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CONTENTS

Mahmoud Ali. The Effectiveness and Safety of Single US guided injection of Hylastan SGL-80 in Primary Hip Osteoarthritis. Preliminary data from a prospective observational stud.....	3
Nestorova. Clinical and sonographic assessment of the effectiveness of collagen injections gunamds in shoulder peri-arthritis with bursitis.....	15
Vetro. Pain relief and functional recovery over a six-month period after intra-articular injections with sodium hyaluronate (MW 1500 - 2000 KDA) in osteoarthritis of the knee.....	25
Mortada. Intra-articular methotrexate: clinical and power doppler ultrasonography study in rheumatoid knee synovitis.....	35
Conti. Implication of mast cells and cytokines in muscular tissue damage.....	41

EDITORIAL

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In this issue of European Journal of Musculoskeletal diseases we focused on the importance of intra-articular therapy in both degenerative and inflammatory diseases. At now there are several studies reporting on the use of different products for the various stages of diseases involving joints and responding to intra-articular treatments.

We have at our disposal data regarding different products such as hyaluronic acid, collagen and Methotrexate, as well as their evolutions and associations. Such data are fragmentary and grant only a partial comprehension of the therapeutic processes granted by the use of such drugs or medical devices. Often, also RCTs reporting on the use of such compounds lack of a precise standardization in methodology, thus affecting reliability of data.

As a consequence, to date, there are a lot of unmet needs for clinicians who deal with intra-articular therapy. Among those unmet needs, one is probably the most relevant: to find the right product for the right patient, in order to achieve the treatment tailoring that is expected to be working better and save costs related to side effects and wrong therapies allocation.

All researchers focusing on this field of joint pathology should begin to collect data and evidences on the different products and on the effects produced on different clinical subsets of joint diseases, so that the clinicians may have different kinds of products available for the different phases of degenerative

diseases like osteoarthritis or inflammatory diseases like Rheumatoid Arthritis or Spondyloarthritis. It is now well known that even for osteoarthritis, that is often considered the Cinderella of Rheumatic diseases, there are different phenotypes of disease, often responding differently to the same therapeutic approach: this makes even more relevant the performing of rigorous RCTs, correctly drawn in methodology and follow-up time.

In this sense, in addition to the collection of data from case series, cohort studies, national and international registers and observational studies, properly designed randomized controlled clinical trials are needed to confirm the results and the clinical indication of a particular product over another for a specific clinical subset, in order to respond to the unmet needs definitively.

Actually, although there are a lot of data obtained from studies with low levels of evidence, the clinicians need further studies with higher levels of evidence. Unless we find an answer, born of methodologically correct studies with high levels of evidence, it will be impossible for clinicians dealing with intra-articular treatments to have a substrate of certainty in their decisions. In this sense, our Journal encourages all studies that bring knowledge and clarity to the still unluckily nebulous world of intra-articular treatments, encouraging well designed studies with precise reports on efficacy and safety of various intra-articular compounds.

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DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

THE EFFECTIVENESS AND SAFETY OF SINGLE US GUIDED INJECTION OF HYLASTAN SGL-80 IN PRIMARY HIP OSTEOARTHRITIS. PRELIMINARY DATA FROM A PROSPECTIVE OBSERVATIONAL STUDY

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Objective: To report preliminary data about the efficacy and safety of single intra-articular ultrasound guided injection of Hylastan SGL-80 in primary hip osteoarthritis of moderate severity. **Materials and Methods:** 20 patients (23 hip joints) were included. Each hip received single ultrasound guided injection of 4 ml Hylastan SGL-80 through a longitudinal antero-inferior approach. Hip examination, visual analogue scale (VAS), McGill Pain Questionnaire (McGill), Western Ontario McMaster Questionnaire (WOMAC), Lequesne Index, and tenderness scale were the main outcome measures for assessment of efficacy. Additionally both local and systemic side effect were screened through phone call 3 days after injection and regular follow up visits during the follow up duration; 1 month, 3 months, 6 months and 1 year post-injection. **Results:** 14 female (70%), 6 male patients (30%), mean age 68.4 years, mean Body Mass Index (BMI) 26.1 kg/m², and average complaint duration: 47.1 months. 23 hip joints were injected. Student-t test was used to compare baseline scales' values with those recorded after injection. 23 hips reached 1 month follow up, 22 reached 3 months, 17 reached 6 months, while 9 patients reached 1 year follow up. A significant improvement was shown at all time-points with (p<0.01) for all scales till T3, and continued till 1 year post-injection with (p<0.01) for WOMAC and (p<0.05) for McGill and Lequesne. The treatment was well tolerated by all patients without systemic adverse effects, only 2 hip joints reported mild localized pain that subsided spontaneously within 3 days post-injection. **Conclusion:** Our preliminary findings suggest that a single injection of Hylastan SGL-80 is safe and effective in patients with moderate primary hip osteoarthritis, and this effectiveness seems to be maintained over one year.

Osteoarthritis (OA) is the commonest joint disease worldwide, characterized by degenerative changes involving the cartilage and many of its surrounding tissues. Despite the immense physical, psychological and socioeconomic impact of this disease on many people (1), few effective non-surgical treatments are

recommended. Viscosupplementation nowadays is increasingly used in the management of osteoarthritic pain; however the intra-articular administration of hyaluronic acid (HA) is still controversial across different organizations' guidelines (2, 3, 4). Different studies have shown that HA injections provide

Keywords: Hip, hyaluronic acid, hylastan SGL-80, ultrasound guided injection, osteoarthritis.

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prolonged relief from symptoms in patients with knee OA (5, 6), but debate still exists over its benefit in the treatment of hip OA; not all results of clinical trials confirm its effectiveness (7, 8, 9). The number of injections is also clinically important particularly in an intra-articular injection in the hip as it is technically more difficult than in the knee, besides that repeated injections might lead to increased risk of local side effects, which could be difficult to manage in a deep joint such as the hip, some previous open-label trials of a single injection of HA for the treatment of hip OA suggested promising results (10, 11) but the efficacy in these studies was evaluated in short term. In this prospective observational study the aim was to report preliminary data about the efficacy and safety of a single intra-articular ultrasound guided injection of Hylastan SGL-80 in patients with primary hip osteoarthritis of moderate severity within one year.

MATERIALS AND METHODS

20 patients were recruited from the outpatient clinic. After checking the inclusion and exclusion criteria (Table I), eligible patients that accepted to participate were asked to sign the informed consent form, after being informed about the study and the study design, the advantages and disadvantages of participation and the adverse effects of the product.

Each hip joint was injected only once with 4 ml of Hylastan SGL- 80 through longitudinal antero-inferior approach under ultrasound guidance, in patients with bilateral hip osteoarthritis the interval between injecting both hips was 3 months. Hylastan SGL- 80 is a cross-linked hyaluronic acid of fermentative origin presented with an innovative feature called “soft- gel”. Which is a mixture of sodium hyaluronate (HA) gel chemically cross-linked with divinylsulfone and a liquid-based HA of low molecular weight (0.9-1.3 MDa) characterized by a 80:20 gel to fluid ratio (13, 14). All included patients were assessed by : History taking, clinical examination, Visual Analogic Scale (VAS) for intensity of hip pain, McGill Pain Questionnaire (McGill) to evaluate the characteristics of the hip pain, Western Ontario McMaster Questionnaire (WOMAC) for pain, stiffness and functional limitations, Lequesne Index for the duration of pain and stiffness, and Tenderness scale (12); that was considered positive if at least one side of hip joint - anterior, lateral or posterior - is tender on palpation. To evaluate safety: Both local and systemic side effect were screened through a phone call 3 days after infiltration

besides regular clinical evaluation in the follow up visits during the whole duration of the study. The patients' assessment was at T0: before injection, T1: 1 month post injection, T2: 3 months, T3: 6 months and T4: 1 year post injection. The injection was performed by the same operator through 4 steps: 1- Patient was examined in supine position with 7.5-10 MHZ linear probe by anterior parasagittal approach lateral to femoral vessels, parallel to femoral neck. 2- After the skin is prepped to create a sterile field, the needle (0.9 x 88mm / 20 Gauge) is advanced at 45° caudo-cranial along the long axis of the transducer aiming for the anterior recess near the junction of the femoral neck with the femoral head (15) (Figure 1). 3- When the needle came in contact with the femoral head-neck junction it is slightly retracted 1mm then a pre-filled syringe with 4 ml of Hylastan SGL-80, was securely attached to the needle, followed by injecting the drug slowly under real time ultrasound guidance (Figure 2). 4- Immediately post injection, reassessment by ultrasound to examine the expansion of the capsule joint in order to ascertain the presence of the drug in the joint space (Figure 3).

RESULTS

Demographic features of the included 20 Patients (Table II): 14 female (70%), 6 male patients (30%), mean age 68.4 years, mean BMI 26.1 kg/m², and average complaint duration 47.1 months. 23 hip joints were injected (hips bilaterally injected in 3 patients, 10 hip joints were grade II and 13 hips grade III according to radiographic Kellgren Lawrence grading scale). The 23 injected hips were followed up to 1 month post-injection, 22 of them reached 3 months, 17 joints reached 6 months, while 9 patients reached 1 year follow up post-injection. Outcomes were evaluated by comparing baseline values with the values recorded at each time point after injection using Student t-test (Table III). All included patients obtained improvement of variable degrees regarding pain and function, no patient judged their condition as worsening or unchanged. The results after 1, 3 and 6 months showed highly significant improvement in all applied scales with p value < 0.01. In 12 months the 9 out of the 20 included patients continued their clinical improvement with highly significant results (p<0.01) in WOMAC, with statistical significant improvement in McGill and Lequesne (p<0.05). Improvement in tenderness scale in T1, T2, T3 and T4 is demonstrated in Table

Table I. *Eligibility criteria*

Inclusion criteria
<ul style="list-style-type: none"> - Diagnosis of primary hip osteoarthritis - Male and female patients aged between 50 to 80 years - Radiographic evidence of OA of the hip (Kellgren Lawrence grade II and III) - Pain refractory to other conservative treatments
Exclusion criteria
<ul style="list-style-type: none"> - Kellgren Lawrence grade I and IV - Known hypersensitivity to hyaluronic acid preparations - Coagulation disorders - Venous or lymphatic stasis of the concerned limb - Side effects due to previous infiltrations - Surgical interventions, infections, fractures, skin lesions of various kinds - Intra-articular hip injection within the previous 6 months. - Psychiatric and Mental disorders

IV. The trend of improvement in the scales' average values of the 9 patients till one year follow up; showed peak of improvement in VAS and McGill at T3 and continuation of improvement in all scales with gradual decline in VAS McGill and WOMAC at T4, but still much better than baseline values (Figure 4). Further analysis regarding efficacy on Kellgren Lawrence grade II (10 hip joints) versus grade III (13 hip joints) showed insignificant difference regarding degree of improvement with P value >0.05 (Table V). It is worth to state that at baseline 10 out of 20 patients consumed pain killers for hip pain, in 1 month post injection 8 patients stopped taking pain killers, 6 of them did not consume pain killers till 6 months, while 4 of the 9 patients continued the 1 year follow up without the need of pain killers

for hip pain. Moreover in 1 year duration there was reduction of the number of patients followed rehabilitation program, from 4 patients at baseline down to 1 patient. Regarding safety; the treatment was well tolerated by all patients, no systemic adverse effects were reported. Only 2 injected hip joints (8.7%) reported mild localized pain that subsided spontaneously within 3 days post-injection. No medications were required and daily function was not affected.

DISCUSSION

In this prospective observational study preliminary data about the efficacy and safety of single ultrasound guided injection of 4 ml Hylastan

Table II. Demographic features

Patient	Gender	Age (years)	BMI (kg/m ²)	Duration Of Complaint (months)
1	F	63	21.4	48
2	M	59	26.9	48
3	F	81	26.0	36
4	F	74	23.7	72
5	F	78	28.8	72
6	F	72	29.3	60
7	F	66	31.6	12
8	F	73	31.2	2
9	F	62	18.9	60
10	F	76	25.4	66
11	F	68	36.5	12
12	M	58	28.0	24
13	M	65	24.6	12
14	M	77	28.1	12
15	M	72	24.7	24
16	F	80	30.5	240
17	F	63	22.3	60
18	F	65	21.6	10
19	F	57	21.5	120
20	M	57	28.0	3
21	F	63	18.9	60
22	F	64	21.4	6
23	F	81	30.5	24
MEDIA	F:14 M:6	68.4	26.1	47.1

SGL-80 in moderate primary hip osteoarthritis was evaluated in 20 patients/23 injected hips, with significant improvement and high patient tolerability lasted till one year post injection. To our knowledge no studies reported the outcome of Hylastan SGL-80 in hip OA is published so far. However, few studies evaluated its efficacy in knee osteoarthritis. Migliore et al., published preliminary data in 2011 suggesting beneficial effects obtained by single intra-articular injection of Hylastan SGL-80 in the knee joint which was evident at 1 month and maintained over 3 months, with a high significant improvement ($p < 0.001$) for every time point, with 2 patients

(7.14% of total patients), for a total of 2 injections (6.06%), reported a transient discomfort for 1–3 days that regressed spontaneously (16). Conrozier and his colleagues in 2010 assessed 2 intra-articular injection regimens of hylastan SGL-80 in knee OA patients through a multicenter, randomized, double-blind study; 391 patients were randomly divided into 3 groups: one group received 1 injection of Hylastan SGL 80 and the second received 2 injections, 2 weeks apart. The third received 1 injection of 40 mg of methylprednisolone acetate. The study reported that both single and multiple injections of Hylastan SGL 80 were well tolerated and comparable to steroid.

