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Original Article

Radiosynoviorthesis with [90Y] Yttrium citrate in refractory synovitis of the knee: Experience of 2 reference hospitals

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ABSTRACT

Introduction: To describe the therapeutic efficacy of radiosynoviorthesis with [^{90}Y]Yttrium citrate (^{90}Y), in patients with chronic knee synovitis refractory to systemic treatments and/or infiltrations, correlating the results with the different etiologies and degenerative changes that they showed, in order to optimize the indication of the technique.
Material and methods: Observational retrospective study with 32 patients (22 men and 10 women) and 34 knees, with refractory chronic knee synovitis, who underwent radiosynoviorthesis between January 2013 and December 2022. Its efficacy was described and analyzed by the subjective improvement referred by the patients and its relationship with the existing etiologies and radiological degenerative changes, expressed by the Kellgren-Lawrence (K-L) scale.
Results: A statistically significant subjective improvement was observed in 70.6% of the cases ($p < 0.001$). There were 92.3% of cases with absent, doubtful or mild degenerative changes (K-L 0-2) who improved, while only 50% with moderate or severe changes (K-L 3-4) improved, showing statistically significant differences ($p = 0.03$). Among patients with chronic inflammatory origin of synovitis (spondyloarthropathies and rheumatoid arthritis), 80% improved, while in those with osteoarthritis (degenerative) origin, only 25% improved with statistically significant differences (p = 0.006).
Conclusions: Radiosynoviorthesis with ^{90}Y is an effective treatment in patients with knee refractory chronic synovitis, especially in the presence of mil degenerative joint changes and chronic inflammatory origin. We must ensure the appropiate selection of patients according to these criteria.

Radiosinoviortesis con [90Y] citrato de ytrio en la sinovitis refractaria de rodilla: experiencia de 2 hospitales de referencia

Palabras clave:
Radiosinovectomía
Sinovitis
Articulación de rodilla
Ytrio-90
Radiosinoviortesis

RESUMEN

Objetivo: Describir la eficacia terapéutica de la radiosinoviortesis con [^{90}Y]citrato de ytrio (^{90}Y), en pacientes con sinovitis crónica de rodilla refractaria a tratamientos sistémicos y/o infiltraciones, correlacionando los resultados con las distintas etiologías y cambios degenerativos presentes, con la intención de optimizar la indicación de la técnica.
Material y métodos: Estudio retrospectivo observacional con 32 pacientes (22 hombres y 10 mujeres) y 34 rodillas, con sinovitis crónica de rodilla refractaria, a los que se les realizó la radiosinoviortesis entre enero de 2013 y diciembre de 2022. Se describió y analizó su eficacia mediante la mejoría subjetiva expresada por los pacientes y su relación con las etiologías y cambios radiológicos degenerativos presentes, expresados éstos mediante la escala de Kellgren-Lawrence (K–L).
Resultados: Se observó una mejoría subjetiva estadísticamente significativa del 70,6% de los casos (p < 0,001). El 92,3% de los que presentaban cambios degenerativos ausentes, dudosos o leves (K–L 0–2) mejoraron, mientras que solo lo hicieron el 50% con cambios moderados o severos (K–L 3–4), mostrando diferencias estadísticamente significativas (p = 0,03). De los pacientes con origen inflamatorio crónico de la sinovitis (espondiloartropatías y artritis reumatoide), el 80% mejoró subjetivamente mientras que en los que el origen era la osteoartritis (degenerativo), solo mejoraron el 25% con diferencias estadísticamente significativas (p = 0006).

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Conclusión: La radiosinoviortesis con ^{90}Y es un tratamiento eficaz en pacientes con sinovitis crónica refractaria de rodilla, especialmente en presencia de cambios articulares degenerativos leves y origen inflamatorio crónico. Debemos procurar la selección adecuada de los pacientes atendiendo a estos criterios.

