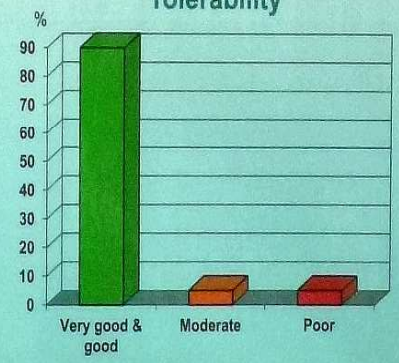


Efficacy was unrelated to sex (p=0.58), age (p=0.87), and guidance (p=0.33).
Efficacy was highly correlated with pain on LS (p<0.0001).

RESULTS

Efficacy

Tolerability



The patient who experienced high level of pain after injection was treated without imaging guidance, suggesting the treatment was not administered intra-articularly.

CONCLUSION

In ankle OA, 3 months after a single injection of HANOX-M-XL in the target ankle, 7 patients out of 10 were satisfied with the treatment, without any safety concern.
These data suggest that HANOX-M-XL is a safe and efficient intra-articular treatment of ankle OA but large scale controlled trials are necessary to confirm these promising results.

Effiacy and Safety of Yttrium-90 Radiosynoviorthesis in Inflammatory Knee Synovitis: a prospective evaluation of 135 procedures in 85 patients

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International Symposium Intra Articular Treatment

Introduction

Radiosynoviorthesis(RSO) consist in intra-articular injection of ß emitting radionuclide in order to destroy pathologic synovium in persistent synovitis (1) The aim of this study was to evaluate effectiveness and safety of RSO with yttrium-90 (Y-90) in persistent knee arthritis with chronic effusion in inflammatory rheumatic diseases, after failure of intra-articular corticoids.

Materiel & Methods

•Patients referred to our hospital between 2002 and 2006 in order to have RSO of the knee were assessed prospectively.
•RSO was performed as recommended (2, 3). Intra-articular injection of Y-90 was performed after joint aspiration, with a mean activity of 4mCi, without corticoid co-injected. Knees were splinted for 72 hours. Incidents after RSO were recorded. **Assessment:** Patient global assessment was the primary endpoint, positive response was defined by a global improvement of at least 30% on a verbal scale (0-100%). Secondary efficacy endpoints included: VAS pain (0-100mm), effusion score (0-3), range of motion by heel-buttock distance (cm) and knee circumference (cm). Patients were reviewed at 1, 3, 6, 12 and 18 months. For the statistical analysis we used the WHO program Epi6.

Results

85 patients(135 Knees) were evaluated in this study (table 1).The percentage of positives responses according to the primary endpoint exceeded 80% for 18 months (table 2). No statistically significant difference was found in positives responses when comparing patients under 30 years and patients over 50 years, when comparing knees with different radiologic stages, and when comparing RA and SpA. (Tables 3,4 and 5). We also noted a significant change in mean scores of secondary endpoints : pain, effusion , and heel- buttock distance from the 1st until the 18th month. A significant decrease in joint circumference was observed from the 3rd month (Table 6). Acute synovitis was observed in half of cases in the evening of RSO(table 7) and was treated by applying ice in 52 cases and NSAIDs were required in 12 cases . We noted no cases of skin radionecrosis nor septic arthritis.

Table 1- Diagnosis and patient/knees characteristics

	Total	RA	SpA	OU	B
Patients (%)	85	42 (49)	22(26)	15 (18)	6 (7)
Knees (%)	135	70(52)	35 (26)	22(16)	8(6)
Unilateral	35 (42)	14 (20)	09 (41)	8	4
Bilateral	50 (58)	28 (80)	13 (59)	7	2
Mean age(years) (range)	38,5±13 (18-71)	44,64 ± 12,5 (20 – 71)	31,04 ±10,7,5 (18 – 52)	31,8 ±10,41 (18 – 52)	40 ±8,85 (29 – 49)
Sex : men	39 (46)	12 (29)	14 (64)	9	4
women	46 (54)	30(71)	08(36)	6	2
Mean duration of disease (years) (range)	8,9 ± 5,9 (1-32)	10,92 ± 6,4 (1 – 32)	7,04 ± 4,81 (1 – 18)	6,13 ± 3,6 (2 – 12)	9 ± 6,4 (2 – 17)
Mean duration of hydarthrosis (months) (range)	50 ± 55,9 (3-240)	60,75 ± 63,5 (3 – 240)	61,31 ± 46,87 (3 – 132)	63, 8 ± 42,7 (12 – 144)	88,4±71,6 (5 – 204)
Mean number of corticoid injection/knee (range)	4± 3 (1-25)	4 ± 3,5 (1-25)	2,89 ± 2,4 (1-11)	3,75 ± 1,6 (1-8)	2,83 ±4,9 (1-15)
Mean ESR (mm) /1ºh (range)	48.35±30.75 (3-120)	54,66±28,75 (4 – 110)	54,82 ± 38,1 (7 – 120)	36,7 ± 24,6 (3 – 85)	30,7± 23 (5 – 68)
Radiological stage*					
I (%)	62 (46)	25 (36)	20 (57)	11	6
II	55 (41)	32 (46)	12 (34)	11	
III	18 (13)	13 (18)	03 (09)		2

RA= rheumatoid arthritis, SpA=spondyloarthritis, OU= oligoarthritis of unknown etiology, B= Behçet disease.
* Steinbrocker radiological classification.

Table 2- Clinical response after RSO with Y-90 (135 knees)

	1 month	3 months	6 months	12 months	18 months
Positive response*					
Absolute value	128	127	119	117	111
(%)	(94,8)	(94)	(88)	(87)	(82)
CI 95%	91-99	90-98	82-93	81-93	75-89

*According to primary endpoint (patient global assessment); CI= confidence interval 95%

Table 3- Clinical response according to age (18 months)

Age (years)	≤ 30 n = 49	≥ 50 n = 25
Positive response	42 (85,71%)	18 (72%)

No statistically significant difference was noted in percentage of positives responses between patients aged under 30 and patients over 50 years

Table 4-Clinical response according to radiological stage (18 months)

Stage*	I N=62	II N=55	III N=18
Positive response	47(76%)	48 (87%)	17 (94%)

* Steinbrocker classification. No statistically significant difference in positives responses between different radiological stages

Table 5-Clinical response according to the disease (18 months)

	1 month	3 months	6 months	12 months	18 months
RA(70 knees)	65	64	64	60	57
(%)	(93)	(91)	(91)	(86)	(81)
SpA (35 knees)	34	34	28	30	29
(%)	(97)	(97)	(80)	(85)	(83)
OU (22 knees)	21	21	20	19	17
B (8 knees)	8	8	7	8	8

No statistically significant difference between RA and SpA

Table 6- therapeutic effect of Y-90 on secondary endpoints

	Before Y-90k	1 monthS	3 months	6 months	12 months	18 months
EVA pain : 0-100mm	54,96±25,21	11,86±21,40 P=10⁻⁶	8,99±20,50	9,02±19,70	6,99±17,96	5,2±17,11
Effusion score (0 – 3)	2,42±0,68	1,00±0,92 P=10⁻⁶	0,72±1,00	0,51±0,87	0,53±0,89	0,33±0,70
Knee circumference (cm)	38,38± 3,76	37,46± 3,69 NS	37,19±3,20 P=10⁻³	36,71±3,45 P=10⁻⁴	36,60±3,26 P=10⁻⁵	35,79±4,81 P=10⁻⁶
Heel-buttock (cm)	20,61±11,82	13,94±8,81 P=10⁻⁴	12,54±8,21	11,68±5,66	10,74±8,27	10,92±9,49

Table 7-Incidents after RSO with Y-90

Incidents	Patients	Knees
Acute synovitis	43	64
Fever+chills*	03	04
Pseudo-septic arthritis (fever, leucocytosis)**	01	01
Rash*	02	03
Abdominal pain*	02	04

* This incidents occured concomitantly with acute synovitis. ** This incident occured 1 week after RSO.

Discussion

•IN our study, the rate of effectiveness of the RSO with Y90 exceeded what is noted in the literature, especially prospective studies (4-13). This is explained by the major criterion of effectiveness chosen which is based on the patient opinion. However the improvement of secondary endpoints confirmed the effectiveness of this treatment.
•In order to evaluate the therapeutic effect in the short term, we did not associate corticoids with Y-90, which is why we had a large proportion of acute synovitis with massive effusion after RSO. This incident was well tolerated by patients and effusion had resolved after a variable period ranging from 1 to 30 days .
• This study had allowed to introduce RSO in our hospital .

Conclusion

Radiosynoviorthesis with Y-90 is a safe and successful treatment of persistent knee synovitis in inflammatory diseases after failure of intra-articular corticoids, and seems effective for 18 months at least.

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Infiltrative therapy of the painful and stiff shoulder

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In the cuff's lesions, the bursa has thickened walls and may contain fluid as a result of chronic inflammation
We distinguish the involvement of the SAD in two types
1 exudative 2 fibroadhesive
We can take into consideration only the fibroadhesive bursitis, as usually appear in painful and stiff shoulder. The shoulder's stiffness is, in our study, correlate to lesion of the rotator cuff
We can correlate elevated levels of infiammatory citochines in the SAD with pathogenesis of inflammation involving in fibrosis. Sodium Hyaluronate suppreses the expression of metalloproteinasis induced by IL1beta. The differentiation of fibroblasts driven by GROWTH FACTOR 1 beta, is the most important source of mio fibroblasts. Exogenous hyaluronate antagonizes this differentiation. Increased expression of IL1beta and conspicuous recruitment of miofibrobasts at the level of SAD, in the lesions of rotator cuff, are related to shoulder's stiffness

Scope

We must demonstrate the efficacy of sodium hyaluronate, injected in SAD, with ultrasound guidance, in patients with painful and stiff shoulder, with broken cuff
In our study, we eliminate the exudative bursitis, preferring fibroadhesive types

Matherial and methods

The infiltrativ approach is lateral. The probe must stay parallel to long axis of sovraspinato. The needle must be conducted by scans beside the greater axis allowing the visualitation until the entrance into the SAD.

Probe = linear, multifrequency 13-5 mHz
Hyaluronic acid used = extracted by growing medium , average molecular weight , at dosage of 10 mg
The needle used had a 23 gauge.
Clinimetric tests = VAS (1-10) and ROAD questionarie (0-32)
The analysis of descriptive statistics on the variables "Delta VAS" and "Delta ROAD" made on a sample of patients show positive trends. The matrix's of Pearson's correlation , who measures the degree of linear correlation between two variables, show the following thoughts
1 Between the variables Delta VAS(for pain) and Delta ROAD (for function) there is not correlation 2 VAS 1 - VAS 2 and ROAD 1 - ROAD 2 show interesting linear correlations.
3 Also the two variables after therapy VAS 2 and ROAD 2 show small but positive correlation. 4 The Delta VAS shows an important negative correlation (discordance) with VAS2, indicator of post-therapy pain. The interpretation of this effect is easier with BAR GRAPH dispersion in which it is placed in relation each value of VAS 2(value post therapy) with Delta VAS (therapeutic effectiveness).
From the graph, we can deduce that increasing the values of VAS2, there is an almost constant reduction of Delta VAS. That is, a smaller efficacy of therapy is associated with increasing of values of pain at the end of therapy. 5The variable Delta ROAD shows a significant positive correlation (agreement) with ROAD 1, indicator of situation before therapy.
The interpretation of this effect is largely facilitated by the Bar graph dispersion where we can put in relation every value of ROAD1 (value before therapy) with the Diff ROAD (efficacy of therapy).
From the graph we can deduce that when there are increasing values, there is an increment nearly constant of Diff ROAD.
That is, when there is an increment of values associated to the pain at beginning of therapy, a greater efficacy of the treatment is associated.

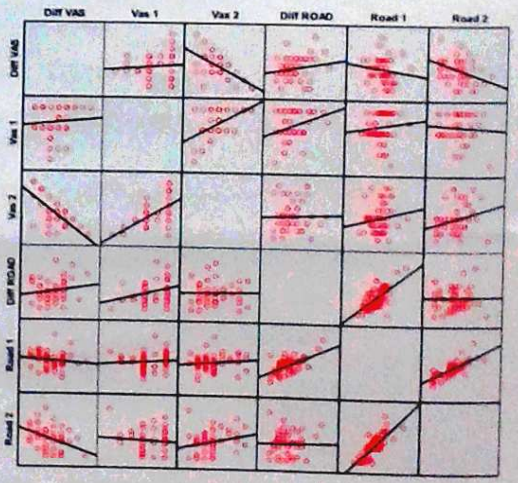
Statistiche

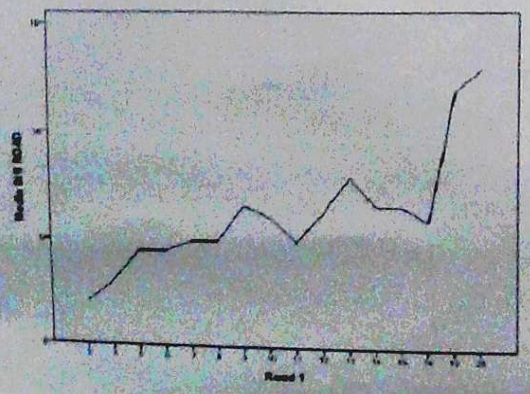
		ETA'	VAS 1	VAS 2	Diff. VAS	ROAD 1	ROAD 2	Diff. ROAD
N Oss.		52	52	52	52	52	52	52
Media		71.27	8.63	3.90	4.69	10.69	4.71	6.12
Deviazione std.		7.105	1.314	1.902	1.579	3.868	3.127	2.479
Quartile	1	66.00	8.00	2.00	4.00	8.00	2.00	4.00
	2 (Mediana)	72.00	8.00	4.00	5.00	10.50	5.00	6.00
	3	76.00	10.00	5.00	6.00	13.00	7.00	8.00

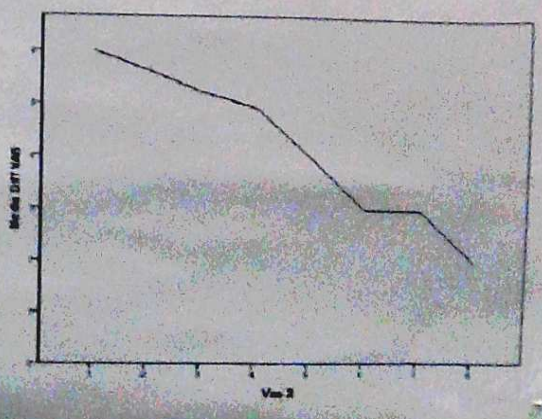
Correlazioni

		Diff Vas	Vas 1	Vas 2	Diff Road	Road 1	Road 2
Diff Vas	Correlazione di Pearson	1	.087	[illegible]	.170	-.122	-.376**
	Sig. (2-code)		.542	[illegible]	.229	.390	.006
	N	52	52	[illegible]	52	52	52
Vas 1	Correlazione di Pearson	.087	1	.598**	.320*	.101	-.064
	Sig. (2-code)	.542		.000	.021	.477	.650
	N	52	52	52	52	52	52
Vas 2	Correlazione di Pearson	-.683**	.598**	1	.032	.153	.259
	Sig. (2-code)	.000	.000		.824	.278	.064
	N	52	52	52	52	52	52
Diff Road	Correlazione di Pearson	.170	.320*	.032	1	.619**	.014
	Sig. (2-code)	.229	.021	.824		.000	.919
	N	52	52	52	52	52	52
Road 1	Correlazione di Pearson	-.122	.101	.153	.619**	1	.750**
	Sig. (2-code)	.390	.477	.278	.000		.000
	N	52	52	52	52	52	52
Road 2	Correlazione di Pearson	-.376**	-.064	.259	.014	.750**	1
	Sig. (2-code)	.006	.650	.064	.919	.000	
	N	52	52	52	52	52	52

** La correlazione è significativa al livello 0,01 (2-code)
* La correlazione è significativa al livello 0,05 (2-code)







Prospective Evaluation Of Local Joint Variables After Intra-Articular Injection With Corticosteroid In Patients With Rheumatoid Arthritis

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INTRODUCTION

Few studies have prospectively evaluated local joint variables responses related to intra-articular injection (IAI). Our objetive was to compare local joint variables in response to IAI with hexacetonide triamcinolone (HT) in short and medium terms in rheumatoid arthritis (RA) patients.