Table III. Comparison of baseline values with the values recorded at each time points post injection.

Evaluation of 23 hips, at T1 compared to T0						
Scales	Mean (SD) T0	Mean (SD) T1	T0/T1 %	t	p	statistical significance
<i>VAS</i>	6.47 (2.1)	3.91 (3.0)	- 40	4.1	0.000	HS
<i>McGill</i>	14.78 (5.3)	6.56 (4.9)	- 56	5.7	0.000	HS
<i>Lequesne</i>	6.97 (3.7)	3.30 (3.1)	- 53	4.9	0.000	HS
<i>WOMAC</i>	35.04 (15)	16.69 (18)	- 52	5.9	0.000	HS
Evaluation of 22 hips, at T2 compared to T0						
Scales	Mean (SD) T0	Mean (SD) T2	T0/T2 %	t	p	statistical significance
<i>VAS</i>	6.50 (2.1)	3.41 (2.9)	-48	4.4	0.000	HS
<i>McGill</i>	14.95 (5.3)	5.95 (5.6)	-60	5.9	0.000	HS
<i>Lequesne</i>	6.84 (3.7)	3.15 (3.1)	-54	4.4	0.000	HS
<i>WOMAC</i>	34.72 (15)	11.86 (14)	-66	6.5	0.000	HS
Evaluation of 17 hip joints, at T3 compared to T0						
Scales	Mean (SD) T0	Mean (SD) T3	T0/T3 %	t	p	statistical significance
<i>VAS</i>	6.52 (1,8)	2.88 (2.7)	- 56	4.7	0.000	HS
<i>McGill</i>	14.88 (5.3)	5.47 (5.9)	- 63	4.9	0.000	HS
<i>Lequesne</i>	7.64 (3.6)	3.38 (3.2)	- 56	4.7	0.000	HS
<i>WOMAC</i>	36.41 (16)	12.17 (12)	- 67	6.2	0.000	HS
Evaluation of 9 hips after 1 year, at T4 compared to T0						
Scales	Mean (SD) T0	Mean (SD) T4	T0/T4 %	t	p	statistical significance
<i>VAS</i>	6.55 (1.7)	4.22 (3.9)	- 36	1.6	0.149	NS
<i>McGill</i>	16.44 (5.1)	7.88 (7.7)	- 52	3.1	0.015	S
<i>Lequesne</i>	7.83 (3.5)	3.77 (3.4)	- 52	2.6	0.032	S
<i>WOMAC</i>	41.77 (16)	17.22 (17)	- 59	4.1	0.003	HS
VAS = Visual analogue scale McGill = McGill Pain Questionnaire WOMAC = Western Ontario McMaster Questionnaire. HS = Highly Significant S = Significant NS = Non Significant						

Furthermore the single injection provided long-lasting pain relief and a safe, convenient alternative to multiple injections with follow up till 26 weeks (17). In the previous two studies, the difference in the evaluating scales compared to baseline were similar to ours; with high significance ($P < 0.01$), the additional note is that the significant results in hip OA of moderate severity in our study seem to maintain up to 12 months. Most of the studies conducted with single HA injection in hip OA patients showed good results; however, in our study non-responders did not exist and no repetition of infiltration was needed to enhance the responsiveness compared to some studies

(18, 19). Our preliminary results suggest maintenance of single Hylastan SGL-80 injection up to 12 months which is similar to Vad et al., 2003 (20) but differs than other studies that reported effectiveness of single HA hip injection till average duration of 5.3 months (19, 21, 22, 23, 24). The insignificant difference between the 10 hips of Kellgren Lawrence grade II and the 13 hips grade III regarding the degree of improvement is inconsistent with the studies stated that viscosupplementation appears to be more efficacious in those with less radiographic changes of OA (26, 27), however small sample size in our study makes this comparison inconclusive. Although

Table IV. *Tenderness scale at T1, T2, T3 and T4 compared to baseline at T0*

TENDERNESS	Before treatment T0 (23 joints)		After treatment T1 (23 joints)		p	Significance
	No.	%	No.	%		
Positive	21	91.3	12	52.2	<0.01	HS
Negative	2	8.7	11	47.8		
TENDERNESS	Before treatment T0 (22 joints)		After treatment T2 (22 joints)		p	Significance
	No.	%	No.	%		
Positive	19	86.4	10	45.5	<0.01	HS
Negative	3	13.6	12	54.5		
TENDERNESS	Before treatment T0 (17 joints)		After treatment T3 (17 joints)		p	Significance
	No.	%	No.	%		
Positive	16	94	9	52.9	<0.01	HS
Negative	1	6	8	47.1		
TENDERNESS	Before treatment T0 (9 joints)		After treatment T4 (9 joints)		p	Significance
	No.	%	No.	%		
Positive	8	88.9	6	66.7	>0.05	NS
Negative	1	11.1	3	33.3		
HS = Highly Significant NS = Non Significant						

the effect of single injection of Hylastan SGL-80 on administration of pain killers or physiotherapy was out of the scope of this study, the decline of the need to concomitant treatments after injection reflects the positive influence of Hylastan SGL-80 on hip OA. Reduction of non-steroidal anti-inflammatory drugs consumption after hip viscosupplementation in hip osteoarthritis patients, was also concluded in few studies, indicating hip OA pain relief (28, 29, 30, 31). Regarding safety, the studies mentioned above using intra-articular viscosupplementation in hip OA reported similar safety profile as with Hylastan

SGL-80 in our study; we reported only 2 injected hip joints (8.7%) experienced mild localized pain that subsided spontaneously within 3 days post-injection, with no medications required and daily function was not affected and with no reported systemic adverse effects. The frequency of adverse events in hip injection ranged from 10 to 30%, which is slightly higher than the rates reported in viscosupplementation treatment of knee OA (32, 33). We believe that these reported local adverse effects may have been a result of effusion, local swelling or needle trauma related to the infiltration process itself rather than the type of

Table V. Comparison between hips Kellgren Lawrence grade II and grade III regarding degree of improvement in VAS, McGill, WOMAC and Lequesne in all time points after injection

Item	Grade II (no of hips)	Grade III (no of hips)	t	p	Sig.
Change in VAS at T1 Mean ± SD	(10) 3.2 ± 3.1	(13) 2.0 ± 2.9	1.0	0.323	NS
Change in VAS at T2 Mean ± SD	(9) 4.7 ± 3.7	(13) 2 ± 2.5	-0.9	0.391	NS
Change in VAS at T3 Mean ± SD	(8) 3.9 ± 3.5	(9) 3.4 ± 3	0.4	0.690	NS
Change in VAS at T4 Mean ± SD	(4) 2.3 ± 5.3	(5) 2.4 ± 4.1	0.6	0.574	NS
Change in McGill at T1 Mean ± SD	(10) 9.4 ± 7.3	(13) 7.3 ± 6.8	0.1	0.899	NS
Change in McGill at T2 Mean ± SD	(9) 12.5 ± 7	(13) 6.5 ± 6.3	-0.8	0.405	NS
Change in McGill at T3 Mean ± SD	(8) 9 ± 9	(9) 11.1 ± 5.5	1.1	0.271	NS
Change in McGill at T4 Mean ± SD	(4) 6.2 ± 11.9	(5) 10.4 ± 4.9	1.3	0.225	NS
Change in WOMAC at T1 Mean ± SD	(10) 20.2 ± 18.2	(13) 16.9 ± 12.1	1.2	0.243	NS
Change in WOMAC at T2 Mean ± SD	(9) 32.7 ± 13.1	(13) 16 ± 15.6	-0.9	0.344	NS
Change in WOMAC at T3 Mean ± SD	(8) 31 ± 15.1	(9) 19.3 ± 13.4	-0.2	0.833	NS
Change in WOMAC at T4 Mean ± SD	(4) 31 ± 15.1	(5) 19.2 ± 17.4	-0.2	0.834	NS
Change in Lequesne at T1 Mean ± SD	(10) 4.5 ± 3.6	(13) 3 ± 3.6	-0.3	0.723	NS
Change in Lequesne at T2 Mean ± SD	(9) 5.8 ± 3.3	(13) 2.2 ± 3.6	-1.1	0.274	NS
Change in Lequesne at T3 Mean ± SD	(8) 5.0 ± 4.2	(9) 3.5 ± 3.3	0.0	0.961	NS
Change in Lequesne at T4 Mean ± SD	(4) 5.5 ± 7	(5) 2.9 ± 1.8	0.4	0.703	NS
VAS = Visual analogue scale, McGill = McGill Pain Questionnaire, WOMAC = Western Ontario McMaster Questionnaire, NS = Non Significant					

medication used. The significant results demonstrated in our study could be referred to the molecular structure of Hylastan SGL-80 which includes the low molecular weight HA that allows rapid onset of action and the cross-linked that increases the residence time of hyaluronic acid in the joint. Furthermore the agent divinylsulfone that allows obtaining a “soft-gel” which

has peculiar viscoelastic characteristics, similar to those of healthy synovial fluid (13, 14). While the peak of hip pain improvement measured by VAS and McGill at 6th months post injection may have been caused by the suggested HA mechanism of action as having stimulating effect on synovial lining cells, with subsequent production of normal hyaluronic

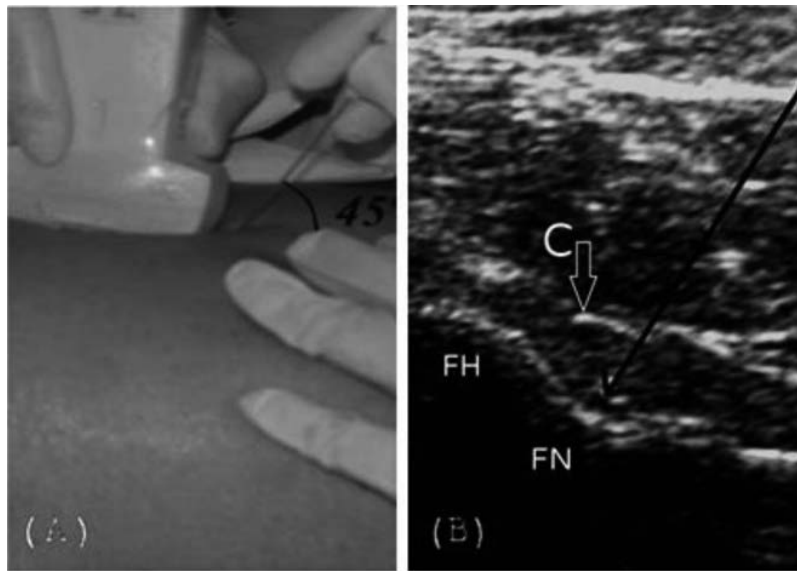


Fig. 1. The antero- inferior longitudinal approach for hip injection (A) the needle is inserted 1 cm distal to the probe with a tilt 45° to the skin surface. (B) The black arrow describes the direction of the needle towards the junction between femoral head and neck. FH, Femoral head; FN, Femoral neck; C, Capsule.



Fig. 2. Pre-filled syringe with 4 ml of Hylastan SGL-80 was securely attached to the needle, followed by injecting the drug slowly under real time ultrasound guidance. P, Proximal; D, Distal.

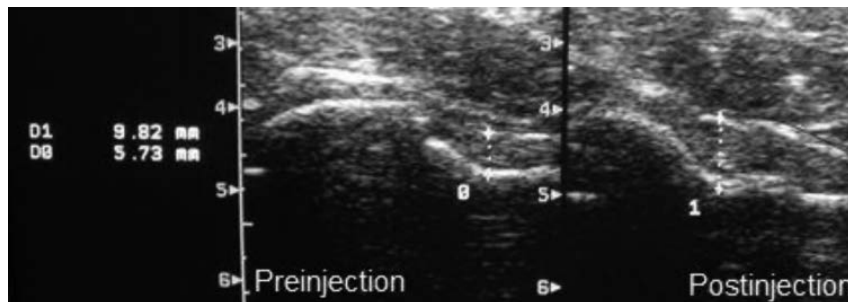


Fig. 3. Reassessment by ultrasound immediately post-injection to examine the expansion of the joint capsule in order to ascertain the presence of the drug in the joint space D0: capsule distention pre-injection = 5.73 mm, D1 capsule distention post-injection = 9.82 mm.

