

# Evaluation of two intra-articular hyaluronic acid preparations in the treatment of osteoarthritis of the knee

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*Key words*

*Hyaluronic acid, formulations, osteoarthritis*

## SUMMARY

**Background:** The use of viscosupplementation for the management of pain in osteoarthritis (OA) has been attempted with hyaluronic acid preparations of different molecular weights. The relative efficacy of different preparations of hyaluronic acid required direct comparisons between such products. The aim of this study was to directly compare the efficacy and tolerability of two hyaluronic acid-containing products: one containing non-chemically modified, fermentation origin hyaluronic acid with an average molecular weight of 1.2 million Daltons (Ostenil<sup>®</sup>), and the other a product containing chemically cross-linked hyaluronic acid extracted from rooster combs with an average molecular weight of about 6 million Daltons (hylan G-F 20- Synvisc<sup>®</sup>).

**Methods:** This was a prospective, open design, randomized study comparing two active treatments. Patients with radiologically ascertained primary knee osteoarthritis (Larsen score I-III) and with persistent daily pain for at least 2 weeks prior to treatment were enrolled into the study. Patients that did not have pain for at least 2 weeks prior to treatment and those with a detectable effusion in the joint to be treated at the time of the first treatment were excluded from the study. Eligible patients were randomly assigned to one of two treatment groups: patients in Group S received 3 intra-articular (i.a.) injections of Synvisc<sup>®</sup> while those in Group O received three injections of Ostenil<sup>®</sup>, both at a

rate of one intra-articular injection per week for 3 consecutive injections. The patients were followed for 150 days. The therapeutic effects of the treatments were assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for overall pain and function. Tolerability of the two treatments was evaluated by asking patients at each study visit whether they had suffered any adverse events since their last visit.

**Results:** Twenty-three male and 27 female patients, average age  $58.9 \pm 17.9$  years, with radiologically ascertained primary knee osteoarthritis (Larsen score I-III) and with persistent daily pain for at least 2 weeks prior to treatment were enrolled into the study. The repeated measures analyses showed significant improvements for both pain and function scores in both groups compared to baseline values. There were no significant differences in efficacy between the two treatments. The incidence of adverse events was higher in Group S (16.7% versus 0% in Group O) and mainly concerned pain at the injection site (95% CI: 5.5-38.2%) ( $P = 0.046$ ), with a patient drop out rate of 3.8% in Group O and 25.0% in Group S ( $p=0.045$ ).

**Conclusions:** Both preparations of hyaluronic acid were effective in reducing pain and improving joint function in patients with knee osteoarthritis, without significant differences between the 2 groups. However, the lower molecular weight, non-chemically modified hyaluronic acid product of fermentation origin (Ostenil<sup>®</sup>) was better tolerated with a lower incidence of adverse events and a lower patient drop-out rate.

#### OBJECTIVE:

Viscosupplementation, using hyaluronic acid preparations of different molecular weights, has been used in the management of osteoarthritis for some time. Studies in humans show that hyaluronic acid with molecular weights between 0.5 – 6 million Daltons administered intra-articularly several times at weekly intervals was effective and safe. Subsequent studies show that products containing hyaluronic acid with molecular weight between 0.5 and 0.75 million Daltons, administered at the rate of one intra-articular injection per week for five consecutive injections, or purified forms of high molecular weight hyaluronic acid were also effective in the treatment of osteoarthritis.

The development of high molecular weight hyaluronic acid molecules was based on the principle that higher concentrations with a higher molecular weights would increase the viscoelasticity of the solution and that this would eventually produce greater pain relief and a greater improvement in joint function. This hypothesis was not confirmed as, in practice, hyaluronic acid products of different molecular weights showed similar symptomatic effects. Some products with a molecular weight between 0.5 - 0.75 million Daltons showed effects that could be considered as structure modifying. The relative effectiveness of the different preparations of hyaluronic acid required a head-to-head comparative study. The objective of this study was to compare the effectiveness and tolerability of two products that contain hyaluronic acid: one that contains non-chemically modified hyaluronic acid of fermentation origin with average of molecular weight of 1.2 million Daltons (Ostenil), and another containing chemically cross-linked hyaluronic acid, with an average molecular weight of 6 millions Daltons, extracted from rooster combs (hylan G-F 20 - Synvisc).

#### MATERIALS AND METHODS:

After signing the informed consent, 23 men and 27 women over 28 years of age were included into the study if they had radiologically confirmed primary osteoarthritis of the knee (Larsen I - III). All patients had to have persistent pain of the target knee, despite analgesic use, and an erythrocyte sedimentation rate less than 40. Patients were excluded if they did not present pain or if they presented effusion in the target

joint at the start of the study. This was a prospective, randomised study, comparing the two groups of active treatment for 150 days. The patients were assigned to receive either three intra-articular injections of high molecular weight hyaluronic acid (Synvisc) (Group S) or three injections of hyaluronic acid with a molecular weight of 1.2 million Daltons (Ostenil) (Group O). Patients completed a 2 week wash-out period for anti-inflammatory drugs before the administration of the first injection. The clinical evaluation was carried out after the wash-out period (Day 0).

An arthrocentesis was carried out before each injection to confirm that joint effusion was not present. The knee joint selected for treatment was injected with 2ml of Synvisc or Ostenil on Days 0, 7 and 14.

Clinical evaluations were carried out before each injection and additionally on Days 21, 28, 35, 60, 120 and 150 after the final injection. The injections were carried out under conditions of asepsis using 20 g needles. They were carried out only by a doctor, who determined the ideal position and the site of administration. The subcutaneous administration of an anaesthetic was optional for the patients. The use of other medications and rescue medication (analgesics) was allowed and was recorded. The therapeutic effect of treatment was evaluated using the WOMAC index. The evaluation was carried out by a masked observer using a 100 mm visual analogical scale for each of these parameters. The data for pain and joint function were summarized to obtain a final result of the overall findings for pain and the overall findings for joint function respectively.