MATERIALS AND METHODS

- Case control study in a cohort of patients with RA
- RA patients with indication to receive IAI with TH (persistent synovitis despite of oral medication for at least one month)

INTERVENTION:

- IAI with TH (mono, pauci or polyarticular)
- Single time
- Joints studied and TH dose used: shoulder (80mg); elbow (40 or 60mg), wrist (30 or 40mg), MCP (10 or 20mg), Knee (40, 60 or 80mg) and ankle (40 or 60mg)

ASSESSMENT:

- "Blinded" observer: T0 (baseline), T1 (1 week), T4 (4 weeks), T12 (12 weeks) and T24 (24 weeks).

OUTCOME MEASURES:

- Visual Analogue Scale (VAS) (0-10 cm): at rest (VASr), during movement (VASm), for swollen joints (VASs)
- Flexion
- Extension (except shoulder)

INCLUSION CRITERIA

RA (ACR criteria), age between 18-65 years; functional Class II or III (ACR criteria); use of stable dose of DMARDs (last 3 months); use of stable dose of systemic corticosteroid (last 4 weeks), able to give written informed consent

EXCLUSION CRITERIA

IA steroid injections in any joint (previous 3 months); suspicion of active systemic or IA infection; severe clotting disorder; any uncontrolled systemic disease (hypertension or diabetes mellitus); allergy to the contrast or radioisotope agent

RESULTS

1. Demografic Data

Mean age (years)	***48.7 (SD 10.68)***
Mean Disease Duration (years)	10.98 (SD 8.39)
Women-to-Men ratio	12:1
Mono-injection	175 patients (60.55%)
Pauci-injection	68 patients (23.3%)
Poly-injection	46 patients (15.92%)
Joints Studied through: • T0 - T4 • T0 - T12 • T0 - T24	 635 403 313
Number of joints assessed through: • Shoulder • Elbow • Wrist • MCP • Knee • Ankle	T4 / T24 35 /0 48/17 160/63 142/103 152/85 98/45

2. Prospective evaluation of joint flexion from T0 through T24

Joint (n)	*Joint Flexion in degrees Mean (SD)*								
	T0	T1	p	T4	p	T12	p	T24	p
Shoulder T0-T4 (n=35)	137,42 (32,50)	148,25 (31,85)	***	156,14 (32,99)	***	NA	NA	NA	NA
Elbow T0-T4 (n=48)	124,72 (12,20)	132,08 (10,14)	***	133,16 (8,45)	***	NA	NA	NA	NA
Elbow T0-T24 (n=17)	126,17 (10,82)	130,58 (11,87)	NS	127,35 (6,40)	NS	126,47 (10,27)	NS	128,52 (7,01)	NS
Wrist T0-T4 (n=160)	42,46 (18,60)	41,57 (21,10)	**	47,73 (19,16)	***	NA	NA	NA	NA
Wrist T0-T24 (n=63)	45,87 (22,31)	47,22 (24,86)	NS	48,53 (21,53)	NS	48,53 (22,66)	NS	46,50 (20,62)	NS
MCP T0-T4 (n=142)	73,72 (18,63)	83,57 (10,85)	***	85,03 (9,40)	***	NA	NA	NA	NA
MCP T0-T24 (n=103)	82,28 (10,65)	84,56 (9,26)	**	85,09 (9,54)	***	85,51 (9,94)	***	84,51 (11,41)	*
Knee T0-T4 (n=142)	116,01 (15,07)	121,25 (15,59)	***	123,49 (17,28)	***	NA	NA	NA	NA
Knee T0-T24 (n=85)	115,94 (13,82)	120,14 (17,36)	**	122,17 (14,22)	***	121,29 (13,02)	***	120,14 (14,26)	**
Ankle T0-T4 (n=48)	28,59 (13,91)	32,34 (13,26)	***	32,85 (14,51)	***	NA	NA	NA	NA
Ankle T0-T24 (n=45)	33,11 (16,42)	34,22 (16,05)	NS	31,77 (16,99)	NS	33,22 (17,22)	NS	32,00 (16,69)	NS

3. Prospective evaluation of joint extension from T0 through T24

Joint (n)	*Articular Extension in degrees Mean (SD)*								
	T0	T1	p	T4	p	T12	p	T24	p
Shoulder	NA	NA	NA	NA	NA	NA	NA	NA	NA
Elbow T0-T4 (n=48)	-4,79 (18,67)	-2,35 (13,87)	NS	-2,04 (15,23)	NS	NA	NA	NA	NA
Elbow T0-T24 (n=17)	8,52 (20,67)	5,58 (15,50)	NS	6,47 (15,81)	NS	6,17 (15,36)	NS	5,88 (13,92)	NS
Wrist T0-T4 (n=160)	41,58 (20,35)	45,34 (19,75)	***	47,46 (20,18)	***	NA	NA	NA	NA
Wrist T0-T24 (n=63)	58,54 (17,16)	60,72 (17,94)	NS	60,64 (20,87)	NS	63,95 (16,72)	***	60,48 (17,54)	NS
MCP T0-T4 (n=142)	62,55 (34,23)	65,66 (32,62)	***	66,93 (31,60)	***	NA	NA	NA	NA
MCP T0-T24 (n=103)	82,20 (10,74)	84,74 (9,13)	*	85,19 (9,43)	***	85,32 (9,50)	**	84,93 (11,39)	*
Knee T0-T4 (n=142)	-3,73 (8,34)	0,44 (6,19)	***	0,47 (5,48)	***	NA	NA	NA	NA
Knee T0-T24 (n=85)	82,20 (10,74)	84,74 (9,13)	***	85,19 (9,43)	***	85,32 (9,50)	***	84,93 (11,39)	***
Ankle T0-T4 (n=48)	11,29 (4,85)	13,17 (5,15)	***	14,38 (6,46)	***	NA	NA	NA	NA
Ankle T0-T24 (n=45)	13,56 (5,10)	13,84 (5,87)	NS	14,77 (5,70)	NS	14,09 (5,97)	NS	12,54 (6,41)	NS

4. Prospective evaluation of VASr from T0 through T24

Joint (n)	*VASr Mean (SD)*								
	T0	T1	p	T4	p	T12	p	T24	p
Shoulder T0-T4 (n=35)	5,42 (1,75)	1,68 (2,63)	***	0,80 (1,93)	***	NA	NA	NA	NA
Elbow T0-T4 (n=48)	4,97 (2,50)	1,08 (1,85)	***	0,77 (1,65)	***	NA	NA	NA	NA
Elbow T0-T24 (n=17)	4,11 (3,47)	1,35 (2,14)	*	1,00 (1,83)	***	1,82 (2,74)	*	1,58 (2,39)	*
Wrist T0-T4 (n=160)	4,66 (2,54)	2,06 (2,36)	***	1,52 (2,17)	***	NA	NA	NA	NA
Wrist T0-T24 (n=63)	3,39 (3,15)	0,88 (1,85)	***	0,74 (1,66)	***	1,98 (2,73)	**	1,82 (2,39)	***
MCP T0-T4 (n=142)	2,96 (2,72)	0,98 (1,91)	***	0,54 (1,50)	***	NA	NA	NA	NA
MCP T0-T24 (n=103)	2,24 (2,76)	0,94 (2,01)	***	0,48 (1,60)	***	0,76 (2,07)	***	0,79 (1,94)	***
Knee T0-T4 (n=142)	5,98 (2,29)	1,96 (2,27)	***	2,23 (3,30)	***	NA	NA	NA	NA
Knee T0-T24 (n=85)	5,83 (2,62)	1,94 (2,20)	***	2,40 (2,61)	***	2,77 (2,79)	***	3,92 (3,06)	***
Ankle T0-T4 (n=48)	4,97 (2,50)	1,08 (1,85)	***	0,77 (1,65)	***	NA	NA	NA	NA
Ankle T0-T24 (n=45)	3,56 (3,15)	1,36 (2,21)	***	1,56 (2,63)	***	1,72 (2,38)	***	2,38 (2,80)	*

5. Prospective evaluation of VASm from T0 through T24

Joint (n)	*VASm Mean (SD)*								
	T0	T1	p	T4	p	T12	p	T24	p
Shoulder T0-T4 (n=35)	7,11 (1,62)	4,74 (2,47)	***	3,31 (2,71)	***	NA	NA	NA	NA
Elbow T0-T4 (n=48)	5,7 (3,29)	2,66 (2,83)	***	1,93 (2,60)	***	NA	NA	NA	NA
Elbow T0-T24 (n=17)	2,05 (2,53)	0,88 (1,96)	NS	0,58 (1,66)	NS	0,29 (1,21)	NS	0,58 (1,66)	NS
Wrist T0-T4 (n=160)	4,76 (3,11)	2,69 (2,87)	***	2,28 (2,57)	***	NA	NA	NA	NA
Wrist T0-T24 (n=63)	1,74 (2,40)	0,55 (1,58)	***	0,79 (1,84)	*	0,82 (1,83)	*	1,66 (2,37)	NS
MCP T0-T4 (n=142)	2,93 (3,18)	1,38 (2,19)	***	1,02 (2,01)	***	NA	NA	NA	NA
MCP T0-T24 (n=103)	1,50 (2,34)	0,63 (1,66)	*	0,33 (1,26)	***	0,38 (1,34)	***	0,67 (1,72)	*
Knee T0-T4 (n=142)	6,16 (2,37)	2,40 (2,37)	***	2,11 (2,39)	***	NA	NA	NA	NA
Knee T0-T24 (n=85)	5,52 (2,69)	1,81 (1,00)	***	1,91 (2,49)	***	2,56 (2,66)	***	3,51 (3,18)	***
Ankle T0-T4 (n=48)	5,30 (3,28)	2,85 (2,91)	***	2,80 (3,05)	***	NA	NA	NA	NA
Ankle T0-T24 (n=45)	2,44 (2,52)	0,77 (1,53)	**	0,88 (1,93)	**	1,66 (2,38)	NS	2,22 (2,51)	NS

6. Prospective evaluation of VASs from T0 through T24

Joint (n)	*VASs Mean (SD)*								
	T0	T1	p	T4	p	T12	p	T24	p
Shoulder T0-T4 (n=35)	3,37 (1,84)	1,31 (0,99)	***	0,62 (0,77)	***	NA	NA	NA	NA
Elbow T0-T4 (n=48)	5,47 (1,32)	2,04 (1,85)	***	1,43 (1,72)	***	NA	NA	NA	NA
Elbow T0-T24 (n=17)	5,47 (2,18)	1,47 (2,34)	***	1,46 (2,34)	***	1,47 (2,33)	***	0,88 (1,96)	***
Wrist T0-T4 (n=160)	5,27 (1,32)	2,83 (2,06)	***	2,23 (2,09)	***	NA	NA	NA	NA
Wrist T0-T24 (n=63)	5,27 (1,32)	2,46 (2,51)	***	1,98 (2,46)	***	3,33 (2,37)	***	3,57 (2,27)	***
MCP T0-T4 (n=142)	5,07 (0,84)	2,05 (2,23)	***	1,25 (1,92)	***	NA	NA	NA	NA
MCP T0-T24 (n=103)	5,07 (0,84)	1,99 (2,45)	***	1,21 (2,15)	***	1,85 (2,41)	***	1,99 (2,45)	***
Knee T0-T4 (n=142)	4,58 (1,68)	1,93 (1,81)	***	1,30 (1,54)	***	NA	NA	NA	NA
Knee T0-T24 (n=85)	4,17 (1,66)	1,48 (1,91)	***	1,05 (1,57)	***	1,17 (1,64)	***	1,50 (1,78)	***
Ankle T0-T4 (n=48)	5,47 (1,32)	2,04 (1,88)	***	1,43 (1,72)	***	NA	NA	NA	NA
Ankle T0-T24 (n=45)	5,47 (1,32)	2,11 (2,49)	***	1,88 (2,45)	***	2,66 (2,52)	***	2,77 (2,51)	***

SD: standart deviation; n: number of joints studied; NS: non significant, NA: not aplicable. Statistical test: Repeated Measures ANOVA *** p<0,001 ** p<0,005 * p< 0,05

CONCLUSION

VASs was the variable that best responded in the short and medium term after IAI, and the variable extension had the worst response. The knee was the only joint that showed improvement in the short and medium term for all variables studied.