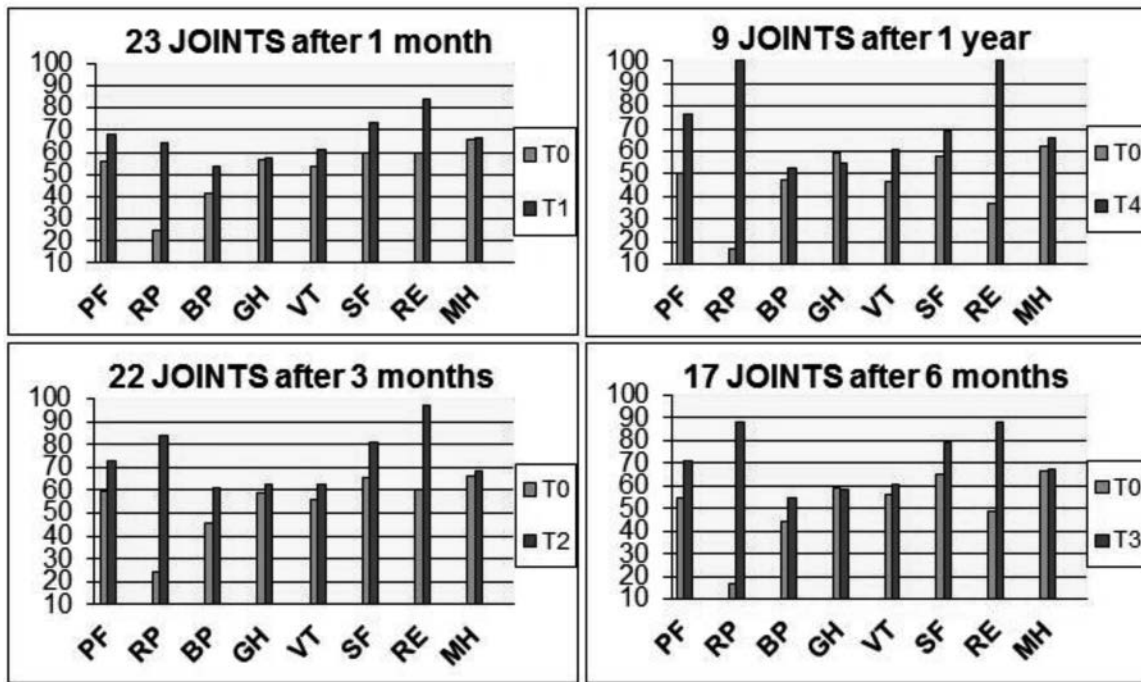


Fig. 4. SF 36 Domains in 1 and 3, 6 and 12 months post injections. PF, Physical Function; RP, Role Physical; BP, Bodily Pain; GH, General Health; VT, Vitality; SF, Social Functioning; RE, Role Emotional; MH, Mental Health.

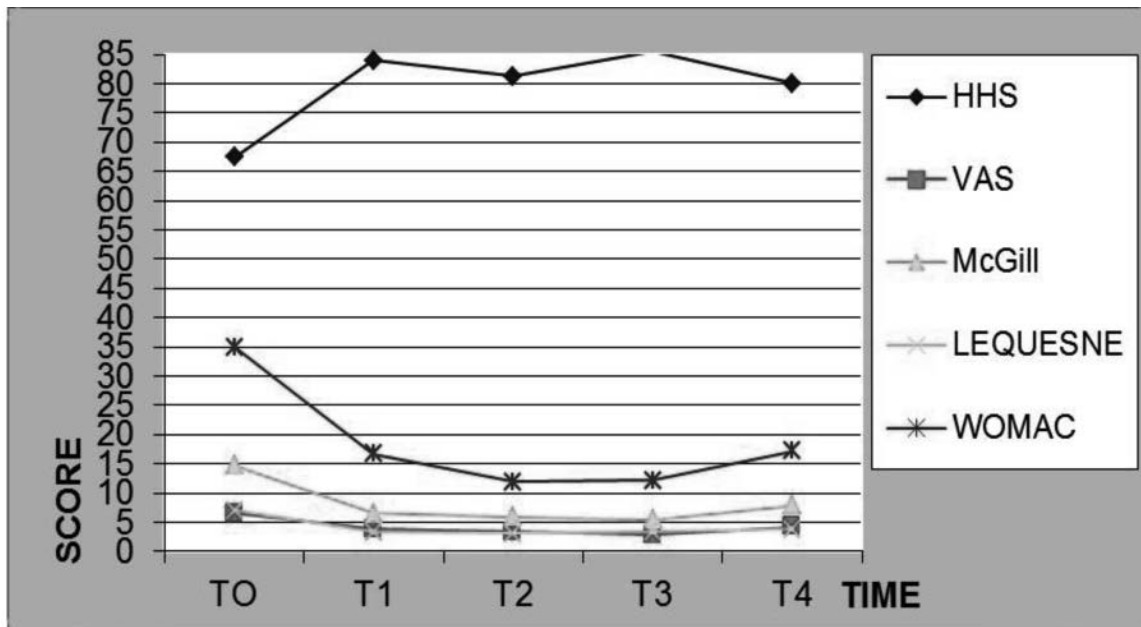


Fig. 5. Trend of the improvement of the scales average values, till one year follow up; showing peak of improvement at T2 and T3.

acid (33), which may take time to demonstrate better improvement later, this is just a possible explanation that could be a fertile background for subsequent studies including more patients for longer term.

CONCLUSION

In the light of our preliminary findings, we imply that a single injection of Hylastan SGL-80 is safe and effective in patients with moderate primary hip osteoarthritis, and this effectiveness seems to be maintained over one year.

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CLINICAL AND SONOGRAPHIC ASSESSMENT OF THE EFFECTIVENESS OF COLLAGEN INJECTIONS GUNA MDs IN SHOULDER PERIARTHRITIS WITH BURSITIS

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The aim of this study was to evaluate the efficacy of collagen Injections GUNA MDs regarding pain and functioning of the shoulder in patients with periarthrititis, subacromial subdeltoid bursitis (SASDB) and duration of symptoms up to 3 months. We studied 20 patients with painful shoulder and sonographic proved SASDB. We applied in the subacromial space a combination of GUNA MD-Shoulder and GUNA MD-Matrix in total course of treatment 8 weeks. Clinical assessment included demographic and clinical data, a visual analog scale (VAS) for pain (0-100), Likert scale, Shoulder Function Assessment (SFA) scale (0-70) and sonographic evaluation of the shoulder at baseline, 60 and 150 days. Evaluation of the efficacy according to the patient and the physician were performed. Results showed significant efficacy on pain which remained after the treatment. There was a statistically significant improvement of SFA index. 80% out of all patients gave a very good and good assessment of the efficacy, which coincided with the opinion of the physician. 80% out of all patients had reduction or lack of bursitis on second and on third visit which was sonographically proved. No adverse events were registered. In conclusion, collagen injections GUNA MDs significantly reduced pain and SASDB edema and increased functional activity of the shoulder, thereby increasing the quality of life.

About 20% of the human population have symptoms of pain and limited mobility of the shoulder. (1)

Shoulder pain correlates with age. Its frequency is between 6 and 11% to 50 years of age and then increases more than two times, and ranges between 16 and 25%. (2)

Main reason for shoulder pain is injury of the rotator cuff (RC) and subacromial subdeltoid bursa (SASDB). RC is composed of collagen, proteoglycans (PG), glycosaminoglycans (GAG), water and cells. Light microscopy shows that the primary damage is decreasing of collagen type I, which fibers become thinner than normal. In the extracellular matrix remodeling occurs by the impact of metalloproteinase enzymes which preceded clinical

signs. Therefore, the only effective treatment would be structural modifying treatment. (3) During the last years humankind is looking for medical products for local injections into the joints which are different from traditional medicines, such as corticosteroids. It is about medical products that combine positive effects on joints with lack of side effects. Treatment with injectable collagen GUNA MDs presents a pharmacological concept based on the synergistic effect of alternative and conventional medicine. (5,6) This concept has gained popularity with the term Physiological Regulating Medicine in which field work different kind of medical professionals: rheumatologists, orthopedists, neurologists, dermatologists, sports medicine specialists, etc. The recovery of collagen structures through the use

Key words: Shoulder periarthrititis, Subacromial subdeltoid bursitis, Ultrasonography, Collagen injections

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of collagen injections GUNA MDs is shown in 7 clinical trials and is used increasingly in practice. The purpose of the local administration of the collagen is essentially structural- to provide mechanical support, to replace, strengthen, structure and protect the zone where is injected. Due to its low dose (300 mcg) collagen acts signally, changing extracellular matrix and leading to activation of cellular functions.(5,6) GUNA MD-Shoulder reduces degenerative changes in the RC of the shoulder through the enhancement and strengthening of the collagen matrix in tendons, muscles, ligaments and joint capsule, which reduces pain. GUNA MD-Matrix improves the functions and regenerates the extracellular matrix, activating the cellular functions. This results accelerate of healing process through faster resolution (drain effect) of swelling. (5,6) The aim of this study was to evaluate the efficacy of Collagen Injections GUNA MDs regarding pain and functioning of the shoulder in patients with periartthritis and bursitis of the SASDB with duration of symptoms up to 3 months. Musculoskeletal ultrasonography (MSU) is an approved imaging technique for diagnosis of Rotator cuff (RC) pathology of the shoulder and monitoring of therapy.(7-18) Patients with previous trauma or chronic inflammatory arthritis were excluded. No patient had received previous physiotherapy or local steroid injection in the shoulder.

MATERIALS AND METHODS

We studied 20 patients with painful shoulder and sonographically proved bursitis of the SASDB. Inclusion and Exclusion criteria were summarized in Table I.

At the baseline visit was made standard X-Ray of the painful shoulder. Clinical assessment included demographic and clinical data, a visual analog scale (VAS) for pain (0-100), Likert scale (0-3) and Shoulder Function Assessment (SFA) scale (0-70) on baseline, on 60-th and on 150-th day. Evaluation of the efficacy according to the patient and the physician were performed.(19-20) Likert scale is a subjective assessment of the movement according to the patient (0- impossible movement of the shoulder; 1-movement with big difficulties; 2-movement with some difficulties; 3-movement without difficulties). The SFA test has 2 items concerning pain on motion and at rest; 4 items for shoulder function in activities of daily living; and 3 objective ROM /Range Of Motion/ measures. The SFA consists of two visual analogue scales (VAS; pain at rest and during movement), four multiple choice questions

about activities of daily living (dressing, combing hair, washing opposite axilla, and using the toilet), and three measures for ROM (total active abduction and two combined movements asking the patient to place the hand on the head with the elbow forward and backward). The overall score ranges from 0 (worst shoulder function) to 70 (best shoulder function).

Sonographic assessment:

All patients were examined with commercial, real-time equipment Mindray M5 (China) using a 7.5-10 MHz linear phased array transducer. A standard scanning protocol including multiplanar, dynamic and bilateral evaluation was followed in order to avoid missing the assessment of one or more anatomic structures of the shoulder. Transverse and longitudinal planes from the Biceps tendon (BT), Subscapularis tendon (SSC), Supraspinatus tendon (SSP), SASDB, Infraspinatus tendon (ISP) and the Acromioclavicular joint (ACJ) were scanned. The BT and ACJ were scanned in neutral position of the shoulder with flexed elbow in 90°. The SSC tendon was assessed in full external rotation of the shoulder. Each patient's arm was put into full internal rotation with the hand placed posterior to the spine for the assessment of SSP tendon. The ISP tendon was assessed in shoulder adduction with the hand on the opposite shoulder. A dynamic view of the SSP tendon was obtained by moving the patient's arm from a neutral position to a 90° abduction in order to detect encroachment of the acromion into the RC (10-17). To objectify the MSU evaluation, two trained and experienced MS sonographers with at least 5 years experience in MSU scanned together each patient and reached consensus on the US findings. MSU assessment was performed on the baseline, on the 60th day and on the 150th day. We applied the combination of 10 amp. Collagen MDs Shoulder and 10 amp. Matrix /a total of 20 amp, 2 ampules for each application/ following the scheme: 2 weeks – 2 applications/weekly and 6 weeks – 1 application/weekly in general course of treatment 8 weeks.

Collagen application technique:

The applications were performed according to generally accepted rules.

The patient's skin was sterilized with alcohol and Braunol. Access to the subacromial space was achieved with a lateral approach, inserting a 21-gauge (0.8X50 mm) needle under the anterolateral aspect of the acromion process, passing it through the deltoid muscle, and directing it medially and slightly anterior to the SASD bursa, with care taken to avoid injection directly into the tendons of the RC.(12)

Statistical analysis:

For VAS and SFA assessment Repeated measures

analysis was used. For assessment of Bursitis χ^2 analysis was used.

RESULTS

1. VAS Pain during the day: on the second visit (day 60-th) the pain during the day reduced 3 fold and continued to reduce till the third visit (day 150-th) more than 5 times compared to the first visit (Fig. 1). VAS Pain during the night: the result was similar with reduction of the nocturnal pain on the second visit (about 3 times) and result has kept on the third visit (Fig. 2).

2. Likert Scale: the estimation on the second visit showed increasing of the point number till 2.5 points which correlated with improvement of the

movement range from “some difficulties” to “without difficulties” (3-4 grade of Likert) with keeping of the efficacy till the third visit (Fig. 3).

3. The index of SFA had a statistically significant improvement of all SFA criteria which correlated with increasing of the point number with 24.8 points. The improvement continued till the third visit also (Fig. 4 and Table II).