The tolerability of the two solutions was evaluated both by examining the injection sites and by asking each patient at each visit whether they experienced any adverse events since the previous visit. The Investigator had to determine whether the observed events were possibly, probably or improbably related to the product administered.

For the statistical evaluations, the quantitative variables were expressed as means and standard deviation while the results of the evaluations for pain and joint function are presented as medians (25 and 75 percentiles). The proportions are expressed with a 95% confidence interval calculated in accordance with the quadratic method of Fleiss. The differences between the

proportions were analysed using the Fisher exact test. For a further exploration of the data, non-parametric analyses using the Friedman ANOVA were carried out in each of the two groups. To evaluate the difference between groups for pain and joint function as a result of the treatment received a series of two-line ANOVA models were carried out considering repeated treatment as a factor (treatment order). In these groups, the results were analysed using tests that measure groups of up to 30 patients.

**RESULTS:**

Twenty-six patients (14 female, 12 male; average age  $58.7 \pm 17.8$  years; height  $164.3 \pm 8.7$  cm) were assigned to Group O and 24 (13 female, 11 male; average age  $59.1 \pm 18$  years; height  $167.8 \pm 10.2$  cm) to Group S. The results obtained for pain in each group at each

assessment time are presented in Table 1 while the results obtained for joint function are presented in Table 2. The results of the medians between the 25 and 75 percentiles are shown in figures 1 (for pain in Group O), 2 (for function in Group O), 3 (for pain in Group S), and 4 (for function in Group S). The means of the graphs showing the difference between the groups for pain and joint function are shown in Figures 5 and 6 respectively. The results of the ANOVA tests for pain and joint function are presented in Figures 3 and 4 respectively. No interaction was observed in any case. The repeated measures analysed were significant both for pain and for joint function. In both groups there was a significant improvement in pain on Days 28, 35, 60, 120 and 150 compared to baseline values. As for the results of joint function, significant differences were obtained from Day 21.

**Table 1. Overall evolution of the pain values**

	Group: Ostenil				Group: Synvisc			
	Mean	SD	Median	25-75 percentiles	Mean	SD	Median	25-75 percentiles
Day 0	23.75	10.12	22.90	15.70-29.65	30.90	14.80	26.45	16.00-46.00
Day 7	22.55	12.83	18.15	13.30-29.50	27.83	15.86	20.85	14.15-45.70
Day 14	19.95	11.99	15.65	11.20-26.35	24.30	16.48	14.75	12.10-43.70
Day 21	15.69	7.70	14.25	9.60-20.90	24.05	16.37	15.10	11.40-44.40
Day 28	12.48	6.75	12.10	6.20-18.45	17.90	15.31	11.10	7.20-33.50
Day 35	9.91	6.00	9.95	3.30-14.50	15.61	14.39	8.70	4.80-28.90
Day 60	8.41	5.61	8.90	2.10-12.55	15.35	15.05	9.90	3.90-19.80
Day 120	7.38	5.13	7.95	2.00-10.95	14.62	15.18	10.70	3.20-23.20
Day 150	5.95	4.78	5.60	1.40-8.65	12.61	13.66	8.25	2.40-17.75

**Table 2. Overall evolution of the joint function values**

	Group: Ostenil				Group: Synvisc			
	Mean	SD	Median	25-75 percentiles	Mean	SD	Median	25-75 percentiles
Day 0	81.21	38.77	76.00	53.00-88.30	104.75	48.47	93.00	59.50-154.00
Day 7	75.75	40.32	63.00	44.00-89.00	90.45	50.82	64.50	49.00-147.00
Day 14	81.36	43.11	66.50	49.00-98.50	97.45	65.21	61.50	43.00-175.00
Day 21	49.33	24.21	45.50	33.00-63.00	67.47	48.45	51.00	36.00-121.00
Day 28	39.64	21.30	36.50	19.00-50.00	59.47	49.61	41.00	25.00-107.00
Day 35	33.71	20.17	31.00	17.00-44.00	52.26	46.56	34.00	17.00-89.00
Day 60	29.10	20.84	27.50	10.00-38.50	50.00	47.55	27.00	17.00-64.00
Day 120	25.45	22.20	23.50	1.90-34.00	48.20	49.60	38.00	9.00-74.00
Day 150	19.95	19.19	16.00	1.00-28.50	37.83	42.13	26.50	10.00-50.50

The results obtained for pain in each group at each assessment time are presented in Table 1 while the results obtained for joint function are presented in Table 2. The results of the medians between the 25 and 75 percentiles are shown in figures 1 (for pain in Group O), 2 (for function in Group O), 3 (for pain in Group S), and 4 (for function in Group S). The means of the graphs showing the difference between the groups for pain and joint function are shown in Figures 5 and 6 respectively. The results of the ANOVA tests for pain and joint function are presented in Figures 3 and 4 respectively. No interaction was observed in any case. The repeated measures analysed were significant both for pain and for joint function. In both groups there was a significant improvement in pain on Days 28, 35, 60, 120 and 150 compared to baseline values. As for the results for joint function, significant differences were obtained from Day 21. Except for the baseline values of the functional assessments, there were no significant differences between the groups.

The incidence of adverse events was 0% in Group O and 16.7% in Group S and mostly concerned pain at the injection site (95% CI: 5.5–38.2%) (P =0.046) with values of 3.8% (95% CI: 0.20–21.6%) and 25% (95% CI: 10.6%-47.1%) respectively (P=0.045).