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Development of hyaluronic acid-based formulations for the treatment of osteoarthritis

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INTRODUCTION

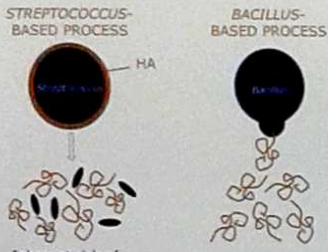
- Osteoarthritis is the most common degenerative joint disease which affects more than 50% of people over the age of 65 worldwide. Among the possible treatment strategies, hyaluronic acid (HA)-based viscosupplementation has become an attractive therapy as an alternative to the injection of analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids.
- Today HA viscosupplementation is based on either non-modified or crosslinked HA and both approaches have demonstrated patient benefit.
- The purpose of this work was to study the properties of benchmark osteoarthritis formulations based on both non-modified and crosslinked HA and compare them to formulations prepared from a novel HA material Hyasis® and crosslinking technology Hyasis® Link.

CONCLUSION

- With their unique set of properties Hyasis® and Hyasis® Link combine many advantages for the formulation of osteoarthritis formulations.
- Hyasis®-based formulations (non-modified HA) with increasing molecular weight allows to cover the properties of most commercial formulations.
- Hyasis® Link-based formulations (crosslinked HA) can be engineered so as to match desired viscoelastic profiles.
- Hyasis® Link gels prepared from Hyasis® integrate the advantages of both technologies: safety, consistency, performance

NON-MODIFIED HYALURONIC ACID-BASED OSTEOARTHRITIS FORMULATIONS

Hyasis®, Novozymes *Bacillus*-derived hyaluronic acid



Inherent risk of
- residual endotoxin
- higher PDI

- Safe bacterial strain which does not produce endotoxin
- Direct extrusion of HA polymer into the fermentation medium allowing mild recovery process
- No animal-derived raw materials
- 100% water-based manufacturing technology (no organic solvents)
- Unmatched purity
- Targeted molecular weight with low polydispersity

An attractive ingredient for osteoarthritis formulations

Unlike other HA material, Hyasis® comes in the form of a spray-dried powder featuring hollowed and porous microparticles. This results in a shorter dissolving time and allows to reduce the manufacturing time of final formulations.

Due to its unmatched purity, Hyasis® also features a superior heat stability. This allows the mitigation of inevitable product viscosity decrease following sterilization by autoclaving.

The rheological properties of benchmark non-modified HA-based osteoarthritis formulations and Hyasis® -based mimic formulations were investigated and are presented below.

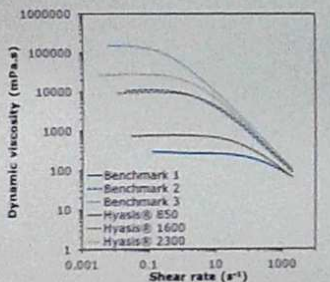


Fig. 1: Flow properties – all formulations

Example of a Hyasis®-based mimic formulation (non-modified HA)

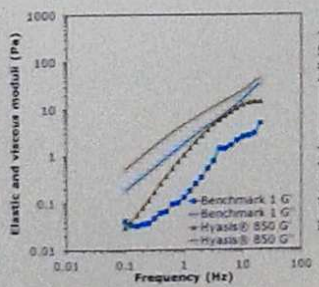


Fig. 2: Viscoelastic properties – viscous formulations

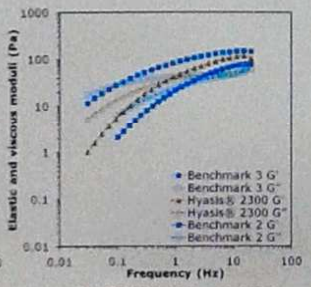


Fig. 3: Viscoelastic properties – viscoelastic formulations

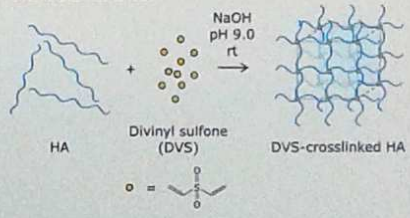
METHODOLOGY - Non-modified HA formulations

Benchmark formulations (with HA concentration 1% and an increasing molecular weight from benchmark 1 to 3) were analyzed "as is". Hyasis® with molecular weight 850, 1,600 and 2,300 kDa was dissolved in a physiological PBS buffer (pH 7.4) at a concentration of 1% w/w. The flow and viscoelastic properties of the formulations were investigated using a rotational rheometer (Physica MCR 301, Anton Paar) equipped with Peltier temperature control system and a plate-plate geometry. Viscoelastic profiles were recorded using a strain of 5%.

CROSSLINKED HYALURONIC ACID-BASED OSTEOARTHRITIS FORMULATIONS

Hyasis® Link, Novozymes hyaluronic acid crosslinking technology

CHEMICAL REACTION



- Proprietary technology (WO2006/056204)
- Residual DVS < 1.5 ppm
- The well-controlled molecular properties of Hyasis® lead to an improved process and reproducible hydrogel properties

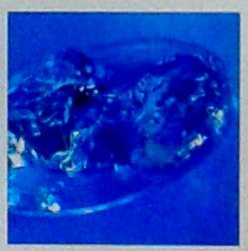
A safe and robust technology for the development of novel osteoarthritis formulations

Hyasis® Link is an improved hyaluronic acid crosslinking technology which results in HA hydrogels with well-controlled and homogenous properties.

The gels are stable to sterilization by autoclaving at standard conditions (121°C, 15 min) with retention of their viscoelastic properties.

Gel properties can easily be customized to produce injectable materials with improved in vivo stability and well-defined rheological characteristics suitable for osteoarthritis applications.

To illustrate this, Hyasis® Link formulations (moderately crosslinked, MCL and lightly crosslinked, LCL) were engineered so as to match the viscoelastic properties of benchmark crosslinked HA-based osteoarthritis formulations.



Example of a Hyasis® Link-based mimic formulation (crosslinked HA)

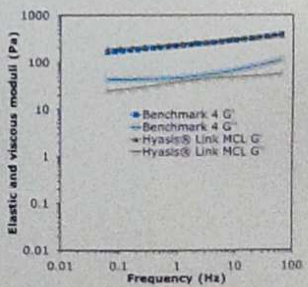


Fig. 4: Viscoelastic properties – comparison with benchmark 4

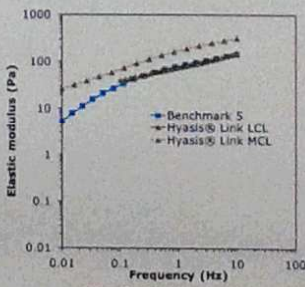


Fig. 5: Elastic properties – comparison with benchmark 5

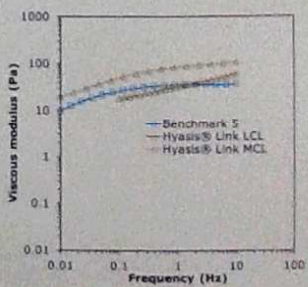


Fig. 6: Viscous properties – comparison with benchmark 5

METHODOLOGY - Crosslinked HA formulations

Hyasis® was crosslinked using divinyl sulfone and various HA/DVS weight ratios. The resulting hydrogels were equilibrated in physiological PBS buffer. Depending on the crosslinking degree, the final HA concentration in the gels was in the range 1.4-2.0 w/v%. The viscoelastic properties of the gel formulations as function of the frequency were measured by small amplitude oscillatory shear test using a rotational rheometer (Physica MCR301, Anton Paar) and a parallel plate geometry.

novozymes

BLINDED VS ULTRASOUND –GUIDED CORTICOSTEROID INJECTIONS FOR THE TREATMENT OF THE GREAT TROCHANTERIC PAIN SYNDROME (GTPS): A RANDOMIZED CONTROLLED TRIAL

Rheumatology Division of Universidade Federal de São Paulo, Brazil
Germana B. Q. Estrela, Rita N V Furtado, Suellen Narimatsu, André Rosenfeld, Jamil Natour*
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INTRODUCTION

The peritrochanteric corticosteroid injections with anesthesics is one of the suggested treatments for the refractory case of the Greater Throcanteric Pain Syndrome. This therapeutic intervention can be guided or not. Although there are still no scientific researches that support the idea of the guided procedure being superior to blinded one.

PURPOSE

To compare the effectiveness of both injections in the Greater Trochanteric pain syndrome treatment: The blinded corticosteroid injections and the ultrasound-guided corticosteroid injections.

MATERIAL AND METHODS

A prospective, randomized, double - blind, controlled study was made involving 60 patients (from 19 – 65 years old) who were diagnosed with GTPS for at least 30 days.

GROUP 1
Blindly injection
(n =30)

60 patients

GROUP 2
Ultrasound* Guided injection (n=30)

*ESAOTE MyLab™60 GOLD Platform **probe LA 435, 6-18 MHz**

Assessement (weeks)

Two blinded observers (clinical and radiology physicians) evaluated the experiment during week 0, 1, 4 and 8 after the procedure, using a visual analogue scale (VAS: 0-10)
T0 – baseline + injection*
T1 – assessement
T4 – assessemnt
T8 – assessement
* Syringue with Betamethasone (6 mg) + Lidocaine (2 cc)

ASSESSEMENT INSTRUMENTS

VAS of spontaneous pain, VAS of Painfull palpation Global health, VAS of external rotation pain, VAS of Pain when testing against resistance repositioning functional testing, "Time up and go" (time in minutes), Test six-minute walk (distance in meters), Lequesne hip, Goniometry hip (flexion, extension and abduction), Ultrasound qualitative and quantitative (in mm) measurements of the gluteus medius and minimum tendons, and trochanteric bursa.

RESULTS

The groups were similar according to general characteristics (table 1). After 8 weeks of follow-up, there was improvement over the initial time (intra-group evaluation) in both groups. Using repeated measures ANOVA, there was no significant difference between the groups for local pain VAS (p = 0.347), VAS of pain on palpation (p = 0.873), EVA external rotation (p = 0.215), test repositioning against resistance (p = 0.855), test "time up and go" (p = 0.062), test the six-minute walk (p = 0.537), Lequesne hip (p = 0.802). There was also no statistical difference in the sonographic assessment (p> 0.1). The variable VAS global health, was the only one that evolved differently between groups over time (p = 0.023) with better intergroup evaluation for group 2. There were no significant adverse effects.

TABLE 1: General characteristics

	Overall N = 60	Group 1 N =30	Group 2 N = 30	
Age (years)/ Mean (± SDP)	54,1 (10,0)	54.2 (9,1)	53.8 (11,1)	p = 0,842
Time of diagnosis/Mean (± SDP)	32,2 (35,8)	33,6 (35,0)	30,9 (37,0)	p = 0,888
Gender F: M	59:1	29: 1	30: 0	p = 1,000
Etnic (W)	54	26	28	p = 0,800
Body mass index	27,6 (4,3)	27,17 (4,61)	28,02 (4,02)	p = 0,450
SD = standart desviation	F=female; M=male;	W = WHITE	qui-square; mann-whitney;T student	

Table 2: Assessement- pain

GROUP 1	VAS OF PAIN MEAN (±SD)	p intragroup	VAS OF PALPATION PAIN MEAN (±SD)	p intragroup	VAS OF EXTERNAL ROTATION MEAN (±SD)	p intragroup	VAS OF TESTE REPOSITION MEAN (± SD)	p intragroup
T0	6.7 (1.5)		7.5 (1.9)		6.9 (2.9)		5.90 (3.14)	
T1	3.5 (2.5)	p < 0.001	5.6 (3.0)	p < 0.001	4.3 (3.6)	p < 0.001	3.53 (3.57)	p < 0.001
T4	4.2 (2.8)	p = 1.000	5.7 (3.1)	p = 1.000	5.0 (3.3)	p = 1.000	3.60 (3.50)	p = 1.000
T8	3.4 (3.1)	p = 1.000	5.2 (3.2)	p = 1.000	3.8 (3.4)	p = 1.000	3.20 (3.38)	p = 1.000
GROUP 2								
T0	7.0 (1.3)		8.2 (1.5)		8.1 (1.2)		6.83 (3.04)	
T1	4.1 (3.2)	p < 0.001	6.8 (2.4)	p < 0.001	5.0 (3.2)	p < 0.001	5.20 (2.94)	p < 0.001
T4	4.1 (3.3)	p = 1.000	6.4 (2.9)	p = 1.000	4.6 (3.5)	p = 1.000	4.83 (3.34)	p = 1.000
T8	4.7 (3.5)	p = 1.000	6.3 (3.2)	p = 1.000	4.8 (4.0)	p = 1.000	4.47 (3.98)	p = 1.000
p intergroup	0.338		0.083		0.335		0.068	

SD: STANDART DEVIATION; ANOVA

TABLE 3: Assessement – tests

GROUP 1	Test "time up and go" (seconds) MEAN (±SD)	p intragroup	Test the six minutes walk (meters) MEAN (±SD)	p intragroup
T0	8.63 (1.81)		290.7 (58.8)	
T1	7.97 (1.33)	p < 0.001	335.4 (56.4)	p < 0.001
T4	8.07 (1.39)	p = 1.000	341.2 (62.5)	p = 0.362
T8	8.27 (1.70)	p = 1.000	336.8 (55.4)	p = 1.000
GROUP 2				
T0	10.17 (3.16)		263.7 (59.3)	
T1	9.27 (2.73)	p < 0.001	312.5 (62.3)	p < 0.001
T4	9.03 (2.22)	p = 1.000	328.0 (72.7)	p = 0.362
T8	8.67 (2.2)	p = 1.000	325.0 (70.0)	p = 1.000
p intergroup	0.038		0.191	

SD: STANDART DEVIATION; ANOVA

TABLE 4: Assessement – Lequesne and VAS global health

GROUP 1	LESQUESNE MEAN (±SD)	p intragroup	VAS GLOBAL HEALTH MEAN (±SD)	p intragroup
T0	12.50 (4.91)		7.0 (1.6)	
T1	6.37 (5.49)	p < 0.001	7.7 (1.5)	p = 0.176
T4	7.33 (5.29)	p = 1.000	7.3 (1.5)	
T8	7.47 (5.77)	p = 1.000	7.5 (1.7)	
GROUP 2				
T0	13.77 (4.01)		5.9 (2.3)	
T1	8.93 (6.30)	p < 0.001	7.1 (1.9)	p = 0.006
T4	9.17 (6.24)	p = 1.000	7.4 (1.5)	p = 0.005
T8	9.17 (6.84)	p = 1.000	7.6 (1.6)	p = 0.002
p intergroup	0.128		p = 0.023	

SD: STANDART DEVIATION; ANOVA

CONCLUSION

There are benefits when it comes to the patient's general perception, but according to this study, the effectiveness of ultrasound guided injection in GTPS patients was superior to subjective perception and ability to stand up.