4. Patient Assessment: the scale had 5 levels of appraisal-from maximal- “Very good” to minimal- “Deterioration”. Minimum 80% of the patients gave a very good and good assessment of efficacy of collagen medical devices (Fig. 5).

5. Physician’s Assessment: The scale was similar: Maximal evaluation- “Very good” to minimal -“Deterioration”. Physicians gave very good and

Table I. Including and excluding criteria.

Including criteria	Excluding criteria
1. Age 18-80 years	1. Joint inflammatory and rheumatic auto-immune disease, infections
2. Clinical diagnosis: Shoulder periarthritis	2. Degenerative arthropathy, traumas, surgery in shoulder /incl. Complete ruptures of the RC/
3. Duration of the symptoms up to 3 months	3. Physiotherapy and topical corticosteroids application within a month before and during the monitoring
4. Pain by VAS over 25mm	4. Other diseases – diabetes mellitus, neurological diseases /incl. brachial plexitis, peripheral neuropathy/
5. Sonographic proved bursitis of SASD bursa	5. Cancer, chemotherapy, radiotherapy

Table II. Results on each of items in SFA.

Pain at rest	F(2, 38) = 7,914, p = 0.001
Pain during movement	F(2, 38) = 74,078, p < 0.001
Dressing	F(2, 38) = 72,724, p < 0.001
Combing hair	F(2, 38) = 63,317, p < 0.001
Washing opposite axilla	F(2, 38) = 25,294, p < 0.001
Using the toilet	F(2, 38) = 14,256, p < 0.001
Active abduction	F(2, 38) = 64,373, p < 0.001
Hand on the head with the elbow forward	F(2, 38) = 33,496, p < 0.001
Hand on the head with the elbow backward	F(2, 38) = 53,451, p < 0.001

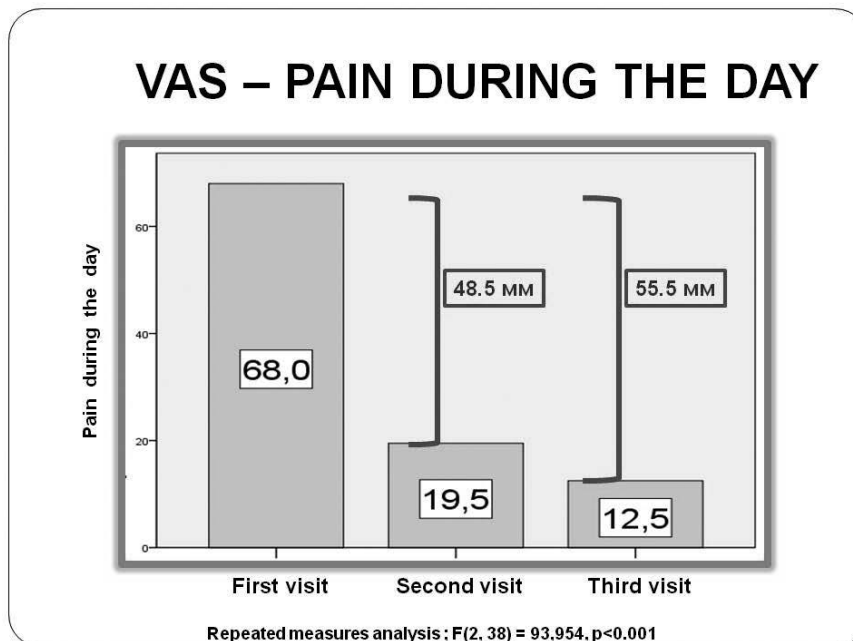


Fig. 1.

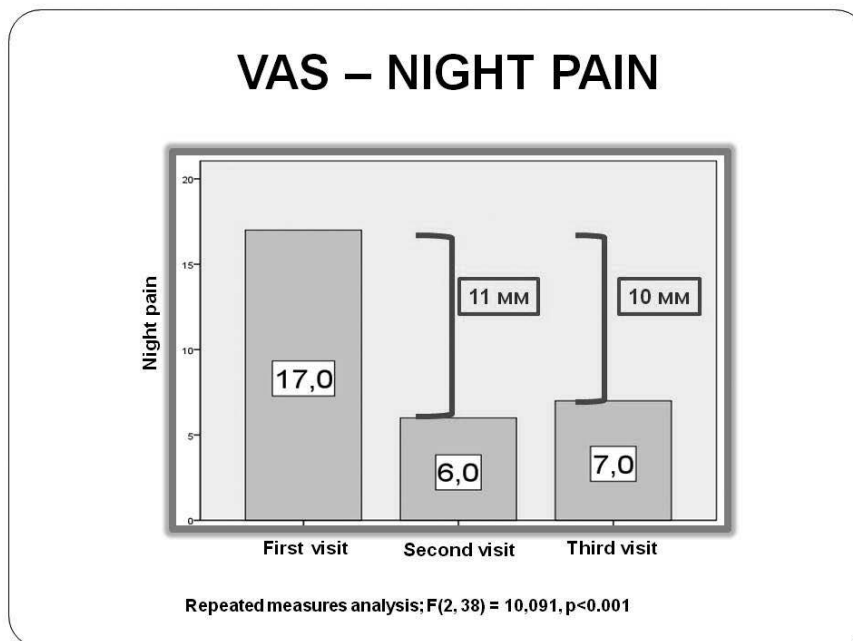


Fig. 2.

good evaluation of the efficacy of GUNA MDs treatment in at least 80 % of patients on the second and third visit (Fig. 6).

6. Bursitis: Sonographic estimation: 80% out of all patients had reduction or lack of SASDB on the second and third visit (Fig. 7).

We present sonographic images in transverse scan of BT showing SASDB before and after the treatment with GUNA MDs. In the Figure 8 (baseline) is shown Increase quantity of fluid in the SASDB /hypochoic distension of the bursa which is visible over the BT/. On the second visit (after

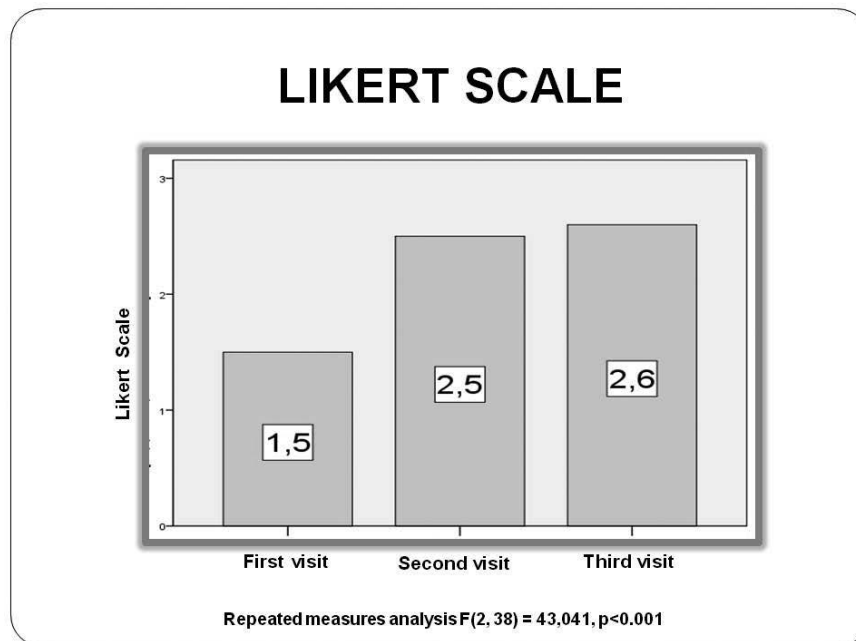


Fig. 3.

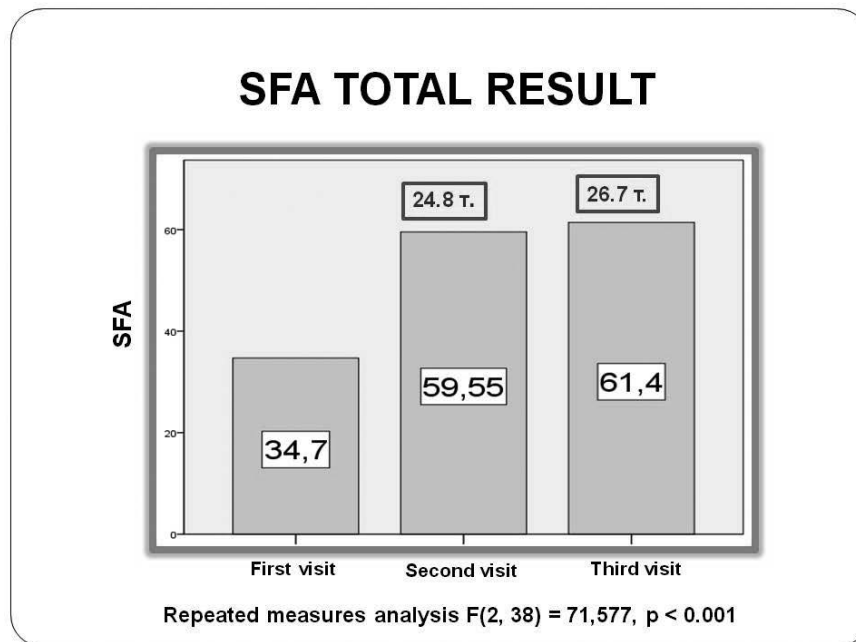


Fig. 4.

treatment) there is no features of bursitis (Fig.9).

DISCUSSION

Collagen injections GUNA MDs significant affected pain, SASDB edema and functional activity

of the shoulder. Efficacy assessment was high: over 80% according to patient and 80% according to the physician. 16 patients (80%) were without bursitis and they had full recovering of the RC on the second and third visit. 4 patients (20%) were without improvement. We found incomplete rotator

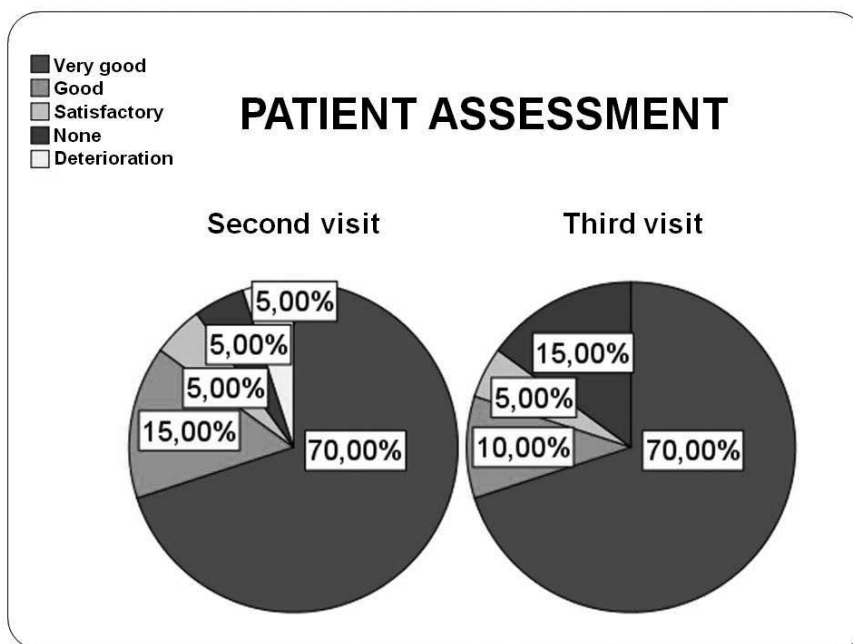


Fig. 5.