**DISCUSSION:**

This study was designed to compare the effectiveness and tolerability of two viscoelastic preparations of hyaluronic acid in patients with knee osteoarthritis. Both products have very different molecular weights: Ostenil (Group O) has a molecular weight of 1.2 million Daltons while Synvisc (Group S) has a molecular weight of more than 6 millions Daltons. Although these two products demonstrated effectiveness in the management of osteoarthritis pain, some authors have postulated that a more viscous preparation could provide a greater analgesic effect and a greater improvement in joint function.

Hyaluronic acid preparations with molecular weight between 0.5 and 0.75 million Daltons seem to have a structure modifying activity in osteoarthritis. The results of this trial show that the two preparations studied produce a significant decrease in pain and a significant improvement in joint function. The magnitude of this improvement was similar in both groups.

**Table 3. Overall values for pain. Results of the two-way ANOVA**

	MS effect	MS Error	F	P
Group	2248.5	725.6	3.37	0.074
Evolution of pain	1461.5	32.8	44.6	<0.00001
Interaction	8.7	32.8	0.26	0.9765

**Table 4. Overall values for joint function. Results of the two-way ANOVA**

	MS effect	MS Error	F	P
Group	21534	7710.2	2.793	0.1036
Evolution of pain	19477	390.2	49.9	<0.00001
Interaction	94	390.2	0.241	0.9827

At baseline, Group S presented higher levels than Group O for both parameters evaluated; but the evolution of the results of these parameters was similar in both groups until the end of the study. The arthrocentesis carried out before each injection could be interpreted as a confounding factor in this study. The incidence of adverse effects was clearly higher in Group S than in Group O, with a high incidence of drop-outs in Group S. Pain at the injection site can be attributed to the viscosity of the solution. Both solutions of hyaluronic acid were effective in reducing pain, without differences between the two groups. The lower molecular weight product was better tolerated with a lower incidence of adverse effects and a lower incidence of drop-outs.

Post hoc results:

Ostenil Group	Baseline vs. Day 28	p<0.0001
	Baseline vs. Day 35	p<0.0001
	Baseline vs. Day 60	p<0.0001
	Baseline vs. Day 120	p<0.0001
	Baseline vs. Day 150	p<0.0001

The other comparisons versus baseline were not significant

Post hoc results:

Synvisc Group	Baseline vs. Day 28	P=0.01
	Baseline vs. Day 35	p<0.0005
	Baseline vs. Day 60	p<0.0001
	Baseline vs. Day 120	p<0.0001
	Baseline vs. Day 150	p<0.0001

The other comparisons versus baseline were not significant

Post hoc results:

Ostenil Group	Baseline vs. Day 21	p<0.0001
	Baseline vs. Day 28	p<0.0001
	Baseline vs. Day 35	p<0.0001
	Baseline vs. Day 60	p<0.0001
	Baseline vs. Day 120	p<0.0001
	Baseline vs. Day 150	p<0.0061