Predictors Of Outcome Related To Intra-Articular Injection In Patients With Rheumatoid Arthritis: A Prospective Analysis.

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INTRODUCTION

Intra-articular injection (IAI) is a widely used procedure in clinical practice of rheumatologists. However, few studies have evaluated predictors of response related to it. Our objetive is to identify clinical variables related to better or worse response in short and medium terms in RA patients submitted to IAI with triamcinolone hexacetonide (TH).

MATERIAL AND METHODS

This case-control study is the result of analysis of five prospective, double-blind, randomised controlled trials conducted at Universidade Federal de São Paulo, Brazil. Only patients fulfilling the ACR criteria for RA with indication to receive IAI with TH (persistent synovitis despite of oral medication for at least one month) were included. In all five trials, patients were prospectively studied after they had been randomically allocated in two distinct groups, one of which was the IAI.

INCLUSION CRITERIA:

- RA (ACR criteria)
- Age between 18- 65 years
- Functional Class II or III (ACR criteria)
- Use of stable dose of DMARDs (last 3 months)
- Use of stable dose of systemic corticosteroid (last 4 weeks)
- Able to give written informed consent

EXCLUSION CRITERIA:

- IA steroid injections in any joint (previous 3 months)
- Suspicion of active systemic or IA infection
- Severe clotting disorder
- Any uncontrolled systemic disease (hypertension or diabetes mellitus)
- Allergy to the contrast or radioisotope agent

INTERVENTION:

IAI with TH (mono, pauci or polyarticular) was performed at a single time in the following joints: shoulder, elbow, wrist, metacarpophalangeal (MCP), knee and ankle. TH dose varied according to each joint as described below:

Joints	Dose
Shoulder	80mg (4ml)
Elbow	40 (2ml) or 60mg (3ml)
Wrist	30 (1,5ml) or 40mg (2ml)
MCP	10 (0,5ml) or 20mg (1ml)
Knee	40, 60 or 80mg
Ankle	40 or 60mg

ASSESSMENT:

In all five trials joints were evaluated by a "blinded" observer at T0 (baseline), T1 (1 week), T4 (4 weeks), T12 (12 weeks) and T24 (24 weeks).

Outcome measures: Visual Analogue Scale (0-10 cm) for joint pain at rest (VASr), during movement (VASmv) and for swollen joints (VASs).

The response to the IAI was evaluated according to percentage of improvement (%) of VASr, VASmv e VASs:

- **< 20%: no response**
- **20-50%: small response**
- **50-70% : moderate response**
- **> 70%: high response**

The studied clinical variables presented at baseline are:

age	sex	skin color	disease duration
rheumatoid factor	dose of TH (small=1, medium=2 and large=3)	functional class	joint type
extra-articular disease	total dose of TH (mg)	polyarticular injection	guided-injection
use of radioisotope or contrast agent	previous articular injection	use of DMARDS	use of NSAIDS or oral corticosteroids

RESULTS

We studied 289 patients with RA.

Demographic characteristics and characteristics related to the IA procedures are described below:

Mean age (years)	48.7 (SD 10.68)
Mean disease duration (years)	10.98 (SD 8.39)
Women-to-men ratio	12:1
Mono- injection	175 patients (60.55%)
Pauci- injection	68 patients (23.3%)
Poly- injection	46 patients (15.92%)
Joints studied through:	
• T0 – T4	635
• T0 – T12	403
• T0 – T24	313

The following variables were not statistically correlated to response to IAI: guided-injection, use of radioisotope and use of contrast agent.

The best outcome predictors to IAI after univariate analysis are shown in Table 1.

Table 1. Predictors to IAI after univariate analysis:

	VASmv			VASr			VASs		
	T4	T12	T24	T4	T12	T24	T4	T12	T24
Elbow	> 70%	-	-	-	-	-	> 70%	-	> 70%
Wrist	-	-	-	> 70%	-	50-70%	< 20%	< 20% 50- 70%	< 20%
MCP	< 20%	>70%	>70%	< 20%	>70%	>70%	>70%	< 20% >70%	>70%
Knee	> 70%	-	50- 70%	>70%	50- 70%	< 20%	-	50- 70%	>70%
Ankle	-	< 20%	-	-	-	-	-	< 20%	-
Dose of TH	3	3 3	3	3 3	3	3	3 3	3	3 3
Poly-injection	< 20%	< 20% > 70%	>70%	< 20%	< 20% >70%	>70%	< 20% >70%	< 20% >70%	< 20% >70%
Total Dose	< 20%	higher higher	higher	< 20%	lower higher	lower higher	higher higher	higher higher	higher higher
Age	younger	younger	younger	-	-	-	-	younger	younger
Sex	-	-	-	-	-	-	-	more men	-
Skin Color	-	NW NW	NW NW	W	NW	W NW	W	NW	NW
RF +	-	-	-	-	-	-	-	-	< 20%
FC	2	2	2	-	2	2	-	-	2
EAD	-	-	< 20% >70%	-	-	-	< 20% (less)	< 20% (more)	-
Disease Duration	longer longer	-	-	longer	-	longer	-	-	-
Chloroquine	lesser use	greater	-	-	-	-	lesser	lesser	-
MTX	lesser use	-	-	greater greater	-	-	lesser	greater	-
LFU	lesser use	lesser	lesser	lesser	lesser lesser	lesser	lesser lesser	lesser	lesser lesser
Total Medication	lesser	lesser	-	lesser	-	-	lesser lesser	-	-
Previous Injection	less	less	-	less	-	-	less	more less	-
NSAIDS T0	lesser use	-	-	-	-	-	>70%	lesser use	-
Co T0	-	-	-	-	-	greater dose lesser dose	greater dose	greater dose lesser dose	-

◆ < 20%
◆ 20- 50%
◆ 50- 70%
◆ > 70%

Statistical tests:
Qui-square
Kruskal-Wallis

NW (non-white); W (white); RF + (rheumatoid factor positivity); FC (functional class); EAD (extra-articular disease); MTX (methotrexato); LFU (leflunomide); Co T0 (dose of corticosteroid at baseline)

The multivariate logistic regression showed **simultaneous improvement > 50% in VASr, VASmv and VASs** in 208 joints at T4, in 183 joints at T12 and in 121 joints at T24. **Table 2** shows the variables associated with response to IAI at those times.

Table 2. Predictors to IAI after multivariate analysis:

VARIABLES	OR T4 208 Joints	p	OR T12 183 Joints	p	OR T24 121 Joints	p
Joint Type (compared to the knee):						
Elbow	-	-	-	-	4,4	0,008
Wrist	0,59	0,03	-	-	-	-
MCP	0,46	0,002			2,75	0,001
Shoulder	-	-	-	-	-	-
Ankle	0,55	0,03	-	-	-	-
Poly-injection (yes/no)	0,26	<0,0001	-	-	2,37	0,02
Sex (male/female)	2,19	0,008	-	-	-	-
Skin color (non-white/white)	2,47	<0,0001	-	-	0,55	0,04
Rheumatoid Factor (yes/no))	-	-	-	-	0,34	<0,0001
Functional Class (3/2)	-	-	0,47	0,001	0,42	0,003
DFC (yes/no)	0,61	0,03	-	-	0,52	0,03
MTX (yes/no)	-	-	-	-	1,76	0,05
Use of oral corticosteroid T0	-	-	-	-	0,95	0,02
Total Dose of TH	0,99	0,0001	-	-	1,004	0,02

Statistical test:
Multivariate Logistic Regression

OR: Odds Ratio
DFC : Chloroquine
MTX: methotrexate
TH: triamcinolone Hexacetonide

CONCLUSION

The clinical variables related to better response to IAI in the medium term in RA patients were: injection of the elbow and MCP and poly-injection.

References: Arnett FC, Arthritis Rheum1988. Hochberg MC, Arthritis Rheum, 1992. Felson DT et al, Arthritis Rheum 1995. Dougados M et al, Clin Exp Rheumatol 2007. Furtado RNV. Santos MF, Clinics (Sao Paulo) 2009.

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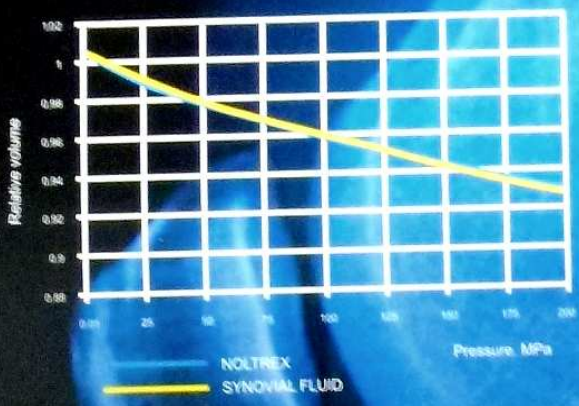
- Proven effect for up to 104 weeks

Viscosity close to natural

Belonenko V.N., Troitskiy V.M., Lopatin V.V., Zar V.V., 2002

Viscosity properties of Noltrex vs. synovia at t = 37 °C

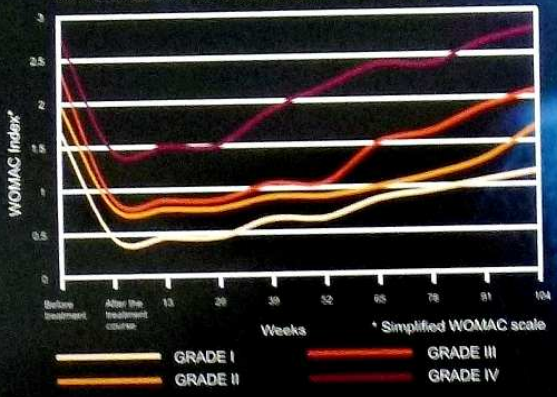


- replaces viscoelastic properties of the synovial fluid for extended period of time
- resistant to decomposition enzymes
- protects hyaline cartilage from damage and accelerates its reparation
- optimizes the metabolism of joint tissues
- performs mechanical stabilization of joint structures
- suppresses microbial colonization of the implant in the joint
- biocompatible
- causes neither allergic reactions

Exceeds all known biodegradable products in effect duration

Zagorodniy N.V., Zar V.V., 2006

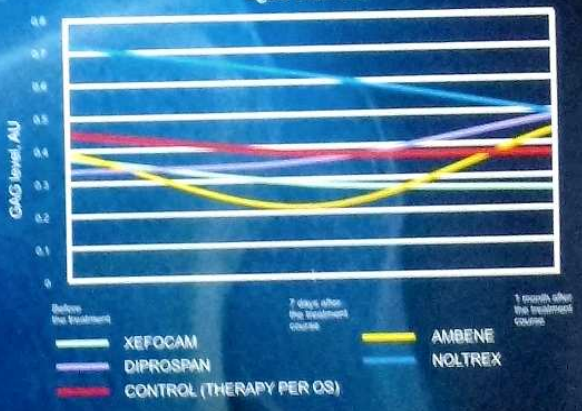
Dynamics of pain syndrome in treatment of 527 patients with unilateral and bilateral gonarthrosis, aged 57,2±7,3



Prevents hyaline cartilage destruction

Agibaeva Z.B., Ivanova R. L., 2007

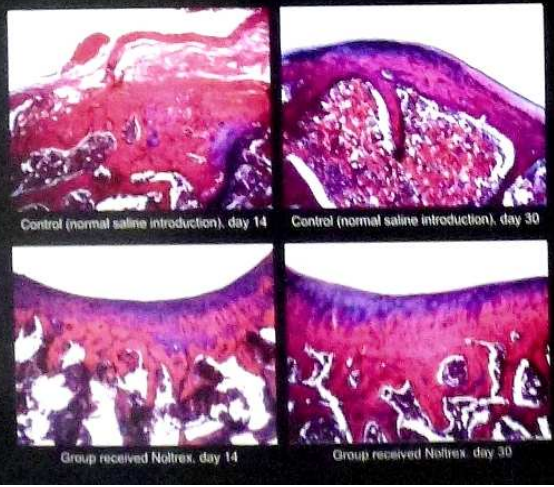
GAG level in plasma from 76 patients with gonarthrosis aged 55,5 ± 3,1



Accelerates reparative chondrogenesis

Slesarenko N.A., Shirokova E. O., 2011

Effect of Noltrex on cartilage condition in experimental animals (induced arthrosis animal model)



In clinical practice it has been shown a long-lasting effectiveness of multiple single-dosed 2.5 ml weekly injections as well as double-dosed monotherapy.

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Tel. +34 928 622 837
E-mail: osteof@telefonica.net

Single intra-articular treatment with 5ml of hyaluronic acid in patients with osteoarthritis of the knee: a randomized, pilot clinical trial compared with standard treatment.

Font P, Romero M, Castro MC, Caracuel MA, Ruiz D, Escudero A.
Rheumatology Department, Hospital Universitario Reina Sofía (IMIBIC), Avda. Menéndez Pidal s/n, 14004 Córdoba, Spain.

BACKGROUND

The efficacy and safety of intraarticular (ia) hyaluronic acid (HA) to treat osteoarthritis (OA) processes have been assessed in numerous clinical trials and meta-analyses.[1-4] Apart from reducing pain and improving articular function, it can normalize synovial fluid characteristics, decreasing synovial tissue inflammation and favoring articular cartilage reparation[5,6]. Tolerability is very good and compared to corticosteroids, HA effects are more lasting. Due to this, the number of patients treated with HA has increased exponentially.

In general, the standard treatment consists of 5 injections of 2.5 ml administered over one week intervals. However, there is a growing demand for shorter treatments which remain effective with a smaller number of visits and cost for both the patient and the hospital. This pilot study compares the efficacy and safety of two new dosing regimes to standard treatment in a population of patients with knee OA.

STUDY OBJECTIVES

To compare the efficacy of HA standard treatment with other two different dosing regimes in patients with primary knee OA. The tolerability of the regimes was also studied.