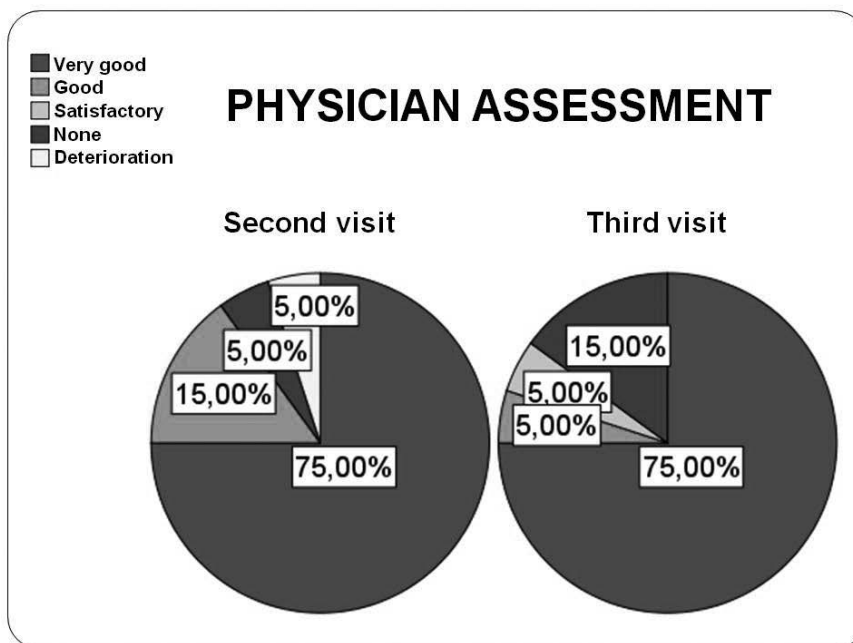


Fig. 6.

cuff lesions in 6 patients (30%) at the first visit. In 5 patients of them on the second and third visits there was significant sonographic improvement of the fibrillar echotexture of the tendons which proved strengthening and restoring effect of GUNA MDs

on collagen structures. The 6-th patient (5%) during the study (just before the second visit), underwent a traumatic fall on the damaged shoulder. As a result, the patient obtained further complication- a full-thickness rupture of the SSP tendon /US proved/

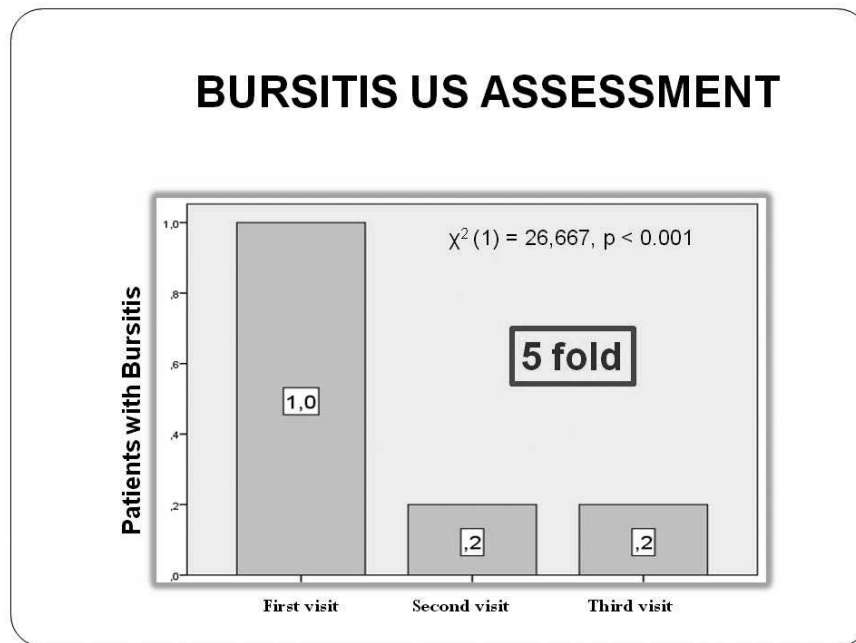


Fig. 7.

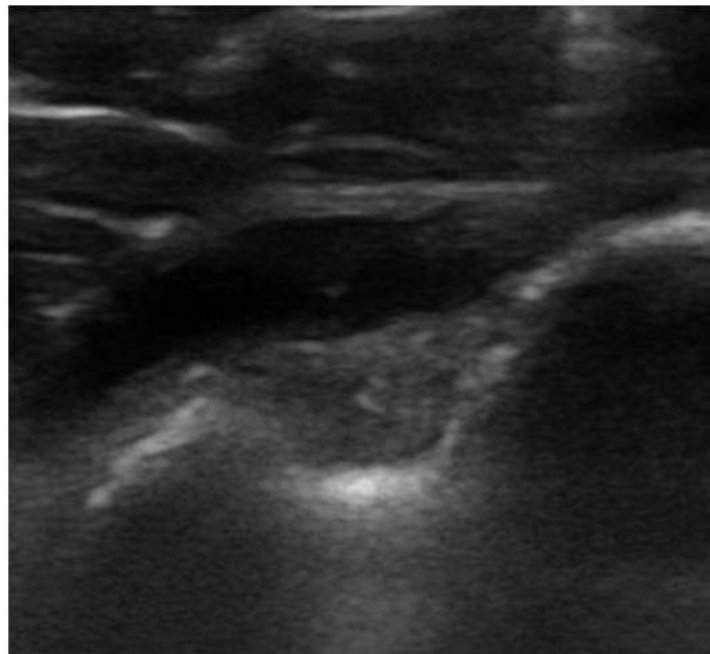


Fig. 8.

and was referred to surgery intervention. We had found calcifications of the RC in 13 patients (65%) on the first visit and 10 of them (50% of all patients) were with improvement of the echotexture of the tendons although calcifications on the second and

third visit. The other 3 patients of this group (15%) were without clinical improvement. Sonographic evaluation showed big calcifications (over 15 mm in diameter) against the background of tendinitis with lack of features for incomplete or full-

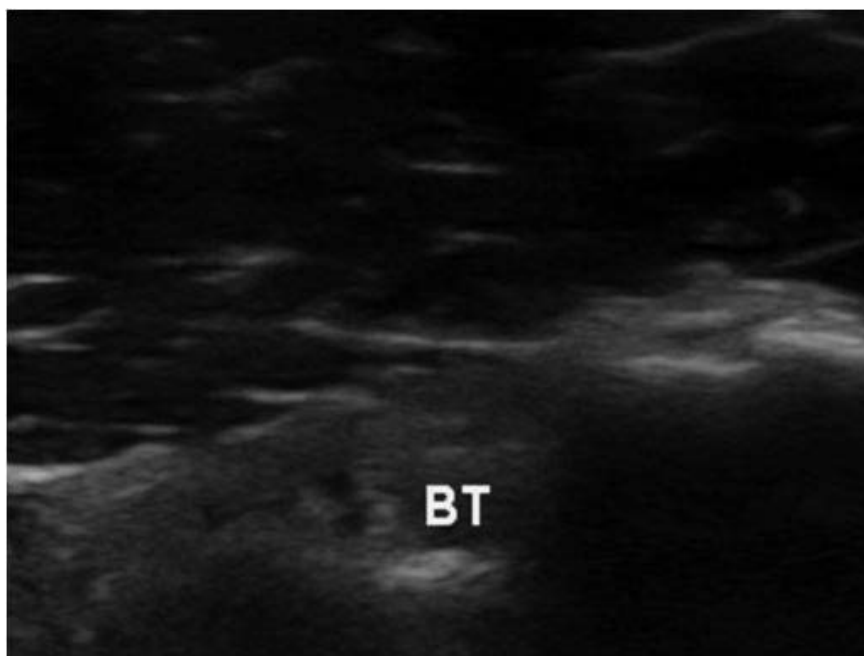


Fig. 9.

thickness lesions. These 3 patients refused surgery intervention. Collagen Medical Devices GUNA in patients with Shoulder periarthritits and bursitis showed the following benefits:

1. High individual clinical response: pain /VAS/, movement /Likert/, Patient assessment
2. High objective clinical response: Tests, SFA, Sonographic assessment, Physicians evaluation
3. Successful treatment of SASD bursitis
4. Strengthening and restoring effect on collagen structures of the RC tendons /recovery in cases of incomplete RC lesions
5. Maintenance of the result beyond the last injection
6. Increasing patient quality of life
7. Total absence of adverse side effects

In conclusion, the collagen injections GUNA MDs are an innovative and effective approach with regenerative and analgesic effect in the treatment of Shoulder periarthritits and bursitis. Their ease application and total absence of side effects makes them a modern device of choice in daily practice of the physician.

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PAIN RELIEF AND FUNCTIONAL RECOVERY OVER A SIX-MONTH PERIOD AFTER INTRA-ARTICULAR INJECTION WITH SODIUM HYALURONATE (MW 1500 - 2000 KDA) IN OSTEOARTHRITIS OF THE KNEE

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The present study aimed to evaluate the effects of a single intra-articular injection of a high molecular weight (MW) (1500-2000 kDa) naturally linear hyaluronic acid (HA) in patients suffering from knee osteoarthritis (OA). One hundred and sixty-eight patients with mild to moderate OA of the knee were enrolled to receive one ultrasound-guided intra-articular (IA) injection of 4ml Sodium Hyaluronate (HyalOne®) and were followed up for 24 weeks. The primary efficacy outcome was the change from baseline to week 24 in patients' pain perception using a 100 mm visual analogue scale (VAS). Additional outcomes included the Western Ontario McMaster Universities Arthritis score (WOMAC) and Knee injury and Osteoarthritis Outcome Score (KOOS) assessed at 4, 12 and 24 weeks. The patients enrolled showed a significant improvement from baseline in all symptomatic outcome measures. Pain significantly decreased after treatment. VAS pain decreased from the baseline mean value of 77.7 mm (SD 8.8, range: 60-90) to the mean value of 13.8 mm (SD 4.9, range: 10-20) at week 24. The analysis of variance for repeated measures conducted on VAS, on each WOMAC subscale, on the total WOMAC score and on each KOOS subscale score showed a significant reduction in all scores at each study point (week 4, 12 and 24) ($p < 0.001$). Comparisons between week 4 and week 12 scores and week 12 and week 24 scores showed a significant and progressive improvement ($p < 0.05$, Wilcoxon test) during the study. The present study suggests that a single IA injection of linear high MW HA in patients suffering from knee OA is well tolerated and provides relief from pain. Benefit to knee function was confirmed by both the WOMAC and the KOOS scores. The patients' overall health status also improved as demonstrated by the high scores registered at the post-treatment KOOS Function in daily Living, Quality of Life and Function in Sport and Recreation subscales.

Osteoarthritis (OA) is the most common joint disorder; in Italy the estimated prevalence is between 10% and 18.3% (1). It is a chronic arthropathy of an entire joint characterised by disruption and potential loss of joint cartilage with other joint changes, including bone hypertrophy (osteophyte formation). Symptoms include gradually developing pain aggravated or triggered by activity, stiffness relieved less than 30 minutes after activity and occasional joint

swelling.

Overall, the knee is the most commonly affected joint and the impact on disability attributable to knee OA is similar to that due to cardiovascular disease and greater than that caused by any other medical conditions in the elderly (2).

There is no known cure for OA and there are no specific pharmacologic therapies that can prevent the progression of joint damage secondary to OA. The

Key words: Hyaluronic acid, Viscosupplementation, Knee osteoarthritis, Ultrasound-guided intra-articular injection.

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search for disease-modifying agents for OA that can prevent radiographic joint space narrowing, indicative of progressive articular cartilage loss, is being addressed through ongoing research (3-5).

The current goal of patient management of OA is to control pain and swelling, minimize disability, improve quality of life and educate the patient. Management is individualized based on patient expectations, level of function and activity, the joints involved, the severity of the disease, occupational and vocational needs and the nature of any coexisting medical problems.

Relevant Treatment Guidelines and Consensus Statements and information from the literature demonstrate that HA may be administered to treat pain associated with OA of the knee (6). A typical HA treatment cycle consists of five injections, 1 injection per week for 5 weeks (7, 8). Some patients report benefit following three-weekly injections (9, 10).

Synovial fluid contains high concentrations of high molecular weight hyaluronic acid which protects the synovial membrane, acts as a filter between haemolymphatic circulation and synovial liquid (11), has beneficial anti-inflammatory, anti-catabolic and pro-anabolic effects and stimulates repair processes (12). In osteoarthritis, both the concentration and molecular weight of HA are reduced (13), leading to a loss in viscoelasticity of the synovial fluid.

Several studies on osteoarthritis of the knee have demonstrated the effectiveness of viscosupplementation, the intra-articular (IA) injection of hyaluronic acid products, in restoring the viscoelasticity of the synovial fluid, improving joint mobility and reducing pain (14–18). The most recent meta-analysis available, published in September 2013 and including 29 randomized studies involving more than 4,500 patients with knee osteoarthritis, found that intra-articular hyaluronic acid (HA) injections provided significant improvement in pain and function compared to saline injections (19). The therapeutic effects of IA HA generally appear to have a slower onset but a longer duration than IA steroids and may be useful in the long term management of this chronic disease (20, 21).

Many hyaluronan preparations, differing in concentration and molecular weight, have been approved for use around the world (22).

HyalOne® (Hyalubrix 60 Italian brand) is a sterile, non-pyrogenic, viscoelastic solution manufactured

with hyaluronic acid sodium salt, obtained by bacterial fermentation from a fraction of high molecular weight with a range of 1,500–2,000 kDa.

The present study aimed to evaluate the use of a single ultrasound-guided intra-articular injection of HyalOne® in patients suffering from knee OA in alleviating symptoms and improving knee functionality in order to delay more aggressive pharmacological approaches to the disease and surgical procedures.

MATERIALS AND METHODS

This was a single-site, investigator-initiated, open, cohort study to assess the efficacy of a single ultrasound-guided IA injection of HyalOne® in reducing pain and improving knee functionality conducted in patients referred to the Centro Medico Mantia Clinic, Palermo, Italy, for knee OA between November 2011 and November 2012.

The study protocol, including informed consent documentation, was approved by the hospital Ethics Committee and the study was carried out in accordance with the International Conference on Harmonization (ICH) Guidelines and the Declaration of Helsinki. Informed Consent was obtained from all patients prior to participation.