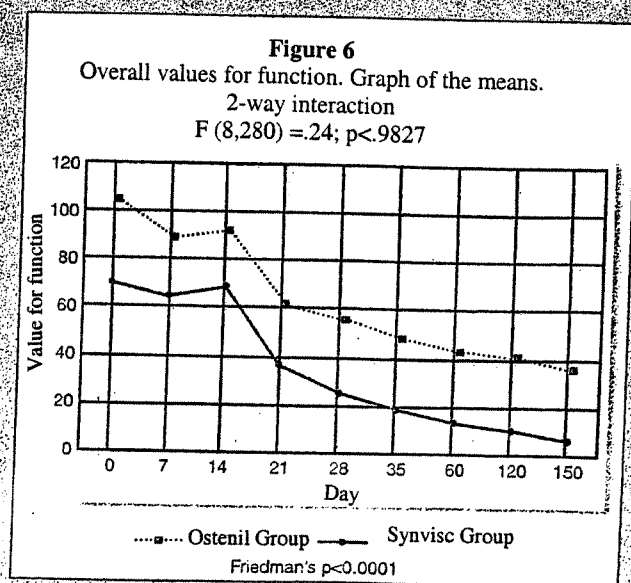
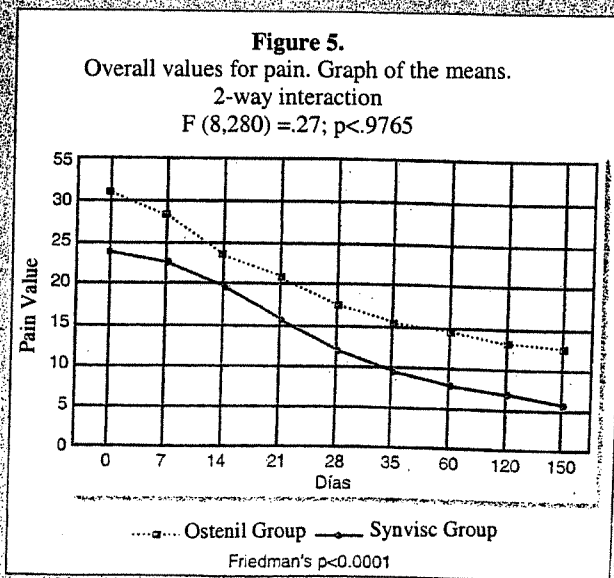
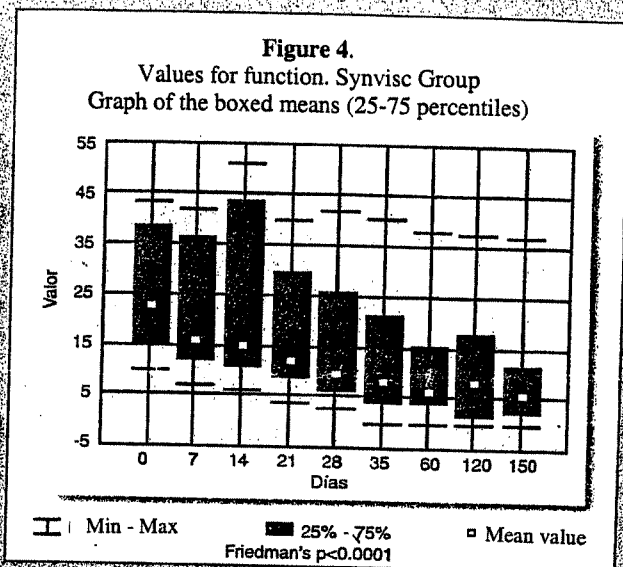
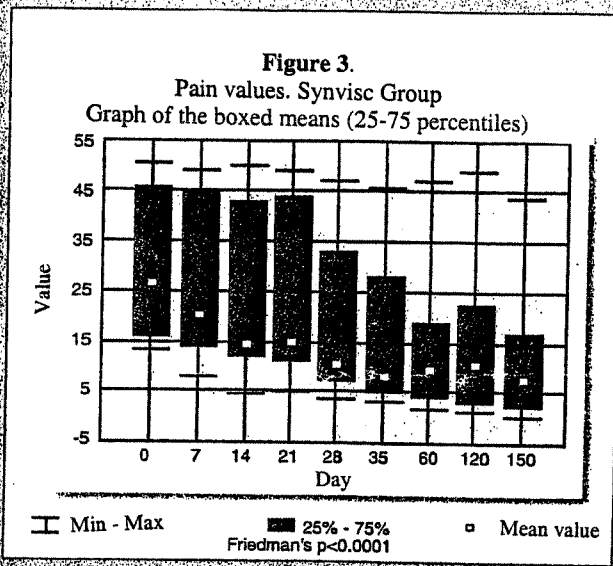
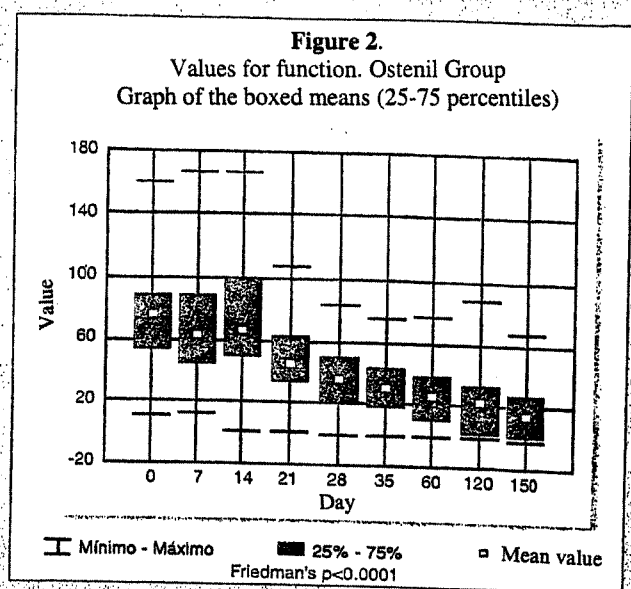
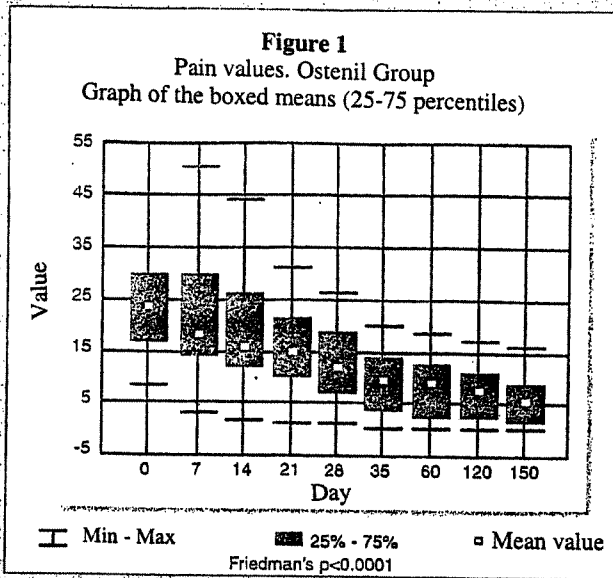
The other comparisons versus baseline were not significant

Post hoc results:

Synvisc Group	Baseline vs. Day 21	p<0.0001
	Baseline vs. Day 28	p<0.0001
	Baseline vs. Day 35	p<0.0001
	Baseline vs. Day 60	p<0.0001
	Baseline vs. Day 120	p<0.0001
	Baseline vs. Day 150	p<0.0001

The other comparisons versus baseline were not significant

Ostenil vs Synvisc: Baseline differences: p = 0.0062



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# Evaluación de dos preparaciones intra-articulares de ácido hialurónico en el tratamiento de la osteoartritis de rodilla

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*Palabras clave:*

*Acido hialurónico, Formulaciones, Osteoartritis.*

## SUMMARY

**Background:** The use of viscosupplementation for the management of pain in osteoarthritis (OA) has been attempted with hyaluronic acid preparations of different molecular weights. The relative efficacy of different preparations of hyaluronic acid required direct comparisons between such products. The aim of this study was to directly compare the efficacy and tolerability of two hyaluronic acid-containing products: one containing non-chemically modified, fermentation origin hyaluronic acid with an average molecular weight of 1.2 million Daltons (Ostenil®), and the other a product containing chemically cross-linked hyaluronic acid extracted from rooster combs with an average molecular weight of about 6 million Daltons (hylan G-F 20-Synvisc®).