METHODS

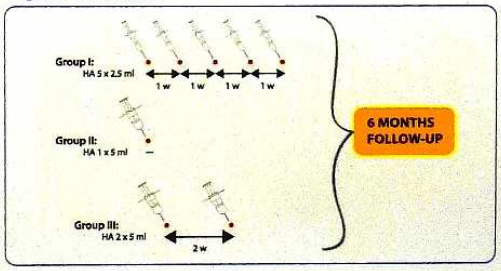
This is a pilot, prospective, unicentre, randomized, evaluator blind, controlled clinical trial with a 6-month follow-up period.

Patients with primary knee OA diagnosis, according to American College of Rheumatology Criteria[7] and radiological Kellgren-Lawrence (KL) grades[8] II-III, were randomly assigned 1:1:1 to receive HA* as follows:

- the standard treatment of 5 ia injections of 2.5ml at weekly intervals (Group I), or
- 1 single ia administration of 5ml (Group II), or
- 2 ia administrations of 5ml each with an interval of two weeks (Group III).

A follow up of six months after the last injection was scheduled (Figure 1). OMERACT-OARSI 2004 Responder Criteria[9] were used for primary efficacy evaluation. As it is a pilot study, p values <0.25 were considered relevant. Adverse events were recorded for safety purposes during all the study period and causal relationship with the treatments was assessed by the investigator using Naranjo's algorithm.[10]

Figure 1. Trial schedule



*Tedec Meiji Farma SA

RESULTS

From the 50 patients initially screened, a total of 45 were randomized 1:1:1 and allocated to Group I, Group II or Group III. All groups were homogenous at baseline and the main characteristics of study population are displayed in Table 1.

In total, 83% of the patients completed the 6-month follow up. At early follow up (1 month), the Groups I, II and III showed rates of OMERACT-OARSI responders (ITT population) of 80%, 67% and 53%, respectively (p=0.30). At late follow up (6 months), the OMERACT-OARSI responders' rate in the ITT population was 92% in Group I, 64% in Group II and 70% in Group III (p=0.21). No differences between Groups II and III were found at both early and 6-month follow up (p=0.46 and p=1.00, respectively) (Figure 2).

The Group II had a high number of patients with KL II at baseline. An additional stratified analysis by radiological degree (ITT) showed that, in Group II, patients with KL II had higher responders' rates than those with KL III (Figure 3).

The results in the PP population were in the same line.

With regards to safety, that of standard treatment it has been exhaustively proven and the present study did not find any adverse reaction from this group. The 5 ml treatment registered one adverse event consisting on an allergic reaction in a patient from Group III, of mild intensity which was considered as probably related.

Table 1. Baseline characteristics of randomized patients

	Standard treatment (n=15)	1 x 5ml (n=15)	2 x 5ml (n=15)	p-value (intergroup comparison)
Age, mean (sd)	61.1 (10.8)	61.8 (6.5)	65.0 (7.1)	0.40
BMI, mean (sd)	30.6 (4.7)	30.6 (3.9)	29.8 (4.3)	0.89
Overweight (BMI ≥30 kg/m²), n (%)	7 (46.7)	8 (53.3)	7 (46.7)	0.91
Sex, Male, n (%)	3 (20.0)	3 (20.0)	3 (20.0)	0.93
KL of the target knee, n (%)				
Grade II	9 (60.0)	12 (85.7)	8 (53.3)	0.28
Grade III	6 (40.0)	2 (14.3)	7 (46.7)	—

Figure 2. Efficacy results: OMERACT OARSI Responder Criteria

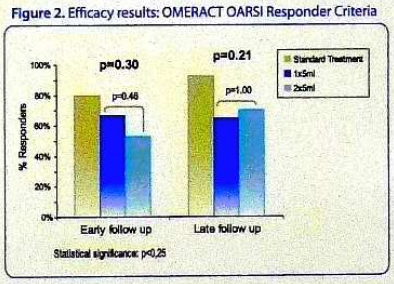
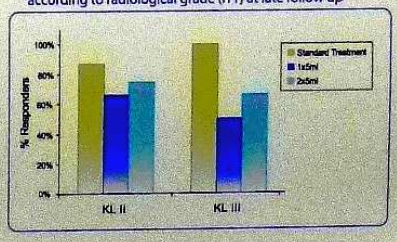


Figure 3. Percentage of responders OMERACT-OARSI according to radiological grade (ITT) at late follow up



CONCLUSIONS

- The three regimes evaluated in this clinical trial provided clinical improvement up to 6 months with no safety concerns.
- At the end of follow up, the standard treatment (Group I) achieved statistically significant differences in responders' rates vs short treatments (Groups II & III).
- No differences between short treatments were found.
- A single dose of 5ml could be an effective option for patients with mild OA KL II or wehere shorter treatments are preferred.

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APPLICATION OF PLATELET-RICH PLASMA IN THE TREATMENT OF KNEE OSTEOARTHRITIS. A PROSPECTIVE STUDY.

Víctor Vaquerizo García, Ester Montes Martínez, Marta García López, Miguel Angel Plasencia
Príncipe de Asturias University Hospital

INTRODUCTION

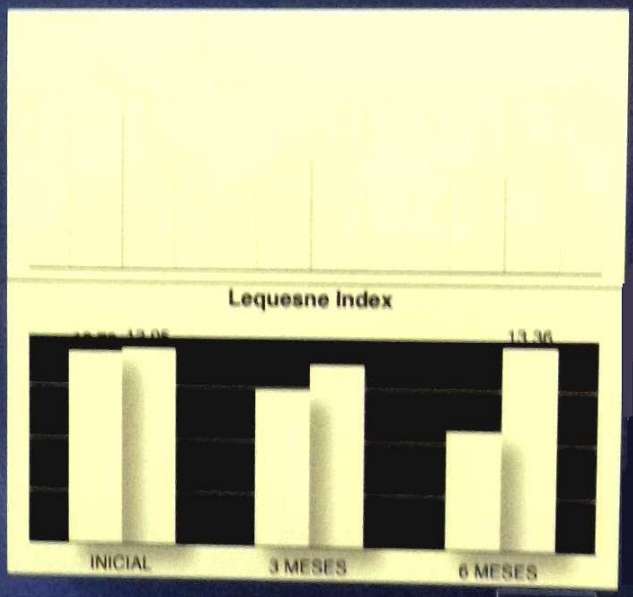
Osteoarthritis is one of the most prevalent diseases and represents a high health and social costs. The aims of medical treatment of Knee OA are the control of symptoms and modify the natural history of the disease. All have limitations as the adverse effects of NSAIDs present, both gastrointestinal as hepatotoxicity and nephrotoxicity, or a loss of efficiency over the medium term. The Plasma Rich in Growth Factors (PRGF ®-Endoret ®) is a new technology whose objective is the regeneration of injured tissues. For this reason the aim of our study was to assess the effectiveness at 6 months of treatment with PRGF compared with hyaluronic acid in patients with Knee Osteoarthritis.

MATERIAL AND METHOD

A prospective clinical trial, single-blind masked and blinded evaluation was performed in June 2011. 96 patients were selected. The distribution of the patients was performed using a simple randomization process in two homogeneous groups. The effect assessment was performed according the results of the questionnaires of Health Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Lequesne Index.

Epidemiological data

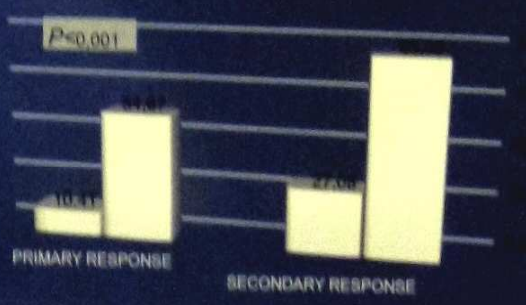
		GLOBAL	PRGF-ENDORET	DUROLANE	P
AGE		63,61 ± 7,24 (50-84)	62,44 ± 6,62 (50-77)	64,79 ± 7,7 (51-84)	0,11
BMI	kg/m²	30,85 ± 4,12 (20,7-42,9)	30,7 ± 3,61 (21,96-40,96)	30,99 ± 4,61 (20,7-42,9)	0,727
KELLGREN	II	32 (33,3%)	14 (29,2%)	18 (37,5%)	0,665
	III	47 (49%)	26 (54,2%)	21 (43,8%)	
	IV	17 (17,7%)	8 (16,7%)	9 (18,8%)	



RESULTS

There were no statistically significant differences between both groups. The mean age was 63.61, SD ± 7.24 years. The gender distribution of the patients was 39.6% men and 60.4% women. 122 knees were infiltrated. A total of 16 patients presented complications, 2 cases of arthritis transitory in the control group (4.2%) and 7 cases of pain secondary to knee infiltrated infiltration (14.6%). On the other hand, in the group of PRGF-Endoret 7 patients (14.6%) had pain during infiltration.

At 6 months follow-up patients of PRGF-Endoret group showed an improvement of the WOMAC scale of 40.72% respect the initial score, 39.94% compared to the control group. Both differences are statistically significant (p<0.001). In case of Lequesne index, patients have presented an absolute improvement of 20.5% compared to its previous level and 22.88% when compared with the final score in the control group.



Finally, to assess the effectiveness of treatment with PRGF-Endoret, we value the results according to the criteria of the OMERACT-OARSI. According to these criteria we obtained 54.67% of patients with a primary response to treatment with PRGF-Endoret and 83.33% of patients with a secondary response to treatment.

DISCUSSION

In the last 10 [illegible] osteoarthritis. In fact there are few clinical trials comparing the effectiveness of PRP regarding hyaluronic acid. One of the major problems raised by published studies is that each has used different AH as a control group so it is possible to question the results by type of AH.

The present study shows that the application of plasma rich in growth factors, PRGF-Endoret ®, is an effective treatment for patients with knee osteoarthritis and therefore we indicated its standardization as a treatment for knee OA. The Plasma rich in [illegible] AHs for improving the quality of life and functional capacity of patients to 40%.

REFERENCES

Efficacy of Knee OsteoArthritis Viscosupplementation Treatment by Combined Hyaluronic Acid and Sorbitol According to Radiographic Severity or Initial Pain Level

Dr. T. CONROZIER– Belfort Hospital - France
Dr. C. KIPSHOVEN – Rottapharm / Madaus – Germany
F. RADENNE – Anteis - Switzerland

Background

Synolis V-A is a visco-antalgic formulation indicated for viscosupplementation in OsteoArthristis. Synolis V-A is composed of highly concentrated non-crosslinked hyaluronic acid (2%) from biofermentation origin combined with a high concentration of sorbitol (4%). Sorbitol is an endogenous molecule which functions as an oxygen free radical (OFR) scavenger. Rapid and strong pain reduction in patients with knee OsteoArthritis (OA) has been observed in several previous studies using Synolis V-A.

Objective

To compare the effectiveness of two dosing regimen (single injection vs. 3 injections one week apart) according to the radiographic and clinical severity.

Patients and Methods

Among 1147 patients with a majority suffering from knee Osteoarthritis (92.9%) enrolled in a Non-Interventional Study conducted by Rottapharm Madaus in 398 centres in Germany following recommendations from the BfArM (Federal Institute for Drugs and Medical Devices) and the Paul-Ehrlich-Institute, 455 patients met the inclusion criteria (reported Kellgren-Lawrence grade and initial pain level at week 0, week1 and/or week 24) and received either 1 or 3 injections of Synolis V-A 2ml (GO-ON matrix in Germany) one week apart – *figure 1*.

The studied population was grouped according to radiographic severity using Kellgren-Lawrence (K-L.) grading system. Two groups were defined: K-L I/II & K-L. III/IV – *figure 2*.

Four sub-groups according to the K-L. Grading and the number of injection of Synolis V-A 2ml were then analyzed: Low K-L. (Gr. I/II)-1 injection; Low K-L.-3 injections; High K-L. (III/IV)-1 injection and High K-L.-3 injections .

This same population was evaluated for Walking Pain (WP) at baseline, using 5-point Likert scale. Level of pain observed was None (1.1%), Mild (8.6%), Moderate (35.8%), Severe (45.1%), Very Severe (7.5%) and Not Reported (2.0%) – *figure 3*.

Four sub-groups according to the Likert score before treatment initiation and the number of injections of Synolis V-A 2ml were then analyzed: Low Pain (mild to moderate)-1 injection; Low Pain-3 injections; High Pain (severe to very severe)-1 injection and High Pain-3 injections

The analysis compared the average response (pain decrease vs. baseline) between sub-groups on the short-term (week 1) and on the mid-term (week 24) following treatment initiation.

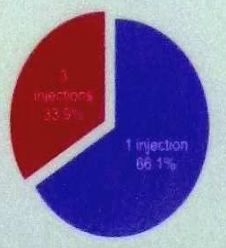


figure 1: Patients repartition by number of injections

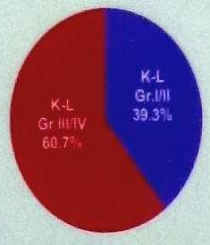


figure 2: Patients repartition based on their Kellgren-Lawrence Grade

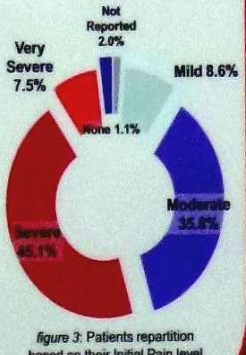


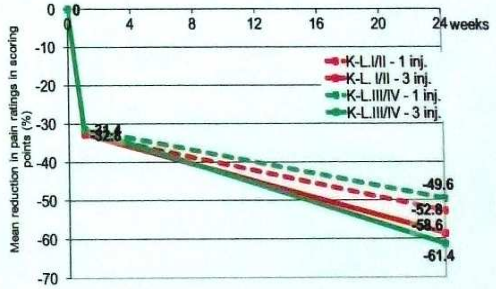
figure 3: Patients repartition based on their Initial Pain level

Results

At week 1, pain decrease in both Kellgren-Lawrence groups (K-L. I/II & III/IV) was similar, with an average pain decrease of 32.6% and 31.4% respectively (p=0.7354) but significant vs. baseline (p<0.001).