The main inclusion criteria were: male or female patients aged 40 years or older with an active lifestyle who had been referred to the clinic for OA pain in one knee and scoring >50 and <90 mm on a 100 mm OA pain visual analogue scale (23, 24) where 0 mm = no pain and 100 mm = worst possible pain; tibiofemoral OA (ACR criteria) (25), Kellgren–Lawrence grade II or III (26) diagnosed by standard X-rays taken within 3 months prior to enrolment; no surgical intervention planned in the study knee in the subsequent 6 months. If taking analgesics, NSAIDs or cyclooxygenase-2 inhibitors, patients were required to comply with a washout period of 1–3 weeks depending on the half-life of the medication. The main exclusion criteria were: patients with bilateral symptomatic knee OA or predominantly patello-femoral involvement of the study knee; knee OA flare with obvious tense effusion at the study knee, diagnosed by clinical examination; clinical symptoms of meniscal instability or significant valgus/varus that required corrective osteotomy; significant ligamentous instability; any prior viscosupplementation therapy or history of sepsis in the study knee; systemic or intra-articular injection of corticosteroids in any joint within 3 months of enrolment; chondrocalcinosis and microcrystal-mediated arthritis, concomitant inflammatory or other rheumatologic, neurological or cardiovascular diseases which could affect the evaluation of knee pain.

Although various imaging modalities such as fluoroscopy, magnetic resonance imaging and computed tomography may be used to assist in injection delivery, the use of musculoskeletal ultrasound (US) guidance is becoming more and more widespread. Not only is its use rapid, safe and simple (27), it also improves accurate delivery of the injected product and clinical outcome (28, 29). Furthermore, studies have found that US guidance is particularly effective in the knee joint in improving accurate needle placement and clinical outcome as well as leading to lower healthcare costs (30, 31).

Ultrasound-guidance is the technique chosen in this study and in our clinical practice to perform injections and ensure accurate delivery inside the target joint. This is particularly important in hyaluronic acid injections given its direct protective effect on joint fluid.

HyalOne® was provided in prefilled syringes each containing 60 mg /4 ml of hyaluronic acid sodium salt for intra-articular injection. The treatment consisted in a single ultrasound image-guided injection into the articular site. The ecoguided treatment used an anterior approach with a 20-Gauge needle after betadine preparation. The ultrasound examination (Technos MPX, Esaote Spa, Genoa, Italy) was performed in all patients by the same radiologist, with a linear transducer (13 MHz) and 45° grades guide, also assessing the capsule with colour power Doppler for blood flow. Injections were performed with the patient in a supine position. Excessive weight bearing and strenuous activity were discouraged for 48 hours after each injection.

Patients received the injection at baseline (T0) and were followed-up at 4 (T1), 12 (T2) and 24 (T3) weeks after the first injection. Safety and efficacy were assessed at each patient visit.

Efficacy assessment

In order to assess the efficacy of HyalOne® in reducing pain and improving knee function the following variables were assessed at each study time point.

The primary efficacy outcome measure was the change from baseline to week 24 in patients' pain perception using a 100 mm Visual Analogue Scale (VAS) where 0 mm = no pain and 100 mm = worst possible pain. At each visit, the patients were asked to respond in terms of their pain "at the present time" by indicating their perceived pain on the VAS.

The secondary endpoints were the improvement in pain, stiffness and functional impairment as measured by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC™) (32) and the patient's assessment of their knee pain and other associated problems as measured by the Knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire at each visit (33).

The WOMAC questionnaire consists of three subscales: the WOMAC pain scale (5 questions), the WOMAC stiffness

scale (2 questions) and the WOMAC physical function scale (17 questions). In the Likert 3.0 of the WOMAC, the version adopted in the study, the patient's response to each of the 24 questions was measured on a 5-point Likert scale with higher scores indicating greater symptom severity (0=none, 1= slight, 2=moderate, 3=severe and 4=extreme).

The KOOS questionnaire consists of 5 subscales: Pain, Other symptoms, Function in daily living (ADL), Function in sport and recreation (Sport/Rec) and knee-related Quality of Life (QOL). Patients were asked to refer to the previous week when answering the questions. Standardized answer options are given (5 Likert boxes) and each question is assigned a score from 0 to 4. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale

Safety assessment

The target knee and systemic adverse events (AE) were monitored throughout the study.

Statistical methods

The primary efficacy hypothesis was evaluated by the change from baseline to the week 24 evaluation in the patient's assessment of target knee OA pain during the previous 48 hours on VAS. The secondary endpoints, WOMAC total score, pain, stiffness and physical function sub-scores and KOOS subscale scores were analysed similarly.

Performance data were analysed using descriptive analysis and the appropriate per pair data analysis (Analysis of variance for repeated measures (MANOVA) or Wilcoxon test).

RESULTS

One hundred and sixty-eight patients (168) were enrolled in the study, 104 female (61.9%) and 64 male (38.1%) with a mean age of 54 years (SD 8.82, range: 40 – 69 years old).

All 168 patients received one ultrasound-guided IA injection at the baseline visit.

Treatment with HyalOne® resulted in a statistically significant improvement from baseline to week 24.

Before treatment patients reported intense pain: the mean VAS value was 78 mm (SD 8.8, range: 60-90); the mean WOMAC pain score was 16.7 (SD 1.80, range: 14-20) and the mean KOOS pain score was 23.6 (SD 11.66, range: 5.56 – 41.68) as well as intense knee stiffness: mean WOMAC score of 6.7 (SD 1.04, range: 5 – 8). Knee functionality was moderately compromised: the WOMAC total score presented a mean value of 79.8 (SD 8.08, range: 64 – 96), the KOOS Function in daily living (ADL) a

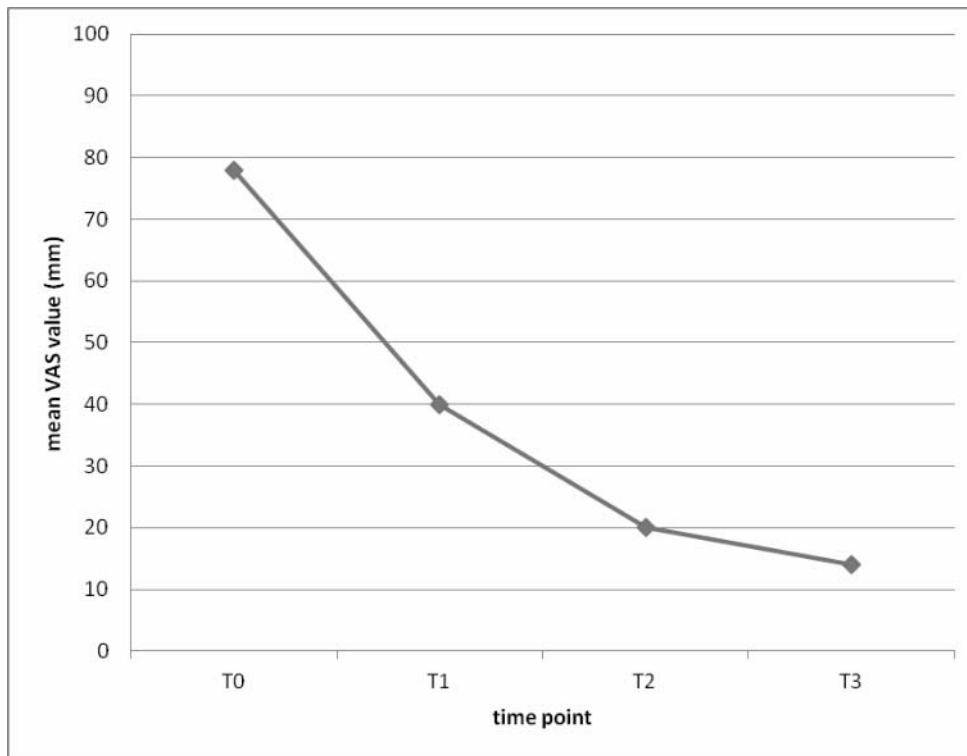


Fig. 1. Decrease in VAS pain (mm) at each study time point following a single baseline IA HA injection.

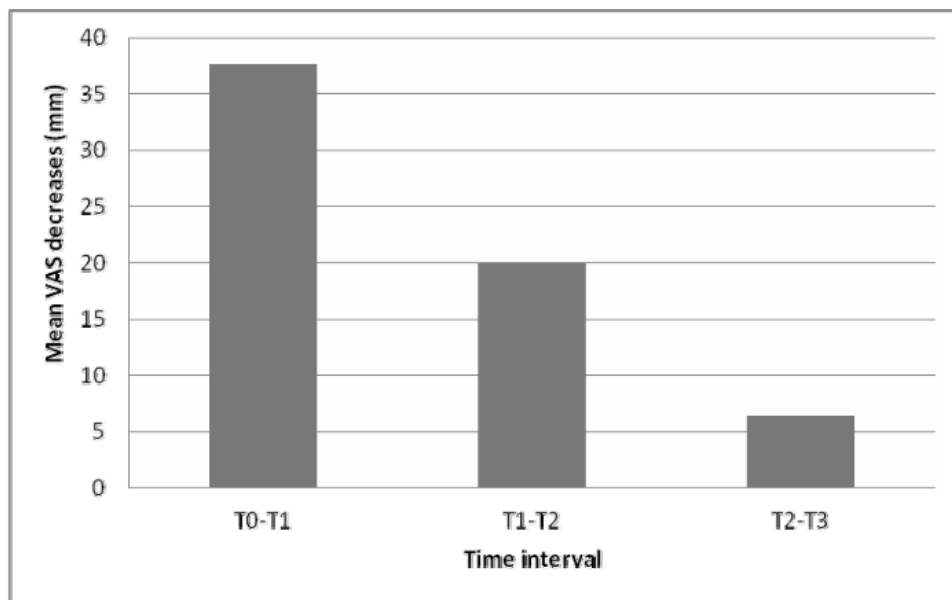


Fig. 2. Incremental decrease in VAS pain (mm) between study time points following a single baseline IA HA injection.

mean score of 26.8 (SD 8.06, range: 11.76 – 38.24) and the KOOS sport/recreation a mean score of 19.0 (SD 9.40, range: 5 - 35).

The baseline mean VAS value significantly and

progressively decreased at each study time point ($p < 0.001$ at the analysis of variance for repeated measures) (Figure 1).

All patients (100% of subjects) reported a

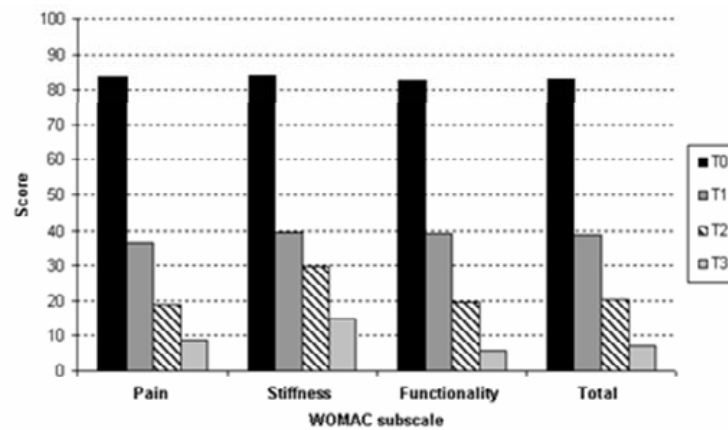


Fig. 3. Decrease in WOMAC subscale scores at each study time point following a single baseline IA HA injection.

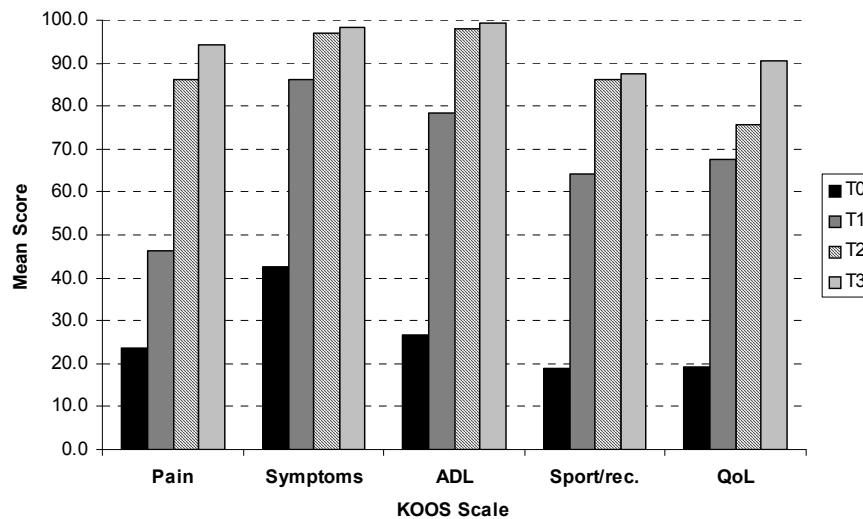


Fig. 4. KOOS subscale score at each study time point

reduction in pain at T1 and a further reduction at T2, while at T3 more than half of the treated patients (87 patients, 52%) reported an additional reduction in pain compared to T2. Pain perception at T3 compared to T2 was unchanged in the remaining 48% of patients.

Patients reported an initial decrease in VAS of 37.6 mm (SD 8.9, range 20 – 50) that subsequently decreased by a further 19.9 mm (SD 5.9, range 10 – 30) at T2 and 6.4 mm (SD 7.0, range 0 – 20) at T3 (Figure 2).