**Methods:** This was a prospective, open design, randomized study comparing two active treatments. Patients with radiologically ascertained primary knee osteoarthritis (Larsen score I-III) and with persistent daily pain for at least 2 weeks prior to treatment were enrolled into the study. Patients that did not have pain for at least 2 weeks prior to treatment and those with a detectable effusion in the joint to be treated at the time of the first treatment were excluded from the study. Eligible patients were randomly assigned to one of two treatment groups: patients in Group S received 3 intra-articular (i.a.) injections of Synvisc® while those in Group O received

three injections of Ostenil®, both at a rate of one intra-articular injection per week for 3 consecutive injections. The patients were followed for 150 days. The therapeutic effects of the treatments were assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for overall pain and function. Tolerability of the two treatments was evaluated by asking patients at each study visit whether they had suffered any adverse events since their last visit.

**Results:** Twenty-three male and 27 female patients, average age  $58.9 \pm 17.9$  years, with radiologically ascertained primary knee osteoarthritis (Larsen score I-III) and with persistent daily pain for at least 2 weeks prior to treatment were enrolled into the study. The repeated measures analyses showed significant improvements for both pain and function scores in both groups compared to baseline values. There were no significant differences in efficacy between the two treatments. The incidence of adverse events was higher in Group S (16.7% versus 0% in Group O) and mainly concerned pain at the injection site (95% CI: 5.5-38.2%) ( $P = 0.046$ ), with a patient drop out rate of 3.8% in Group O and 25.0% in Group S ( $p=0.045$ ).

**Conclusions:** Both preparations of hyaluronic acid were effective in reducing pain and improving joint function in patients with knee osteoarthritis, without significant differences between the 2 groups. However, the lower molecular weight, non-chemically modified hyaluronic acid product of fermentation origin (Ostenil®) was better tolerated with a lower incidence of adverse events and a lower patient drop-out rate.

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#### OBJETIVO:

El uso de procedimientos de viscosuplementación para el manejo de la osteoartritis ha sido realizado con ácidos hialurónicos de diferente peso molecular. Los estudios en humanos mostraron que los ácidos hialurónicos con un peso molecular entre 0.5 - 6 millones Daltons administrados varias veces en intervalos semanales por la vía intra-articular fueron efectivos y seguros. Estudios subsiguientes mostraron que productos con ácido hialurónico con peso molecular de 0.5 a 0.75 millones Daltons administrado en forma de 1 infiltración durante 5 semanas o formas purificadas de ácido hialurónico de alto peso molecular fueron también efectivos en el tratamiento de la osteoartritis.

El desarrollo de moléculas de alto peso molecular estuvo basado en el principio de que concentraciones mayores con mayor peso molecular incrementarían la viscoelasticidad de la solución y que esto produciría finalmente un mayor aumento en la analgesia y una mejoría en la función articular. Esta hipótesis no fue confirmada en la práctica ya que los ácidos hialurónicos de diferentes pesos moleculares mostraron similares efectos sintomáticos. Algunos productos con pesos moleculares entre 0.5 y 0.75 millones Daltons mostraron efectos que podrían ser considerados como modificadores de la estructura.

La relativa eficacia de los diferentes preparados de ácido hialurónico exigían un estudio comparativo entre ellos. El presente estudio fue dirigido para comparar la eficacia y tolerabilidad de dos productos que contienen ácido hialurónico, uno que contenía ácido hialurónico de origen fermentativo, no modificado químicamente, con 1.2 millones de Daltons promedio de peso molecular (Ostenil), y el otro producto conteniendo ácido hialurónico extraído de las crestas de gallo, unido químicamente y con un peso molecular promedio de 6 millones de Daltons (hylan G-F 20- Synvisc).

#### MATERIALES Y MÉTODOS:

Después de firmar el consentimiento informado, 23 hombres y 27 mujeres de una edad superior a 28 años fueron enrolados en el estudio si tenían el diagnóstico de osteoartritis primaria confirmada radiológicamente (Larsen I-III). Todos los pacientes tenían que tener dolor persistente de la articulación en estudio, a pesar del uso de analgésicos y una eritrosedimentación menor a 40. Los pacientes fueron excluidos si no presentaban dolor o si presentaban derrame articular en la articulación al comenzar el estudio. Este fue un estudio prospectivo, randomizado, comparando los dos grupos con tratamiento activo por 150 días. Los pacientes fueron asignados a recibir: grupo S tres inyecciones intraarticulares de ácido hialurónico de alto peso molecular (Synvisc) o grupo O para re-

cibir tres inyecciones de ácido hialurónico de 1.2 millones Daltons de peso molecular (Ostenil). Los pacientes completaron 2 semanas de lavado de anti-inflamatorios antes de la administración de la primera inyección. La evaluación clínica fue realizada luego del período de lavado (día 0).

La artrocentesis fue realizada antes de cada inyección para confirmar que no había derrame. La articulación seleccionada para tratamiento fue inyectada con 2 cm<sup>3</sup> de Synvisc u Ostenil al día 0, 7 y 14.

Evaluaciones clínicas adicionales fueron realizadas antes de cada inyección y a los días 21, 28, 35, 60, 120, y 150 después de la última inyección. Las infiltraciones fueron realizadas en condiciones de asepsia con agujas 20 g. Fueron realizadas solamente por un médico que determinó cual era la posición ideal y el sitio de administración. La administración subcutánea de anestesia fue opcional para los pacientes. El uso de otras medicaciones y medicación de rescate (analgésicos) fue permitido y anotado. El efecto terapéutico de tratamiento fue evaluado a través del WOMAC. La evaluación fue realizada por otro evaluador ciego usando una escala analógica visual de 100 mm para cada uno de estos parámetros. Los resultados de la evaluación final correspondiente al dolor y a la funcionalidad fueron resumidos para obtener un resultado final del resultado general del dolor y el resultado general de la funcionalidad respectivamente.