At week 24, 3 injections provided greater pain relief than single injection whatever the patients' sub-groups. Never the less, for the K-L. I/II group, the 3-injection regimen brought 11% additional average pain decrease vs. the 1-injection (p=0.0363), whereas for the K -L. III/IV group, the 3-injection regimen brought 24% additional pain decrease vs. the 1-injection (p=0.0003) – *figure 4* .

figure 4: pain decrease in scoring points (%)

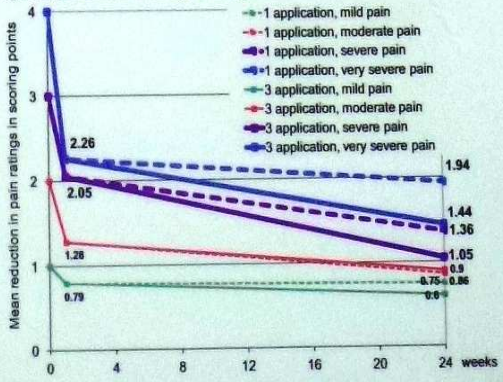


In WP based groups (Likert scores 1, 2, 3 & 4) at week 1, pain decrease correlated to the pain score observed at baseline: Patients with very severe pain scored an average of 1.74 points below; Patients with severe pain scored 0.95 points below; Patients with moderate pain scored 0.72 points below and patients with mild pain scored 0.21 points below.

At week 24, average pain (for patients with Mild to Very Severe pain receiving 1 or 3 injections) dropped by 56.5% from an average baseline score at 2.52.

More precisely, pain scores reported at week 24 after 3 injections were significantly lower than after 1 injection for Very Severe and Severe initial pain, with respectively 26% and 23% better average score. This difference was not observed for Moderate to Mild initial pain – *figure 5*

figure 5: pain decrease in average scoring points



Conclusion

At week 24, average pain decrease vs. baseline was correlated to both the number of injections and the radiographic severity, with a higher benefit of the 3-injection regimen for K-L Gr. III/IV, despite the absence of observed correlation at week 1.

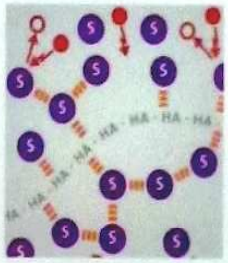
A fast pain relief proportional to the initial pain level has been observed soon after the first injection of Synolis V-A (week 1). Despite the pain decrease trend preserved until week 24 even with one single injection, patients with Very Severe to Severe pain at baseline particularly benefited from the 3-injection regimen.

Knee OsteoArthritis Radiographic Severity and Initial Pain Level Influencing Short and Mid-Term Response Rate After Viscosupplementation Treatment by Combined Hyaluronic Acid and Sorbitol

Dr. T. CONROZIER– Belfort Hospital - France
Dr. C. KIPSHOVEN – Rottapharm / Madaus – Germany
F. RADENNE – Anteis - Switzerland

Background

Synolis V-A is a visco-antalgic formulation indicated for viscosupplementation in OsteoArthristis. Synolis V-A is composed of highly concentrated non-crosslinked hyaluronic acid (2%) from biofermentation origin combined with a high concentration of sorbitol (4%). Sorbitol is an endogenous molecule which functions as an oxygen free radical (OFR) scavenger. Rapid and strong pain reduction in patients with knee OsteoArthritis (OA) has been observed in several previous studies using Synolis V-A.



Objective

We hypothesize that one of the dimensions of average pain reduction is a variable response rate to treatment. In addition, we hypothesize that this variable response rate could be associated to radiographic severity, initial pain level and intra-articular injection regimen.

Patients and Methods

Among 1147 patients with a majority suffering from knee Osteoarthritis (92.9%) enrolled in a Non-Interventional Study conducted by Rottapharm Madaus in 398 centres in Germany following recommendations from the BfArM (Federal Institute for Drugs and Medical Devices) and the Paul-Ehrlich-Institute, 455 patients met the inclusion criteria (reported Kellgren-Lawrence grade and initial pain level at baseline, at week1 and/or at week 24) and received either 1 or 3 injections of Synolis V-A 2ml (GO-ON matrix in Germany) one week apart.

This population was then grouped according to two severity evaluation factors:

- Two groups were created according to Kellgren-Lawrence (K-L) based severity (K-L.) I/II (39.3%) & K-L. III/IV (60.7%) – *figure 1*.
- Two groups were created according to Walking Pain (WP) at baseline (5 points Likert scale): None (1.1%), Mild (8.6%), Moderate (35.8%), Severe (45.1%), Very Severe (7.5%) and Not Reported (2.0%) – *figure 2*. The Low Pain group combined patients with Mild/Moderate pain and the High Pain group combined patients with Severe/Very Severe Pain.

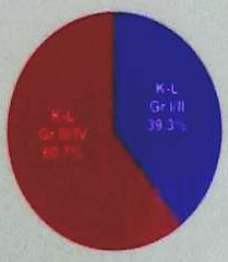


Figure 1: Patients repartition based on their Kellgren-Lawrence Grade

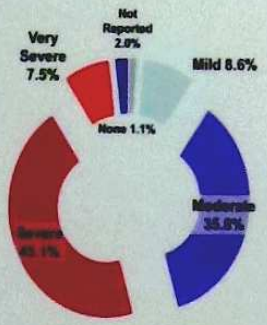


Figure 2: Patients repartition based on their Initial Pain level

Two analyses were conducted comparing at week 1 and week 24 vs. the rate of responders for both 1 and 3 injections regimen vs. baseline, for Low K-L. (I/II) and High K-L. (III/IV) on one hand, and for Low Pain (Mild to Moderate) and High Pain (Severe to Very Severe) on the other hand.

Patients defined as responders were patients with pain decrease of at least 1 point on the Likert scale vs. baseline.

Results

For both Low and High K-L patients groups, the percentage of responders was similar at week 1 with respectively 68.6% and 66.1%.

At week 24 all sub-groups of patients (Low and High K-L groups receiving either 1 or 3 injections) obtained an average response rate above 80%. However, when patients from the Low K-L group receiving 1 or 3 injections and patients from the High K-L goup receiving 1 injection had comparable average response rate, comprised between 81.3% and 82.7% of responders; patients from the High K-L group who received 3 injections obtained a much higher responders rate of 93.1% - *figure 3*.

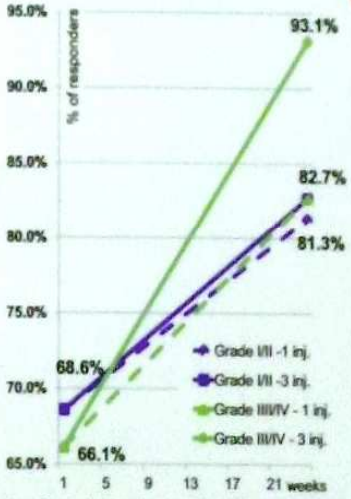


figure 3: rate of responders according to K-L and inj. regimen

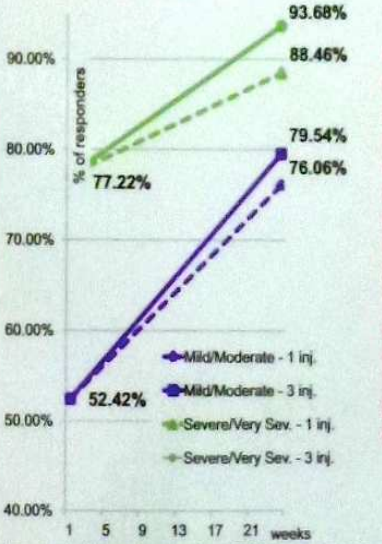


figure 4: rate of responders according to WP Pain and inj. regimen

On the other hand, the percentage of responders between Low Pain and the High Pain groups was different right from week 1 with respectively 52.4% and 77.2%.

At week 24 all sub-groups of patients (Low and High Pain groups receiving either 1 or 3 injections) obtained response rate above 75%. Three injections regimen always provided better response rate vs. 1 injection regimen with respectively 79.5% vs. 76.1% for the Low Pain group and 93.7% vs. 88.5% for the High Pain group – *figure 4*.

Conclusion

This study suggests that the fast average pain relief commonly observed after the first injection of Synolis V-A could partly be explained by the high number of responders reported at week 1 (67.1%).

On the short-term, the initial pain level seemed to be a better predictor of response rate, with a response rate 47.3% higher for High vs. the Low Pain group; which could be explained by the non-linear pain scoring system used.

At week 24, the radiographic severity seemed to be an efficient indicator for adapting the injection regimen, suggesting the use of 3 injections for K-L Gr. III & IV patients since the observed response rate was 12.6% higher than for the single regimen.

International Symposium Intra Articular Treatment

3-5 October 2013

Observational study on the efficacy and safety of administration of cross-linked hyaluronic acid on hip osteoarthritis. Follow up at 12 months.

Wolenski Luciano M.D., Wolenski Valentina M.D.

INTRODUCTION

Among the various preparations of cross-linked hyaluronic acid (HA), safety of administration of Hylastan SGL-80 can be considered also in hip osteoarthritis, even when associated with elevated clinical and ultrasound signs of phlogosis. Treatment often includes systemic NSAID or COXIB - based therapy. However, the presence of inflammation together with a high radiological grading of disease (III-IV Kellgren-Lawrence) are closely related to the reduction of treatment effectiveness.

AIM

This study aimed to evaluate efficacy and safety of hylastan SGL-80 administration in patients affected by hip osteoarthritis in clinical practice.

MATERIALS AND METHODS

30 patients affected by hip osteoarthritis and treated with hylastan SGL-80 were included in the study, performed between April 2012 to April 2013. 18 subjects were affected by a primary form of disease and 12 by secondary form. Characteristics of patients affected by secondary form of OA as follow: 5 post traumatic OA (2 with acetabular fractures and 3 with diaphyseal and cervical femoral fractures); 3 with previous DCA; 1 with previous juvenile femoral epiphysiolysis; 3 with arthrosis post arthritis (2 psoriasic arthritis, 1 rheumatoid arthritis).
All patients were Kellgren-Lawrence grade I-II and were negative to meniscal calcifications, as assessed by RX. The localization of the disease was on the right in 21 patients and on the left in 9. At recruitment mean age was 62.5 years (range 41-85) and BMI 27.5 (range 24-31).
Each patient received 3 intra-articular Hylastan SGL-80 infiltrations under ultrasound guide at 0, 1 and 6 months. Clinical, functional and sonographic assessments were performed at 0, 6 and 12 months and compared to baseline. V.A.S. scale (visual analogue) and the WOMAC index (in its three areas A, B, C) were used as algometric index. Variations of the distance between capsule and bone and the presence of "spot" to the vascular power Doppler (PWD), were used for ultrasound evaluation.
8 patients exhibited ultrasound important effusion, arthrocentesis-mediated (capsule-bone distance equal to or greater than 10 mm). Of these patients only two had positive PWD signal. All patients were treated in the 15 days preceding the first injection with either naproxen or etoricoxib depending on the co-existence or absence of CV risk. They belonged to 2 of the 3 post-arthritis OA patients were in this group. The latter patients did not report positive vascular signals at PWD thus indicating a non-active synovitis. One case of 30 patients with an important ileum-psoas bursitis was treated with needle-aspiration at month 0, 1 and 6. The same treatment was performed at the 8 patients with synovial implication.

INFILTRATIVE TECHNIQUE

The US-guided infiltrative therapy was performed with mono-operator technique (caudal-cranial) and with either anterosuperior Migliore-Tormenta Technique (Fig. 1, 2) or antero-inferior access (Fig. 3, 4). Note that for the ileum-psoas bursa effusion aspiration the needle was located caudally and a bit medially (with respect to the intra-articular injection point) passing below the neurovascular bundle (fig. 10). The latter technique was used in the 8 cases with effusion >10mm undergoing arthrocentesis before each infiltration. A linear 10-5MHz frequency probe was employed in both accesses with ultrasound Siemens Acuson X150. The "field" image of this linear probe is a less wide than that of the convex. Due to the viscosupplementant injected, a spinal needle of 20 Gauge was used. This needle was well tolerated also in those patients with scarce subcutaneous adipose tissue. It must be also taken into consideration that the "size" determines the optimal vision to follow the trajectory during the procedure.

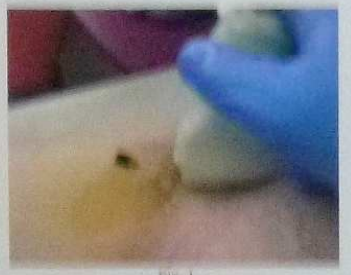


Fig. 1

Fig. 2

Fig. 3

Fig. 4

RESULTS

At 6 months 80% of patients had a statistically significant improvement in clinical and functional outcome. In this group of patients 9 were grade I and 5 grade II (respectively 40.90% and 22.72%). At 12 months percentage of patients with significant improvement increased to 78%. The remaining 22% of patients showed no worsening of algo-functional index. Only 2 patients (1%) interrupted the treatment at 6 months (drop out<10%). No local or systemic adverse event were registered at any time.
From 6 to 12 months there is an increase in the " gap" between the results on patients staged I or II. The first increased from 9 to 15 while the others from 5 to 7 (40.90-68%, 18% vs 22.72% -31.81 %). Regard to the VAS scale the average score was 7.6 at time 0, it was reduced to 4.1 at 6 months and to 2.9 at 12 months (Fig. 5). The average total WOMAC index at time 0 was 62.40 %, decreasing to 31.80 % at 6 months and to 17.2% at 12 months (Fig. 6).

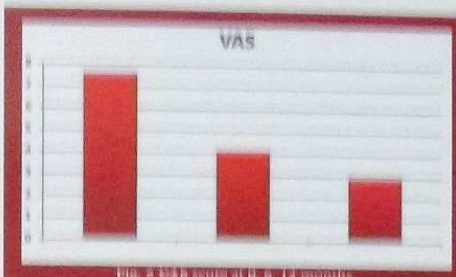


Fig. 5 VAS score at 0, 6, 12 months

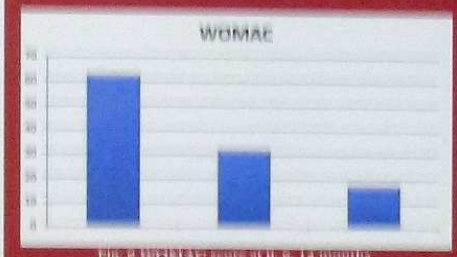


Fig. 6 WOMAC score at 0, 6, 12 months

In our experience, other preparations even with lowest molecular weight, it can sometimes happen to find presence hyperechoic intra- capsular microcrystalline-like forms of the injected HA into the joint, even later than 6 months after the injection. US did not expose any sign of presence of Hylastan SGL-80 residues, not even 1 month later than the first injection.
At baseline, in the 20 patients with no effusion, the capsule -bone distance measured from a minimum of 3.4 to a maximum of 6.4 (average value: 4.9); moreover in 6 cases it was between 5.8 and 7.2 mm at 6 months (a.v. 6.3), reducing at 4 to 4.1 mm at 12 months. At 1 year follow-up, all 20 had values in the range between 2.4 and 4.2 (a.v. 3.3) resulting a percentage decrease of 32.65% . Among the 8 cases with US important effusion, it ranged at baseline from 10 to 12.6 (a.v. 11.3). At 6 months 2 cases (both primary forms 1 M and 1 F) had a decrease of 3 and 4.2 mm while it remained unchanged in the other 6 (with a decrease <10 %). At 12 months, just 1 patient showed a total absence of effusion with a decrease of the distance capsule - bone > 65% (from 11.4 mm at baseline to 3.6 mm) .
The vascular Power Doppler signal did not change in 2 of the 8 cases with effusion at 0, 6 and 12 months indicating that the presence of moderately active synovial inflammation remained unchanged. The effusion in the ileum-psoas bursa associated with primary osteoarthritis (stage II) found at 6 months was totally absorbed at month 12.