During the study the WOMAC normalised pain score decreased from the mean value of 83.7 registered at T0 (SD 8.98, range: 70 – 100) to a mean score of 8.7

(SD 3.28, range: 5-15) at T3.

The stiffness score decreased from a mean value of 84.2 at T0 (SD 12.99, range: 63 – 100) to a mean score of 14.8 at T3 (SD 8.83, range: 0-25); the functionality score decreased from a mean value of 82.8 at T0 (SD 9.16, range: 65-100) to a mean value of 5.7 (SD 4.41, range: 3 – 12) at T3.

Consequently, the total WOMAC score also decreased from the T0 mean value of 83.1 (SD 8.41, range: 67 – 100) to a T3 mean value of 7.1 (SD 1.86, range: 4-11). The results are summarised in Figure 3.

The analysis of variance for repeated measures conducted on each WOMAC subscale and on the total

WOMAC score showed a significant reduction in pain and stiffness and an increase in knee functionality at each study point (T1, T2 and T3) after treatment ($p < 0.001$). Comparisons between T1-T2 score and T2-T3 score evidenced a significant and progressive improvement in pain, stiffness and functionality ($p < 0.001$, Wilcoxon test) during the study.

Mean baseline values of all KOOS subscales progressively increased at each study time point to reach the highest value at T3.

The analysis of variance for repeated measures conducted on each KOOS subscale showed a significant improvement against baseline in all scales (pain, symptoms, daily activities, sport/recreation and quality of life) at T1, T2 and T3 ($p < 0.001$) (Figure 4).

The comparison between post-treatment time points (T1-T2 and T2-T3) also showed a progressive improvement over time ($p < 0.05$, Wilcoxon test).

Safety

The treatment was well tolerated.

Mild transient adverse events were reported in 5 patients. These device-related local AE's consisted mostly of mild or moderate post injection pain and swelling which resolved spontaneously after a few days. Patients' daily activities were unaffected by these events.

No serious adverse events were reported by the patients during the treatment.

DISCUSSION

Currently published data mainly refer to the use of HyalOne® in hip OA, where the product proved to be effective and well tolerated (34-36); however, HyalOne® differs only in volume from Hyalubrix, an IA Hyaluronan product which is marketed in several European countries and although it is indicated for the treatment of all joints, it has been used largely in the treatment of knee OA. Two post-marketing studies on patients suffering from knee OA supported its clinical efficacy, safety and tolerability in reducing pain and improving mobility and quality of life in patients with OA (35, 37). In another study, the use of Hyalubrix after arthroscopic meniscectomy led to a significantly more favourable post-operative clinical outcome, both in terms of function and pain symptoms, as compared with the same procedure performed without this

treatment (38). Other authors reported improvement in clinical findings in most gait analysis parameters after IA injection of Hyalubrix in the knee (39).

The present study aimed to provide evidence supporting the effectiveness and safety of a single IA injection of Hyaluronic Acid (HyalOne®) in alleviating pain and improving knee function in patients suffering from knee OA.

The mono-injection strategy is a HyalOne® characteristic that exposes patients to a lower risk of administration-related site effects (e.g. pain at injection site, infection) and requires a lower number of patient visits to the clinic, resulting in a money-saving opportunity for the patients (fewer visits and decrease in loss of working days).

Results from this study demonstrate that treated patients reported significant pain reduction as early as 1 month after treatment and that pain continues to decrease up to 6 months from the single administration.

In real practice HyalOne® treatment seems to cause a statistically significant reduction in algofunctional indices at 6 months after the injection; all patients (100% of subjects) reported a reduction in pain at T1 and a further reduction at T2, while at T3 more than half of treated patients (87 patients, 52%) registered an additional reduction in pain compared with T2. These results were confirmed with a similar trend in the assessment with the functional scales (WOMAC and KOOS).

Improved knee functionality is also confirmed by both the WOMAC and the KOOS scores, as well as an improvement in patients' general health status as demonstrated by the high scores recorded at the post treatment KOOS ADL, QoL and sport/recreation subscales.

These results may be maintained over time through cyclical and personalized repetition of US guided injections, at least one injection every 6 months.

A key result of the study was the complete absence of drop-outs, probably due to the single injection treatment, the rapid decrease in pain and the results persisting over time. It is also easy to repeat the treatment in case of need.

Although this study confirms the effectiveness of HyalOne® in knee OA, limitations in the study design (open-label study with no control group) prompt suggestions for further randomized controlled studies to be carried out comparing HyalOne® to a similar

product/placebo to confirm the results from this study.

In conclusion, these study data demonstrated that HyalOne® may be an effective alternative treatment option in the management of knee OA.

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INTRA-ARTICULAR METHOTREXATE: CLINICAL AND POWER DOPPLER ULTRASONOGRAPHY STUDY IN RHEUMATOID KNEE SYNOVITIS.

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Background: The effects of intra-articular methotrexate (I/A MTX) in knee synovitis in rheumatoid arthritis have been previously evaluated with inconstant results. Ultrasonography (US) has been little studied in I/A MTX. **Objectives:** To test the efficacy of I/A MTX in rheumatoid arthritis patients with knee synovitis resistant to systemic methotrexate and other disease modifying antirheumatic drugs (DMARDs). **Methods:** 10 mg of methotrexate was injected every week for 8 weeks intra-articularly in 41 knees in 29 consecutive RA patients with one or both knees arthritis resistant to systemic DMARDs including methotrexate and other joints in clinical remission. Clinical evaluation includes visual analogue scale (VAS) and Global index of knee arthritis (GIKA). Evaluation was done before the 1st injection (W0), before the 6th injection (W5), one week after the last injection (W8), 12 weeks later (W20) and 24 weeks after the last injection (W32). On the same days Power Doppler US was done. Synovial thickness in suprapatellar region was measured. The intra-articular power Doppler signal was graded on a semi quantitative scale from 0 to 3 during the US examination. **Results:** There was significant reduction in VAS (mean value± SD) between W0 (7.84±1.16) and W8 (1.17± 0.77) $p < 0.001$, W0 and W20 (2.56 ± 1.02) $p < 0.001$ and between W0 and W32 (3.16 ±0.72) $p < 0.01$, GIKA reduced significantly between W0 (8.26 ± 1.2) and W8 (2.58± 0.92) $p < 0.001$, W0 and W20 (2.53± 1.05) $p < 0.001$ and between W0 and W32 (2.04± 0.95) $p < 0.01$. Gray US showed that synovial thickness was reduced significantly between W0 (7.09 ±1.33 mm) and W8 (3.45 ± 0.87 mm) $p < 0.001$, between W0 and W20 (3.67± 0.80 mm) $p < 0.001$ and between W0 and W32 (4.01± 0.80) $p < 0.01$. There was insignificant increase in VAS, KJAI and synovial thickness between (W8 and W20) and between (W8 and W 32). Power Doppler signals reduced significantly between (W0 and W5, W8, W20 and W32) $p < 0.001$ while between W5 and W8 the significance level was $p < 0.05$. **Conclusions:** Repeated I/A MTX resulted in a decrease in degree of knee synovitis both clinically and by power Doppler US. While the clinical effects and the decrease in synovial thickness by gray US continue after 6 months, power Doppler signals tends to increase after 6 months. To the best of our knowledge this the first study to detect the effect of I/A MTX by power Doppler US.

Achieving remission is the main target of treatment of rheumatoid arthritis patients. (1) Although there are many new biologic and disease modifying anti rheumatic drugs which help in reaching remission, complete remission couldn't be reached in all patients. Many rheumatoid arthritis patients who are regular on treatments have one or

more joint with active arthritis while other joints are in quite remission. (2,3) Intra-articular (IA) therapy is the treatment of choice in cases of mono/oligoarthritis. (4) Intra-articular therapy has the advantage of applying the drug directly into the inflamed joint with the aim of achieving maximal effect with very minimal systemic side effects. (1)

Key words: methotrexate, ultrasound, Doppler, intra-articular injection

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Corticosteroids are the most common drug used as an intra-articular therapy. Intra-articular steroid injections result in improvement of pain and range of motion for 1–3 months. (5-7) Methotrexate (MTX) is the most commonly used systemic disease modifying anti rheumatic drugs in treatment of rheumatoid arthritis either as a monotherapy or in combination with other DMARDs or biologic drugs. (8) Intra-articular methotrexate is previously investigated with inconstant results and rare side effects. (9-12) Repeated Intra articular MTX therapy results in a strong decrease of Synovial fluid granulocyte counts. This effect may be due to the impairment of IL-8 mediated chemotaxis by decreased IL-8 synthesis in synovial fluid mononuclear cells. (13) Power Doppler ultrasonography (PDUS) is a sensitive and reliable method for longitudinal assessment of inflammatory activity in rheumatoid arthritis. PDUS is a valid method for monitoring response to different forms of therapy in RA; results obtained by PDUS are reproducible and sensitive to change. (14) This study was performed to assess the efficacy of intra-articular injection of methotrexate in rheumatoid arthritis patients with knee synovitis resistant to systemic disease modifying antirheumatic drugs (DMARDs). To the best of our knowledge this the first study to evaluate the effect of I/A MTX by power Doppler US.

MATERIALS AND METHODS

Patients: Twenty nine consecutive RA patients with arthritis in one or both knees attending the outpatient clinic of rheumatology & rehabilitation department, faculty of medicine, Zagazig University were selected for the study. All patients fulfill the 1988 revised ACR criteria for the classification of rheumatoid arthritis. (15) All patients were in quite remission with DAS28 ESR < 2.6 with one or both Knees arthritis resistant to systemic DMARDs including methotrexate. Patients known to have hepatitis C or B infection were excluded from the study due to the potential hepatic toxicity of methotrexate. All patients were on their regular DMARDs including methotrexate without any modification of doses. None of patients included in the study were received biologic therapy.

Methotrexate injection: 10 mg of methotrexate was injected intra-articularly without dilution in the inflamed knee/s. The injection was once weekly for 8 weeks. Clinical, ultrasonographic and power Doppler US evaluation was done before the 1st injection (W0), before

the 6th injection (W5), one week after the last injection (W8), 12 weeks later (W20) and 24 weeks after the last injection (W32).

Clinical evaluation: The visual analog scale (VAS) for pain was calculated using a 10-cm horizontal scale with ten possible scores.

Global index of knee arthritis (GIKA) was recorded as previously prescribed (16); Joint tenderness was measured by firm pressure over the knee joint margin (graded 0-3); joint swelling was recorded as detectable synovial thickening, with or without loss of bony contours or cystic synovial proliferation (graded 0-3); ‘bulge sign’ and/or ballottement of the patella by lateral and medial palpation of the patella or by compression of the suprapatellar pouch, respectively (graded 0-2); range of knee joint flexion (150-90°) (grade 0-3) and extension (90-0°) (grade 0-3) was recorded. The sum of these grades was taken as a global outcome measure (global index: GI) of joint inflammation (0-14).

Ultrasonographic examination: US of the inflamed knee was performed with a 5-12 MHz linear probe (madison R3). Synovial thickening as a criterion of active inflammation was evaluated by US (visualized as hypoechoic structures within the joint margins). Synovial thickness was measured with the patient supine and the knee in neutral position. Measurements were done 2 cm above the superior pole of the patella, both in the transverse and longitudinal scans. The mean values of each couple of results were calculated.

Power Doppler Ultrasonography: Synovial blood flow was evaluated in the same joints. Active synovitis was defined with power Doppler signals. Intra-articular power Doppler signal was graded on a semiquantitative scale from 0 to 3.

Statistical analysis: Data presented as means \pm SD and differences between follow up periods were estimated by paired t test. Doppler US presented as number and percentage and differences between follow up periods were estimated by Wilcoxon Signed Ranks Test.

RESULTS

This study included 41 knees in 29 consecutive RA patients, 9 male (31%) and 20 female (69%) with mean age of 39.9 ± 8.02 years and mean disease duration of 4.37 ± 3.06 years.

There was significant reduction in VAS between (W0 and W5), (W0 and W8), (W5 and W8), and between (W8 and W20) $p < 0.001$. KJAI reduced significantly between (W0 and W5) $p < 0.001$, (W0 and W8) $p < 0.001$, (W5 and W8) $p < 0.001$, (W8 and W20) $p < 0.001$ and between (W0 and W32) $p <$

Table I. Results for clinical and ultrasonographic parameters:

Weeks Parameters	Week 0	Week 5	Week 8	Week 20	Week 32
VAS (X±SD) * Δ©®	7.84±1.16 *Δ®◇	3.07±0.93©	1.17± 0.77	2.56 ± 1.02	3.16 ±0.72
GKA (X±SD) *Δ©®	8.26 ± 1.2 *Δ®◇	3.6 ± 1.06 ©	2.58± 0.92	2.53± 1.05	2.04± 0.95
Synovial thickness (X±SD) *Δ©®	7.09 ±1.33 *Δ®◇	4.58± 0.91 ©	3.45± 0.87	3.67± 0.80	4.01± 0.80

VAS: visual analogue scale GKA: global index of knee arthritis Δ significant difference (week 0 versus week5): $P \leq 0.001$ Δ significant difference (week 0 versus week8): $P \leq 0.001$ © significant difference (week 5 versus week8): $P \leq 0.001$ ® significant difference (week 0 versus week20): $P \leq 0.001$. ◇ significant difference (week 0 versus week32): $P \leq 0.01$.