Los datos de la tolerabilidad de las dos soluciones, fueron evaluados preguntando a cada uno de los pacientes en cada una de las visitas después de la primera infiltración, reportando los resultados adversos experimentados desde la visita previa, además de examinar los sitios de infiltración. Fue tarea del investigador determinar si los eventos observados estuvieron posible, probable o improbablemente relacionados con el medicamento.

Para la evaluación, las variables cuantitativas fueron expresadas como media y desviación estándar, los resultados de las evaluaciones funcionales y dolor se mostraron como medianas (percentilos 25 y 75).

Las proporciones son expresadas con 95% de intervalo de confianza calculado de acuerdo con el Método cuadrático de Fleiss. Las diferencias entre las proporciones fueron analizadas a través del test exacto de Fisher. Para la exploración de las evaluaciones se realizaron estudios no paramétricos de Friedman anova en cada uno de estos grupos. Para evaluar la diferencia entre los grupos en dolor y funcionalidad a través del tratamiento, una serie de modelo de anova de dos colas fue realizado considerando la medición repetida de un factor (pedido de tratamiento). En estos grupos, los resultados fueron analizados con tests que miden grupos de hasta 30 pacientes.

## RESULTADOS:

El grupo inicial de pacientes fue de 26 en el grupo O (14 mujeres, 12 hombres, edad 58.7 ± 17.8 años y altura 164.3 ± 8.7 cm) y 24 en el grupo S (13 mujeres y 11 hombres, edad promedio 59.1 ± 18 años y una altura de 167.8 ± 10.2 cm). El resultado de los valores del dolor para cada grupo durante cada momento examinado se observa en la tabla 1 y la de resultados funcionales en la tabla 2.

Los resultados de medianas entre los percentilos 25 y 75 son mostrados en la figura 1 (para el grupo O, para dolor), 2 (para el grupo O, para funcionalidad), 3 (para el grupo S, para dolor) y 4 (para el grupo S, para funcionalidad). Las medias de los dibujos mostrando la diferencia entre los grupos en las exploraciones de dolor y funcionalidad se muestran en la Figura 5 y 6 respectivamente. Los resultados de anovas fueron analizados en la tabla 3 para dolor y 4 para funcionalidad. No se observó interacción

en ningún caso. Las repetidas medidas analizadas resultaron significativas tanto para dolor como para los resultados funcionales.

En ambos grupos la diferencia en términos de los resultados del dolor entre los valores basales y los valores registrados en los días 28, 35, 60, 120 y 150 resultaron en una significativa mejoría. En cuanto a los resultados funcionales, diferencias significativas fueron obtenidas desde el día 21.

Exceptuando los valores iniciales de los resultados de los exámenes funcionales no se observó diferencia significativa entre ambos grupos.

La frecuencia de los eventos adversos fue 0% para el grupo O y 16.7% para el grupo S, sobretodo dolor en la zona de infiltración. (95% CI: 5.5 – 38.2%) (P =0.046) con un abandono de 3.8% (95% CI: 0.20 – 21.6%) y 25% (95% CI: 10.6%-47.1%) respectivamente (P=0.045).

Tabla 1

**Evolución de los valores de dolor en conjunto**

	Grupo Ostenil				Grupo Synvisc			
	Promedio	DS	Media	25-75 percentilos	Promedio	DS	Media	25-75 percentilos
Día 0	23.75	10.12	22.90	15.70-29.65	30.90	14.80	26.45	16.00-46.00
Día 7	22.55	12.83	18.15	13.30-29.50	27.83	15.86	20.85	14.15-45.70
Día 14	19.95	11.99	15.65	11.20-26.35	24.30	16.48	14.75	12.10-43.70
Día 21	15.69	7.70	14.25	9.60-20.90	24.05	16.37	15.10	11.40-44.40
Día 28	12.48	6.75	12.10	6.20-18.45	17.90	15.31	11.10	7.20-33.50
Día 35	9.91	6.00	9.95	3.30-14.50	15.61	14.39	8.70	4.80-28.90
Día 60	8.41	5.61	8.90	2.10-12.55	15.35	15.05	9.90	3.90-19.80
Día 120	7.38	5.13	7.95	2.00-10.95	14.62	15.18	10.70	3.20-23.20
Día 150	5.95	4.78	5.60	1.40-8.65	12.61	13.66	8.25	2.40-17.75

Tabla 2

**Evolución de los valores de función en conjunto**

	Grupo Ostenil				Grupo Synvisc			
	Promedio	DS	Media	25-75 percentilos	Promedio	DS	Media	25-75 percentilos
Día 0	81.21	38.77	76.00	53.00-88.30	104.75	48.47	93.00	59.50-154.00
Día 7	75.75	40.32	63.00	44.00-89.00	90.45	50.82	64.50	49.00-147.00
Día 14	81.36	43.11	66.50	49.00-98.50	97.45	65.21	61.50	43.00-175.00
Día 21	49.33	24.21	45.50	33.00-63.00	67.47	48.45	51.00	36.00-121.00
Día 28	39.64	21.30	36.50	19.00-50.00	59.47	49.61	41.00	25.00-107.00
Día 35	33.71	20.17	31.00	17.00-44.00	52.26	46.56	34.00	17.00-89.00
Día 60	29.10	20.84	27.50	10.00-38.50	50.00	47.55	27.00	17.00-64.00
Día 120	25.45	22.20	23.50	1.90-34.00	48.20	49.60	38.00	9.00-74.00
Día 150	19.95	19.19	16.00	1.00-28.50	37.83	42.13	26.50	10.00-50.50