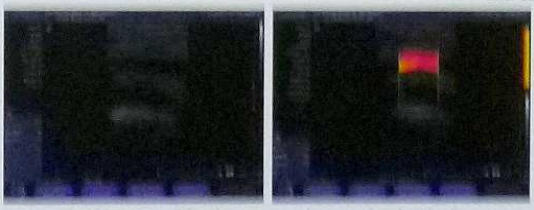


Fig. 7a-7b: US image of the ileum-psoas bursitis (under the femor vessels) without (a) and with (b) PWD signal

Fig. 8: US image of Hylastan SGL-80 injection in the joint: hyperechogenic stripe below the capsule without rear shadow-cone

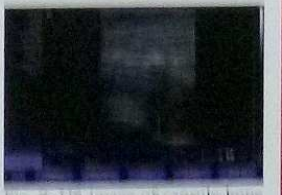


Fig. 9: US image of capsule-bone distance calculation to compare with the contralateral hip

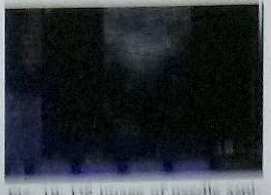


Fig. 10: US image of needle aspiration of the ileum-psoas bursa effusion

CONCLUSIONS:

Results analysis of the study shows a significant increase in the "gap" between stage I and stage II during the transition from 6 to 12 months. This shows that the "symptomatic" benefits of long half-life HA in the long term regards mostly patients with mild to moderate structural damage with respect to those with medium severity.
Our study shows that viscosupplementation with last generation cross-linked HA preparations could be an advantageous method in terms of compliance and safety even in patients presenting with important arthritic synovitis. However, efficacy is inversely related to disease grade and influenced by the presence of abundant effusion, especially when the latter is persistent during treatment or relapses rapidly after arthrocentesis. Finally, the results show that most responsive cases were those with less severe radiological grade disease and with little or no sonographic signs of inflammation. For this reason a preliminary integration among various imaging methods is necessary before treatment.

ULTRASOUND GUIDED DISTENSION WITH SALINE SOLUTION AND SELECTIVE INJECTION OF CORTICOSTEROIDS AND HYALURONIC ACID IN SUBACROMIAL BURSA (SAB) FOR SHOULDER IMPINGEMENT SYNDROME (STAGE II NEER) TREATMENT

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PURPOSE

To assess the effectiveness of ultrasound (US) guided distension with saline chaser followed by selective injection of corticosteroids and hyaluronic acid in subacromial bursa (SAB) in shoulder impingement syndrome stage II Neer for treating inflammation and restore the mechanical function of the bursal buffer.

Impingement syndrome represents the most common cause (about 80%) of chronic pain and restricted shoulder movement.

Neer described three stages of impingement: stage 2 tipically affects patients aged 25-40, represents irreversible changes, such fibrosis and tendinitis of the rotator cuff tendon which usually does not respond to conservative treatment.

Diagnosis is based on the clinical examination and imaging (including standard radiographs, ultrasonography and magnetic resonance).

Management includes physical therapy, injections, and, for some patients, surgery.

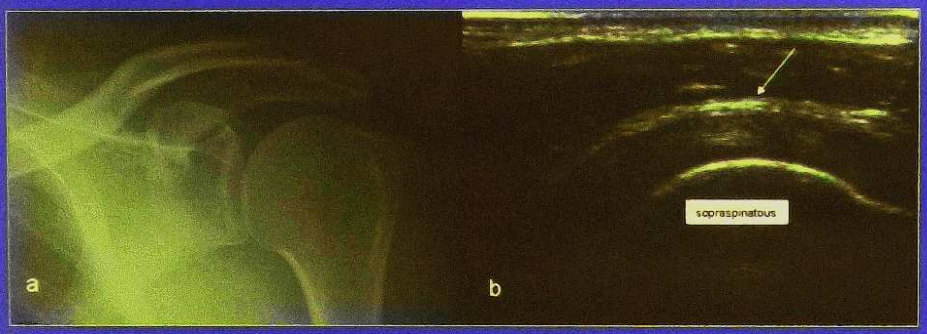


Fig.1 No radiological bony changes are observed (a); at US is appreciable the thickening of the SAB (arrow) without effusion or irreversible lesion such as tendon tears (b).

MATERIALS AND METHODS

From 2010 to 2012 we have selected 129 patients with painful shoulder, they were classified as affected by shoulder impingement syndrome, stage II Neer, after radiological and US evaluation (fig.1) and treated by US guided distension with saline chaser followed by injection of corticosteroids and hyaluronic acid in SAB (fig.2). The procedure was performed percutaneously, using a sterile technique, with US guidance and local anesthesia puncturing selectively the SAB with a 16G needle, respectively for the mechanical rupture of intrabursal adhesions with saline chaser and for the selective injection of corticosteroids and low molecular weight (750 kDa) hyaluronic acid. US constant monitoring (with 7-12 MHz linear transducer) depict the correct positioning of the needle tip inside the SAB and shows the progressive fluid distension of the same (fig. 3). Clinical improvement after treatment was evaluated using a standard ten points visual analogic scale (VAS-score), comparing post-procedural score, assessed at 3 and 6 months after treatment, with the pre-procedural value.

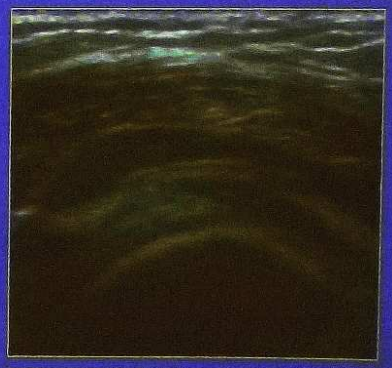


Fig.3 Us monitoring shows the progressive mechanical detachment of intrabursal fibrous septa and adhesions that are usually followed by reduction of symptoms.

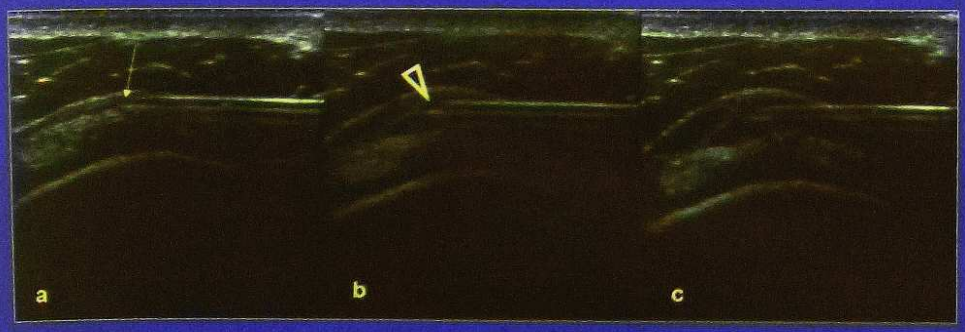
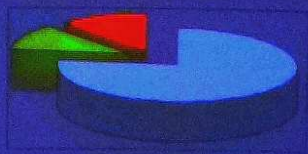
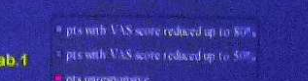


Fig2. US monitoring during the procedure: the needle tip is inserted into the thickened SAB (arrow a); during the injection a bursal distension (arrowhead b) can be appreciated (b-c).

RESULTS



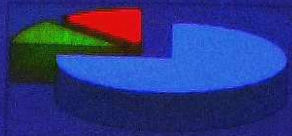
Tab.1



3 months after treatment a clinical improvement was observed (VAS score reduced up to 80% in 89 patients, and 50% in 36 patients) while 4 cases resulted unresponsive (tab.1). The cases unresponsive to the treatment were revaluated and ascribed to an incorrect enrolment. At 6 months the same results where confirmed in 110 patients with the exception of 15 cases in whom shoulder pain recurred (tab.2). The explanation of recurrence is the persistence of more factors underlying chronic impingement.

CONCLUSIONS

Our data suggest how the distension with saline chaser followed by selective injection of corticosteroids and hyaluronic acid in SAB, achieved by US guidance, provides a significative improvement of pain and function in patients affected by shoulder impingement syndrome. This clinical outcome was related both to the biochemical effects of corticosteroids and hyaluronic acid and the mechanical rupture of intrabursal post-inflammatory adhesions by the saline solution.



Tab.2

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Epidural injection with corticosteroid via sacral hiatus for treatment of cronic refractory lombosciatalgia

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Introduction:

The epidural injection with corticosteroid is one of the options for the treatment of refractory lombosciatalgia (RL). The Hiatus Sacralis can be used as access way for this procedure. It isn't estabilished in the literature whether the effectiveness of this procedure is related to the number of injections repetitions, or the predictive good response factors to it.

Objectives:

-To compare the effectiveness of the corticosteroid epidural injection via Hiatus Sacralis (EIHS) (pain, function and perception of improvement) according to the number of repetition (from 1 to 3). To identify which number of epidural injection repetition was related to the greatest pain improvement. To compare the EIHS effectiveness regarding the presence of spinal canal stenosis and fibromyalgia.

Material and methods:

It was carried out a controlled study with 59 adult patients with chronic lombosciatalgia refractory to the clinical treatment

Intervention:

-Patients were divided in two groups, according to the number of EIHS administered:

Group 1 — 3 EIHS (n=25)
- T0- injection 1
- T1- injection 2 + evaluation
- T2- injection 3 + evaluation
- T7- no injection, just evaluation

Group 2 — 2 EIHS (n=34)
- T0- injection 1
- T1- injection 2 + evaluation
- T2- no injection, just evaluation

-Injections were administered blindly, with a one-week break between each other. Prednisolone acetate (40 mg) was the corticosteroid used and xylocaina (2ml) plus saline solution (10ml) was used preceding the injection. Posterior 40-minute bed rest was oriented.

Assessment:

The patients were evaluated, by a blind observer, in the following times: T0 (baseline), T1 and T2 weeks after the EIHS in Group 2 and T0 (baseline), T1, T2 and T7 weeks after the EIHS in Group 1.

Assessment instruments: -Visual Analog Scale for pain (0-10cm) (VAS); -Roland Morris functional questionnaire (RM); -Scale (1-5) of improvement evaluation (Likert Scale).

Results:

The groups were similar according to demographic characteristics (table 1). Eighteen patients had fibromyalgia diagnosis and 28 spinal canal stenosis. In group 1, improvement of pain VAS related to T0 was observed in T1 (p=0.006), T2 (p<0.001) and T7 (p=0.011). Furthermore, in T7, the improvement of pain was statistically different just from T0, that is, this improvement wasn't different from T1 and T2 (p=1.000 and p=0.830). Group 2 has improved of pain VAS in T1 and T2 (p<0.001). Improvement in RM related to T0 was observed in T2 (p<0.016) and in T7 (p=0.032) in group 1 and in T1 (p=0.17) and in T2 (p<0.001) in group 2. In group 1, neither T7 was stastically diferent from T1 and T2 (p=1.000 for both) nor was T1 from T0 (0.953). The two-week evaluation (T2) (after 2 EIHS) was the greatest improvement time of pain VAS and of RM. There was no difference intra and intergroups for the Scale of improvement (Likert Scale). There was no difference between Groups 1 and 2 in the analysis of the variables VAS, RM and Scale of improvement. There was no difference in the subanalysis according to the presence or absence of either fibromyalgia or spinal canal stenosis

Table 1: Demographics characteristics

	General Group N=59	Group 1 3 EIHS N=25	Group 2 2 EIHS N=34	
Age (years) Mean (± SDP)	59.50 (16.8)	63.9 (13.5)	55.6(18.7)	p=0.123
Gender (F:M)	32:27	15:10	17:17	p=0.446
Skin color (white)	28	13	15	p=0.824

SD= standard deviation; F=female; M=male; B=branco; qui-square; mann-whitney

Table 2: Evaluation: Pain VAS and Roland Morris

	VAS of PAIN Mean (± SD)	p intragroup	ROLAND MORRIS Mean (±SD)	p intragroup
GROUP 1 N=25				
T0	7.09 (1.59)		17.71 (3.32)	
T1	5.87 (1.63)	p=0.006	16.38 (4.07)	
T2	4.09 (2.13)	p<0.001	12.71 (4.97)	p<0.016
T7	5.13 (2.51)	p=0.011	14.33 (6.61)	p=0.032
GROUP 2 N=34				
T0	7.03 (2.04)		17.17 (5.24)	
T1	5.90 (2.53)	p<0.001	15.47 (5.47)	p=0.017
T2	5.03 (2.79)	p<0.001	14.20 (6.76)	p<0.001
p intergroup	p=0.143		p=0.166	

SD= standard deviation; ANOVA

Conclusion:

There was no difference between two or three EIHS in this sample of patients with RL. The greatest effectiveness for pain and function was observed with 2 EIHS. There was no effectiveness difference of the EIHS according to the presence or absence of fibromyalgia or spinal canal stenosis in these patients.

Effectiveness of imaging-guided intra-articular injection: A comparison study between fluoroscopy and ultrasound

Rheumatology Division of Universidade Federal de São Paulo, Brazil

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Introduction:

Intra-articular injections (IAI) with glucocorticoids have been used for more than half a century for the treatment of refractory articular disorders. Imaging methods easily available, such as ultrasound (US) and fluoroscopy (FC) can be used to guide IAI and improve its accuracy , especially in deep joints with the greatest chance of technical error, such as the hip.