Table II. Results for Doppler ultrasonographic parameters.

Weeks Doppler	Week 0		Week 5		Week 8		Week 20		Week 32	
	N	%	N	%	N	%	N	%	N	%
Doppler grade 0	0	0	0	0	7	17.1	0	0	0	0
Doppler grade 1	7	17.1	19	46.3	22	53.7	21	51.2	17	41.5
Doppler grade 2	24	58.5	20	48.8	12	29.3	17	41.5	17	41.5
Doppler grade 3	10	24.4	2	4.9	0	0	3	7.3	7	17.1

N: number

0.001. Gray scale US showed that synovial thickness was reduced significantly between (W0 and W5), (W0 and W8), (W5 and W8), and between (W8 and W20) $p < 0.001$. There was insignificant increase in VAS, KJAI and synovial thickness between (W8 and W20) and between (W8 and W 32).

Power Doppler signals reduced significantly between (W0 and W5, W8, W20 and W32) $p < 0.001$ (figure 1) while between W5 and W8 the significance level was $p < 0.05$.

Safety: Only 3 participants reported adverse

events during the study. One patient (who had received I/A injections in both knees at the same time) reported nausea for 2 days after injection. Nausea disappeared after I/A injections of one knee only. Two patients reported multiple oral ulcerations (in the first case after the 5th week and in the second case after the 8th week). No symptom flare, increase in liver enzymes, local skin reaction, or signs of infection or any other reactions at the joints or their surroundings were seen on the clinical or ultrasound examinations.

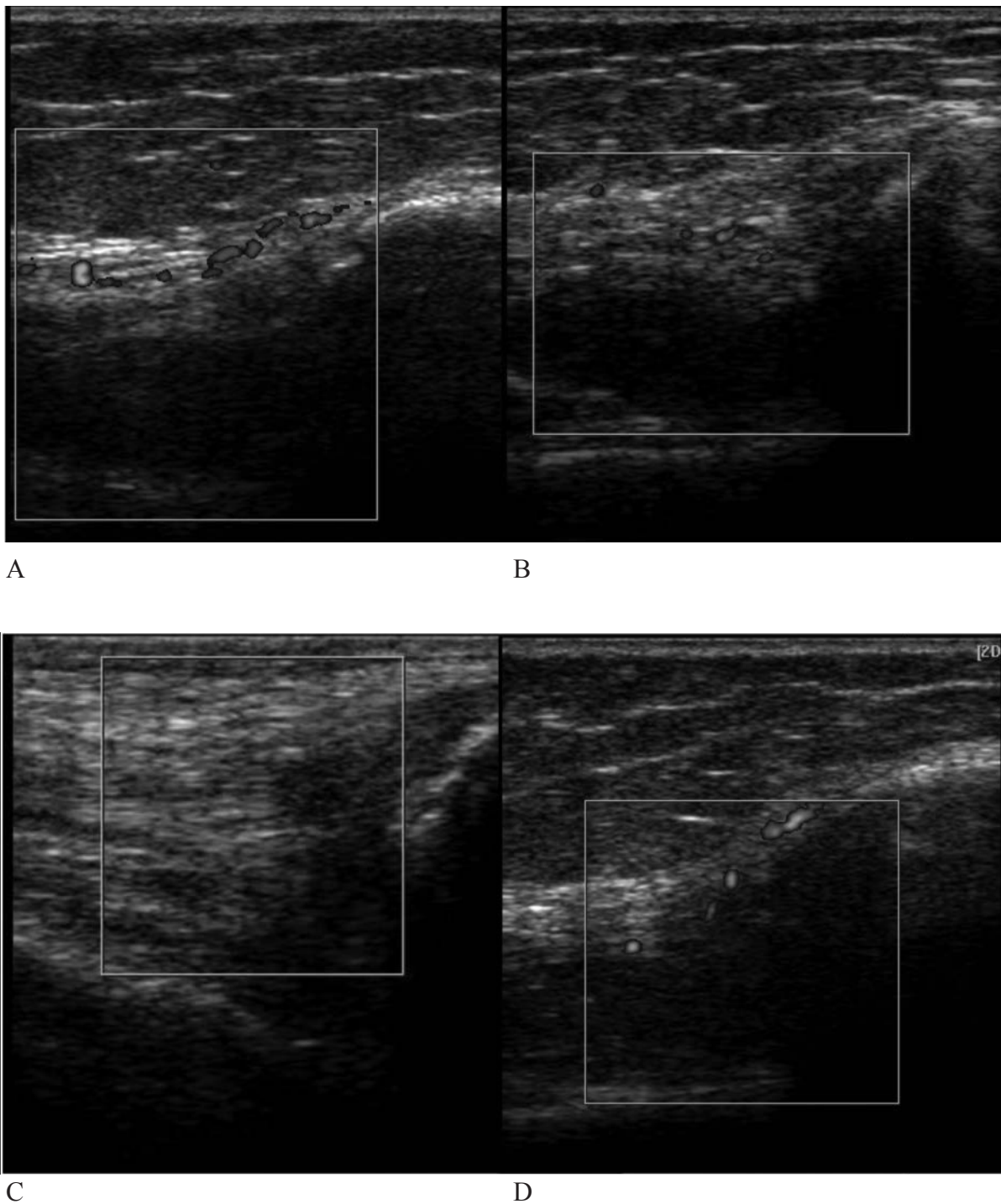


Fig. 1. Power Doppler ultrasonography of knee of a patient with RA showing : (A) Doppler activity of grade 3 before intra_articular MTX injection (WEEK 0), (B) Doppler activity (grade 2/3) 5 weeks after intra_articular MTX injection (WEEK 5), (C) No Doppler activity (grade 0/3) 3 months after intra_articular MTX injection (WEEK 20) , (D) Doppler activity (grade 2/3) 6 months after intra_articular MTX injection (WEEK 32)

Discussion: The results reported suggest that intra-articular methotrexate has potent anti-inflammatory effects which appeared as improvement in visual analogue scale for pain and in global index of knee arthritis. The effects of intra-articular methotrexate was confirmed by the decrease in synovial thickness detected by gray scale ultrasonography and the decrease in the blood flow in the synovial tissue as detected by power Doppler ultrasonography. The improvement in clinical response (VAS & GIKA) and the imaging signs (synovial thickness detected by US & PDUS signals) begin to be evident after the 5th intra-articular methotrexate injection and reached the maximum improvement after the 8th injection. The significant decrease of VAS, GIKA, and synovial thickness between W5 & W8 refers to the importance of continuation of the injections up to 8 injections. The improvement in clinical response (VAS & GIKA) continue for 6 months after the last intra-articular methotrexate injection which may be considered as a long duration taking in consideration that intra-articular steroid injections Improvement of pain and range of motion continue for 1–2 months.⁵⁻⁷ Six months after the last intra-articular methotrexate injection PDUS signals returned to the increased state. As PDUS has the ability to predict flare of arthritis,¹⁷ this may predict the efficacy of intra-articular methotrexate injection will end shortly which has to be confirmed in a more longitudinal studies. As regards side effects, only three patients have minor systemic effects (one patient has nausea and 2 patients have multiple oral ulcerations) but none of our patients has elevated liver enzymes or other systemic side effects. This may refer to the minor systemic absorption which has to be investigated in further studies. None of our patients has a local side effects including flare of arthritis. In conclusion, the present report shows that repeated intra-articular injection of methotrexate resulted in a decrease in degree of knee synovitis both clinically and by power Doppler US for a relatively long duration with a minor local or systemic side effects. This may be an option of management of a group of RA patients who have knee arthritis while other joints in quite remission.

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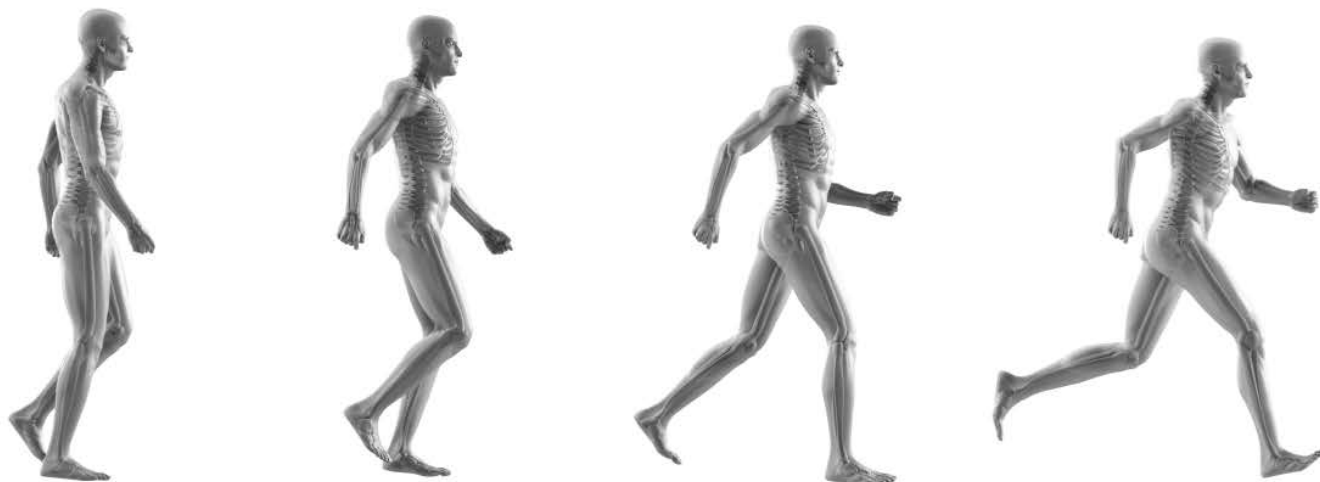
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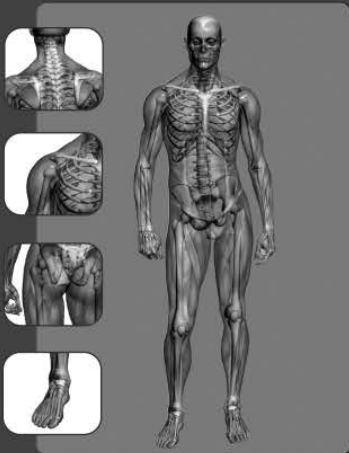
Collagen Medical Devices

INJECTABLE AMPOULES

MEDICAL DEVICE



Description



A special characteristic of Collagen Medical Devices, which contain collagen and ancillary ingredients, is that they offer a refined and innovative approach to the treatment of painful diseases affecting the musculoskeletal system.

The ancillary ingredients of natural origin allow a better and more targeted positioning of Collagen in certain areas.

The collagen is of pig origin. Injections are periarticular, intraarticular, intramuscular and intradermal. Collagen provides a mechanical support, which has a positive impact on stabilizing joint hypermobility, movement, pain, and life quality. Collagen Medical Devices have a structural function: replace, strengthen, protect and build the structure of cartilage, tendons, ligaments, joint capsules, etc, thus improving the histological structure of the collagen fibres of all the anatomical structures made up of collagen. This provides mechanical support to the affected areas.

Key word:

**Collagen Medical Devices,
13 Medical Devices to treat
different osteoarthro-
myofascial pathologies**

Composition

- **MD-HIP** (Hip):
Collagene, Calcium phosphate
- **MD-ISCHIAL** (Sciatic nerve):
Collagene, *Rhododendron*
- **MD-KNEE** (Knee):
Collagene, *Arnica*
- **MD-LUMBAR** (Lumbar):
Collagene, *Hamamelis*
- **MD-NECK** (Neck):
Collagene, *Silica*
- **MD-SHOULDER** (Shoulder):
Collagene, *Iris*
- **MD-SMALL JOINTS**
(Small joints):
Collagene, *Viola*
- **MD-THORACIC** (Torax):
Collagene, *Cimicifuga*
- **MD-MATRIX** (Extracellulare matrix):
Collagene, Citric acid, Nicotinamide
- **MD-MUSCLE** (Muscle):
Collagene, *Hypericum*
- **MD-POLY** (Joints):
Collagene, *Drosera*
- **MD-NEURAL** (Nerves):
Collagene, *Colocythis*
- **MD-TISSUE** (Soft tissues):
Collagene, Ascorbic acid, Magnesium gluconate, Pyridoxine hydrochloride, Riboflavin, Thiamine hydrochloride

Therapeutic protocol

MD-HIP
MD-ISCHIAL
MD-KNEE
MD-SMALL JOINTS

1 treatment weekly
for 10 consecutive weeks.

MD-MUSCLE
MD-NECK
MD-NEURAL
MD-POLY
MD-SHOULDER

1-2 treatment/s weekly
for 10 consecutive weeks.

MD-LUMBAR
MD-MATRIX
MD-THORACIC
MD-TISSUE

2 treatments for the first 2 weeks;
then, 1 treatment weekly until
symptoms improve
(8-10 sessions on average).

Packaging

- Box of 10 x 2ml ampoules.
- Box of 50 x 2ml ampoules.

CE 0373



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