**DISCUSIÓN:**

Este estudio fue diseñado para comparar la eficacia y tolerabilidad de dos suplementaciones viscoelásticas de ácido hialurónico en pacientes con osteoartritis de rodilla. Ambos productos tiene un muy distinto peso molecular, uno tiene 1.2 millones Daltons en el caso de Ostenil (grupo 0), más de 6 millones Daltons para el Synvisc (grupo S). A pesar de que estas dos sustancias demostraron eficacia en el manejo de dolor de la osteoartritis, algunos autores han postulado que una preparación más viscosa podría proveer una analgesia superior y mejoría de la función articular. Las preparaciones de ácido hialurónico con peso molecular entre 0.5 y 0.75 millones Daltons parecen tener actividad modificadora de la estructura de la osteoartritis. Los resultados de este estudio muestran que las dos sustancias estudiadas producen una disminución significativa del dolor y una mejoría de la función articular. La magnitud de esta disminución fue similar para ambos grupos.

El grupo S presentó niveles en la visita basal más alto que en el grupo 0 para ambos factores evaluadores; pero la evolución de ambos resultados fueron paralelos hasta el final del estudio. La artrocentesis puede ser interpretada como un factor confundidor en este estudio. La incidencia de efectos adversos fue claramente superior en el grupo S que en el grupo 0 con un alto índice de abandono

**RESULTADOS POST HOC:**

Grupo Ostenil    Inicio vs. Día 28            p<0.0001  
                          Inicio vs. Día 35            p<0.0001  
                          Inicio vs. Día 60            p<0.0001  
                          Inicio vs. Día 120          p<0.0001  
                          Inicio vs. Día 150          p<0.0001  
                          Resto de comparaciones en contra del inicio no fueron significativos

Grupo Synvisc    Inicio vs. Día 28            p=0.01  
                          Inicio vs. Día 35            p<0.0005  
                          Inicio vs. Día 60            p<0.0001  
                          Inicio vs. Día 120          p<0.0001  
                          Inicio vs. Día 150          p<0.0001  
                          Resto de comparaciones en contra del inicio no fueron significativos

Tabla 3

**Valores de dolor en conjunto.  
Resultados de ANOVA de dos maneras**

	Efecto MS	Error MS	F	P
Grupo	2248.5	725.6	3.37	0.074
Evolución de dolor	1461.5	32.8	44.6	<0.00001
Interacción	8.7	32.8	0.26	0.9765

Tabla 4

**Valores de función en conjunto.  
Resultados de ANOVA de dos maneras**

	Efecto MS	Error MS	F	P
Grupo	21534	7710.2	2.793	0.1036
Evolución de dolor	19477	390.2	49.9	<0.00001
Interacción	94	390.2	0.241	0.9827