Objective:

Compare the effectiveness between ultrasound and fluoroscopy to guide intra-articular injections in selected cases.

Material and Methods:

A prospective study in our outpatient clinics at the Rheumatology Division at UNIFESP, Brazil was conducted to compare the short-term (04 weeks) effectiveness of ultrasound and fluoroscopy-guided IAI in patients with rheumatic diseases.

Adults with refractory synovitis undergoing IAI with glucocorticoid. All patients had IAI performed with triamcinolone hexacetonide (20mg/ml) with varying doses according to the joint injected.

Inclusion criteria:

- age between 18-65 years-old; - adults with refractory synovitis; - synovitis with duration of at least 01 month

Excluded Critéria:

- uncontrolled hypertension or diabetes mellitus; - damage of any kind to the skin site to be punctured; - suspected infection; - severe clotting disorder; - known allergy to contrast media

Results:

A total of 71 rheumatic patients were evaluated (52 women, 44 whites). Mean age was 51.9±13 years and 47 of them (66.2%) were on regular DMARD use (table 1). Analysis of the whole sample (71 patients) and hip sub-analysis (23 patients) showed that significant improvement was observed for both groups in terms of pain ($p < 0.001$) (table 2) (table 3). Global analysis also demonstrated better outcomes for patients in the FC in terms of joint flexion ($p < 0.001$) and percentage change in joint flexion as compared to the US (table 2). Likert scale score analyzes demonstrated better results for the patients in the US as compared to the FC at the end of the study ($p < 0.05$). No statistically significant difference between groups was observed for any other study variable.

Injected joints: (n=71)

	IAI guided by fluoroscopy	IAI guided by ultrasound
naviculocuneiforme (n)	0	1
glenohumeral (n)	4	3
acromioclavicular (n)	0	2
hip (n)	12	11
wrist (n)	1	30
ankle (n)	5	0
first metacarpophalangeal (n)	1	0
sacroiliac (n)	1	0
total n (%)	24 (33.8)	47 (66.2)

Table 1: Demographic and general characteristics: whole group (n=71)

	FC Group (n=24)	US Group (n=47)	P value
Age in years (+- SD)	62 (16.9)	49 (10.8)	0.006
Gender (M/F)	8/16	10/36	0.292
Skin Color (White/no white)	12/9	32/12	0.141
Initial VAS for pain (±SD)	7.4 (2.2)	6.6 (1.9)	0.076
Initial Joint Flexion (±SD)	74.7° (29.3)	53.2° (28.3)	0.001

SD= standard deviation; t-student test; chi square

Table 2: Visual analogue scale (VAS) for pain, joint flexion and Percentage change for joint flexion between groups: whole group analysis (n=71)

	FC Group (n=24)	US Group (n=47)	Intergroup p value
VAS for pain (cm)			0.076
T0 (+- SD)	7.4 (2.2)	6.6 (1.9)	
T4 (+-SD)	3.4 (2.8)	2.6 (2.3)	
Intragroup p	<0.001	<0.001	
Joint Flexion (°)			<0.001
T0 (+-SD)	74.7° (29.3)	53.2° (28.3)	
T4 (+-SD)	96.0° (33.7)	56.8° (31.0)	
Intragroup p	<0.001	0.074	
Change for Joint Flexion (°)			0.016
T4 (+-SD)	23.5° (46.1)	8.1° (27.7)	

Anova, t-student

Table 3: Visual analogue scale (VAS) for pain, joint flexion and Percentage change for joint flexion between groups: hip sub-analysis (n=23)

	FC Group (n=12)	US Group (n=11)	P value
VAS for pain (cm)			0.753
T0 (+- SD)	7.8 (1.6)	7.6 (2.0)	
T4 (+- SD)	3.4 (3.2)	3.1 (2.3)	
Intragroup p	<0.001	<0.001	
Joint Flexion (°)			0.692
T0 (+- SD)	70.0° (19.1)	82.7° (21.0)	
T4 (+- SD)	96.6° (19.4)	89.9° (23.6)	
Intragroup p	<0.002	<0.002	
Chance for joint flexion (°)			0.070
T4 (+- SD)	39.0° (50)	10.0° (30.5)	

Anova, t-student

Discussion/Conclusion:

Imaging-guided IAI improves regional pain in patients with various types of synovitis in the short term. For the vast majority of variables, no significant difference in terms of effectiveness was observed between fluoroscopy and ultrasound-guided IAI.

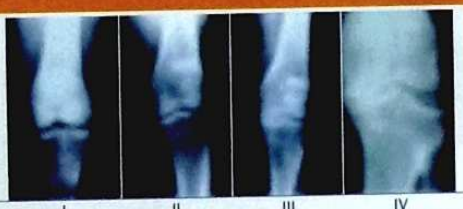
INTRA-ARTICULAR INJECTION WITH HYLASTAN SGL-80: LONG-TERM EXPERIENCE

MA De Pascalis
Distretto IX ASL RMC

Introduction: the international literature reports that viscosupplementation is an effective treatment for knee OA, with beneficial effects on pain, function and patient global assessment especially at the 5 to 13-week period. However, few data are available regarding efficacy, patient's preferences and acceptability of a long-term course of intra-articular HA. Hylastan SGL-80, derived from bacterially fermented hyaluronan, is a sterile, non-pyrogenic mixture of Hylastan gel and HA fluid (80:20 ratio) displaying elastoviscous properties similar to those of synovial fluid and superior to those of unmodified hyaluronan solution. Aim of this study was to evaluated long-term effect of Hylastan SGL-80 intra-articular injection.

Patients and Methods: This is an open, non-controlled, prospective study. The patients, men and women over 18 years of age, were eligible for study entry if they had chronic primary OA of the of Kellgren-Lawrence radiographic grade I to IV (Figure 1). Between November 2010 and November 2012 we selected 86 patients with symptomatic knee OA (50F, 36M; aged 39-84 years) Kellgren-Lawrence grade I (N=18), grade II (N=38), grade III (N=25) and grade IV (N=5) (Figure.2).

Figure 1. Kellgren and Lawrence Radiographic Criteria for Assessment of OA*

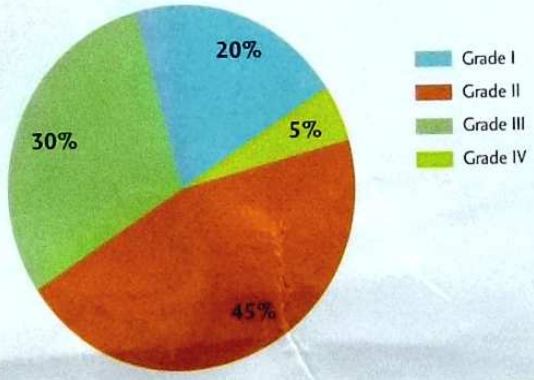


Radiographic grade	0	I	II	III	IV
Classification	Normal	Doubtful	Mild	Moderate	Severe
Description	NO features of OA	Minute osteophyte; doubtful significance	Definite osteophyte; normal joint space	Moderate joint-space reduction	Joint space greatly subchondral sclerosis

Cooper C et al. In Erand KD, Doerny M. Lohmander LS et al. eds Osteoarthritis Oxofrd NY Oxoford University Press 1998; 237-249

*Radiographic does not reliably correlate with symptoms

Figure 2. Kellgren-Lawrence distribution



One week before the infiltration, all patient were treated with 90mg/day of etoricoxib per os to reduce inflammation. The anti-inflammatory therapy was continued for additional 7 days after the infiltration. Patients were positioned sitting up with a support brace and with knee flexed to approximately 100 degrees. In order to ensure efficacious infiltration access to joint was performed through the external hemirima. Injections were always performed under strict aseptic conditions. Patient's assessment was measured by a single question using a VAS scale (0-10, 10 as worst pain) at all time points. The primary outcome criterion was change from baseline in VAS score. Patients were evaluated at 2,6,12,18 and 24 months after first injection. Between-group comparison of improvements from baseline were calculated by one-way analysis of variance.

Results: Short and long-term treatment effectiveness was reported after Hylastan SGL-80 injection. Significant improvements from baseline were maintained up to months 24 as assessed by patient's VAS ($p<0.01$). Table 1 shows the mean (±SD) VAS scores assigned by the patients during the 24 months study period.
Overall 37/86 patients (47%) repeated the treatment, mainly after 6 (21/37) or 12 (10/37) months from the first injection.The majority of patients indicated satisfaction with the treatment, showing good functional recovery. Some patient complained of pain in the access point. Pain was ascribed to the reduction of the articular surfaces and resulting adhesion of the joint capsule itself, as a result of repeated inflammatory processes and poor reduction of inflammation. Even patients with more severe forms showed an improvement in quality of life with marked pain reduction during exercise. The knees were dry with good articulation function and no signs of discharge or inflammation. Gait was painless. No patient experienced clinically significant complications.

Baseline (n=86)	2 m (n=86)	6 m (n=60)	12 m (n=39)	18 m (n=29)	24 m (n=19)
6.2 (±0.9)	0.9 (±0.9)	1.6 (±1.9)	1,6 (±1,7)	0.9 (±1,3)	0.8 (±0,7)

Table 1. Pain intensity during movements of the knee (mean ± SD), as assessed by the patient using a 10-mm visual analogue scale (VAS; 0= no pain, 10= unbearable pain). P<0.01

Conclusions: These data confirm that Hylastan SGL-80 produces a good effect due to its long duration of action. Repeat administration after 6 or 12 months showed a tolerability profile similar to that of the initial injection. Very good results were achieved in most patients with six-monthly single-dose treatment showing risk reduction, modest complications and patient satisfaction. In view of these results, we can say that intra-articular knee injection with Hylastan SGL -80 is highly innovative and invaluable in treating gonarthrosis.

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Viscosupplementation with a new Soft-Gel cross-linked Hyaluronic Acid (Hylastan SGL-80) in the management of joint pain in osteoarthritis: a six months clinical trial

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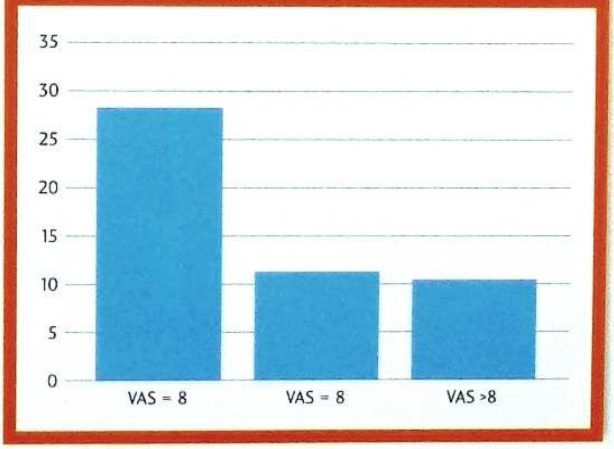
Increasing prevalence of painful knee osteoarthritis has created an additional demand for pharmacologic management to prevent or delay surgical treatment.
Viscosupplementation, via intra-articular injection of hyaluronic acid (HA), aims to restore the favorable milieu present in the no arthritic joint. The safety profile of intra-articular HA injections for painful knee osteoarthritis is well established in a number of large first level studies. Most common adverse effect being a self-limited reaction at the injection site.
Different HA formulations are currently available worldwide: from the reference low MW preparation to more recent cross-linked, high MW formulations. Hylastan SGL-80 (Jonexa®) is a new cross-linked hyaluronic acid produced by bacterial fermentation presented as an innovative technology called "soft-gel" in monoadministration.

Methods: This is an open, non controlled, prospective study. The study selected 53 patients (24M and 29F) evaluated by MRI (chondropathy grades I-IV). All patients enrolled had a history of symptoms for at least 12 months and insufficient/failed response to analgesics and/or regular non-steroidal anti-inflammatory and had failed treatment with steroids infiltration (Figure 1).
40 patients had pain in the walking uphill, while the other 13 complained of pain on the way down. Before undergoing viscosupplementation, with Hylastan SGL-80, all patients underwent arthrocentesis (with volumes between 30 and 70 ml, after local anesthesia with lidocaine 2%) and therapy with pulsanting magnetic field (47-57 Gauss, 30-45 min a days for 14-16 days) in order to reduce inflammation of the joint. Evaluation was carried out at 7-15 days and at 3 and 6 months by patients self-administered VAS (score 0-10).

Figure 1. Baseline Pain Score



Results: In the first 7/10 days after infiltration with Hylastan SGL-80, 43 patients reported pain (VAS score >6) or a feeling of articular "kneading"; after 15 days only 8 patients reported pain (VAS score >6). After 3-4 weeks, the majority of patients (40/53) reported a marked functional improvement (up and down the stairs) and reduction in pain (VAS score 2-4). 10 patients reported improvement after 40/45 days from infiltration (VAS score 4-5). Only 3/53 patients did not have a significant improvement and were subjected to total knee replacement. After 3 months 50/53 patients had maintained the improvement induced by the infiltration (VAS score 2-4) while after 6 months 37/53 still showed a good functional component with occasional intake of NSAID only after prolonged exercise or long walks.
Transient swelling sensation were recorded by some patients and disappeared in all case a few days after treatment. None of the patients reported adverse effects.

Table 1. Pain Score after treatment

Day after treatment	Number of patients	VAS Pain Score
7-10	43	>6
15	8	>6
21-28	40	2-4
90	50	2-4
180	37	2-4

Conclusions: It is important to highlight that 31/53 patients were subjected to infiltration with a low molecular weight HA 1-3 years before treatment with Hylastan SGL-80 has without obtaining substantial improvements. Particularly impressive the percentage of patients reported high satisfaction with treatment and a relevant improvement of joint function (ability to climb stairs, walk on uneven ground) just 15 days after the infiltration with Hylastan SGL-80.This study showed that Hylastan SGL-80, administered after a treatment with pulsalting magnetic fields (47-57 gauss) with the aim to reduce joint inflammation, produced a marked reduction in pain and a good improvement that were maintained for a period of at least 6-8 months. In conclusion, it can be stated that treatment with Hylastan SGL-80 can be an effective alternative therapy in the treatment of knee OA as it reduces the need to hire NSAIDs as an improvement of joint function and gait, making it very pleasing to patients because it reduces threefold/five fold the need for further infiltrations and some patients got benefits so high that required a second treatment for fear of losing their achievements.