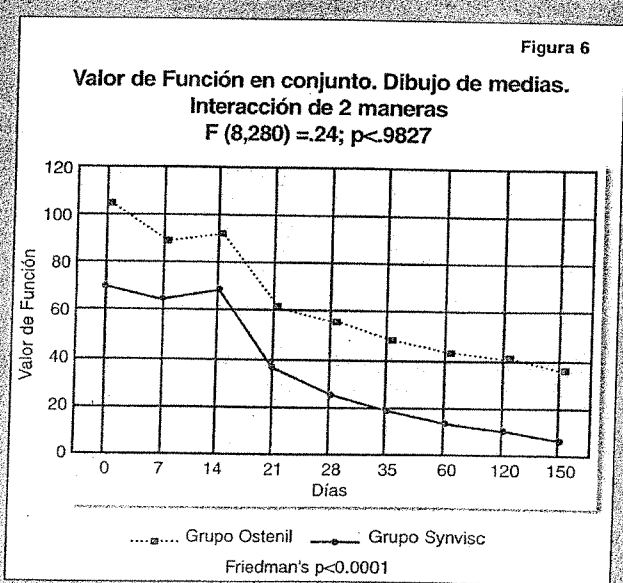
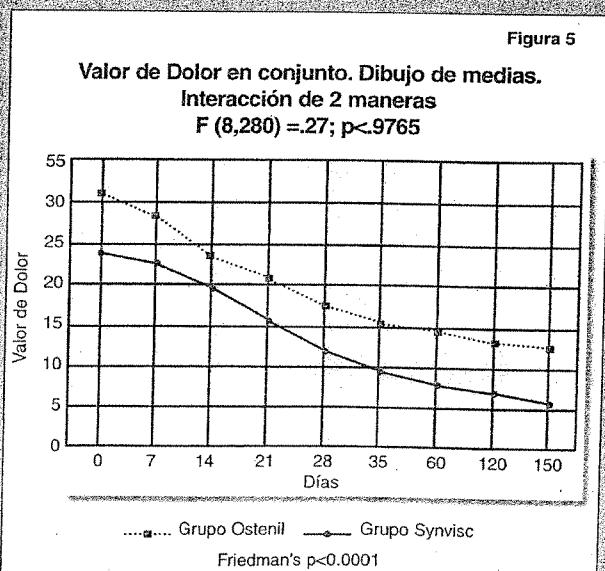
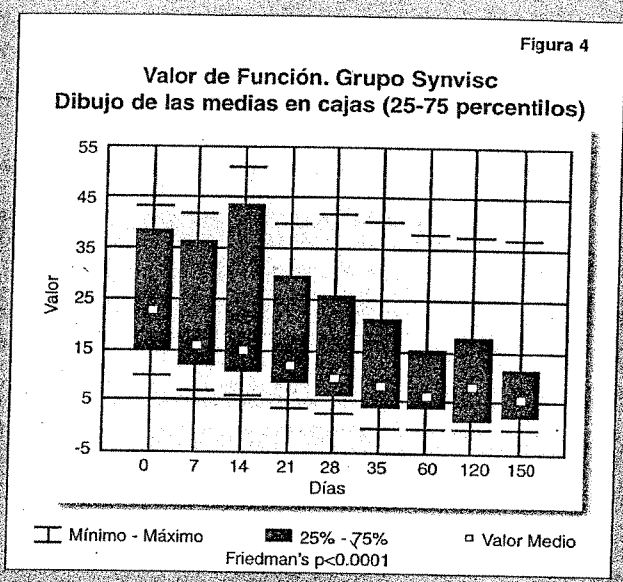
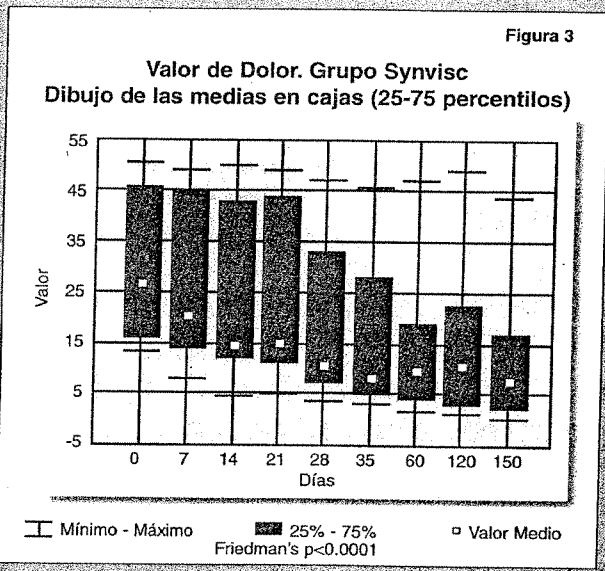
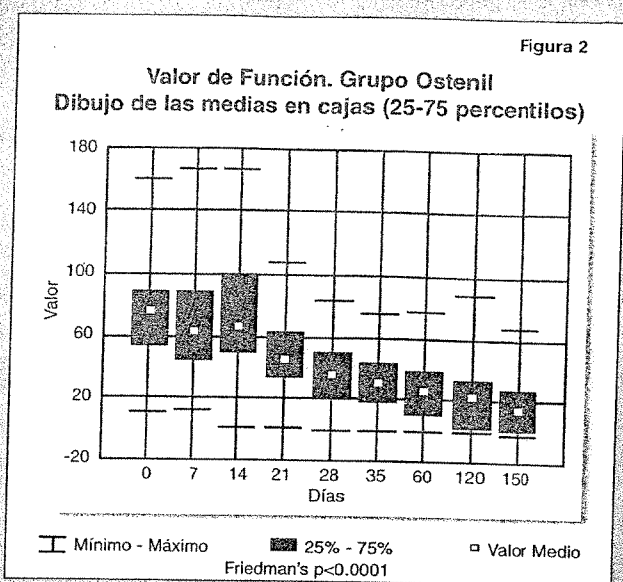
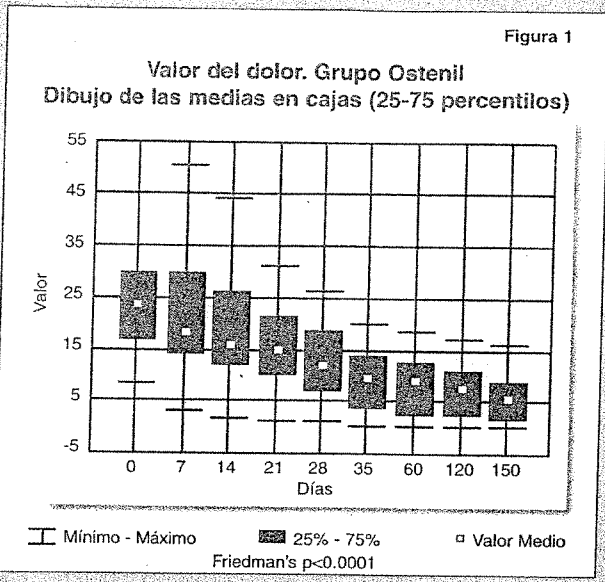
no en este grupo. El dolor en el lugar de inyección es un hecho que puede ser atribuido a la viscosidad de la solución. Ambas soluciones de ácido hialurónico fueron efectivas en reducir el dolor, sin diferencias en ambos grupos. El de bajo peso molecular fue mejor tolerado con menor frecuencia de efectos adversos, y menor frecuencia de abandonos.

**RESULTADOS POST HOC:**

Grupo Ostenil    Inicio vs. Día 21            p<0.0001  
                          Inicio vs. Día 28            p<0.0001  
                          Inicio vs. Día 35            p<0.0001  
                          Inicio vs. Día 60            p<0.0001  
                          Inicio vs. Día 120          p<0.0001  
                          Inicio vs. Día 150          p<0.0061  
                          Resto de comparaciones en contra del inicio no fueron significativos

Grupo Synvisc    Inicio vs. Día 21            p<0.0001  
                          Inicio vs. Día 28            p<0.0001  
                          Inicio vs. Día 35            p<0.0001  
                          Inicio vs. Día 60            p<0.0001  
                          Inicio vs. Día 120          p<0.0001  
                          Inicio vs. Día 150          p<0.0001  
                          Resto de comparaciones en contra del inicio no fueron significativos

Ostenil vs. Synvisc    Diferencias iniciales: p = 0.0062



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