Introduction

Arthritis of the knee continues to be a highly prevalent chronic disease in our setting, representing a great daily healthcare load that covers different modalities of treatment at a multidisciplinary level. These alternative therapies include systemic treatments with non-steroid anti-inflammatory drugs, disease modifiers or biological treatments ranging from local intraarticular administration of corticosteroids or radioactive isotopes to surgical synovectomy.

Radiosynoviorthesis by intraarticular administration of beta particle emitting radiopharmaceuticals has demonstrated effectiveness in arthritis of multiple etiologies, and [^{90}Y]yttrium citrate (^{90}Y) radiosynoviorthesis was already studied in the 1970s.[1] Following infusion, the radiocolloid particles are phagocytosed by the macrophages of the surface of the synovial membrane irradiating towards the deepest layer, producing fibrosis and sclerosis of the membrane.

According to their radiophysical characteristics based on the size of the joint, the following beta-particle emitter radiocolloids can be used: (^{90}Y) for large joints (the knee), [^{186}Re] rhenium sulfide (^{186}Re) for medium-sized joints (the hip, elbow and the shoulder) and [^{169}Re] erbium citrate (^{169}Er) for the remaining small-sized joints. The characteristics of these radioisotopes, described in the guidelines of the European Association of Nuclear Medicine (EAMN) are shown in Table 1.[2]

The advantages of this technique lie in its minimally invasive nature compared with the surgical alternative (synovectomy) and it carries a shorter time of hospitalization and rehabilitation and provides a better cost-effectiveness ratio. In addition, intraarticular administration of radiocolloids produces longer-lasting favorable response than intraarticular injections of corticosteroids, the effect of which is shortened with treatment repetition, leading to an increase in the risk of osteonecrosis.[2,3]

In addition, the role of external radiotherapy in the treatment of synovitis has been described[3]; however, intraarticular injection with radioisotopes allows more selective radiation of the synovial membrane with greater preservation of the peripheral tissue compared to external radiotherapy.

Although the technique of radioisotopic synoviorthesis has relevant established efficacy, it is usually requested in advanced phases of the disease when the osteodegenerative changes are already moderate or advanced and the technique is less effective.

Thus, the aim of this study was to perform a control and analysis of the evolution of our patients to improve the indication and effectiveness of the treatment. The main objective was to describe the therapeutic efficacy of the intraarticular administration of ^{90}Y in patients with chronic synovitis of the knee refractory to systemic treatments and/or infiltrations with corticosteroids, according to the different etiologies, the degenerative changes present and the radiological evolution.

Table 1
Radioisotopes used for performing synoviorthesis.

	^{169}Er	^{186}Re	^{90}Y
Half-life (h)	225.4	89.25	64.1
Gamma energy (keV)	8.4	137	
Beta Energy (MeV)	0.34	0.98	2.26
Mean range of penetration (mm)	0.3	1,2	3,6

Material and methods

This was a retrospective observational study of 32 patients (22 men and 10 women) and 34 knees (both knees were treated in 2 patients), with a mean age of 50 ± 13.6 years. In our sample, 24 patients were from the healthcare area of the Hospital Virgen Macarena of Sevilla and 8 were from that of the Hospital Juan Ramón Jiménez of Huelva (HJRJ).

All the patients presented refractory chronic synovitis of the knee and underwent radiosynoviorthesis between January 2013 and December 2022. After providing signed informed consent for the intervention, between 185 and 259 MBq of ^{90}Y was administered intraarticularly in aseptic conditions and according to the usual protocol[2] followed by a dose of 40 mg of triamcinolone or 1 mL of betamethasone. In two cases, the technique was ultrasound-guided, since in HJRJ this type of improvement is being implemented, allowing verification of correct localization of the needle and distribution of the radiopharmaceutical. In the remaining interventions without ultrasound guidance, we verified intraarticular localization of the needle by aspirating the synovial fluid in the case of leakage or by visualizing needle withdrawal through the synovival fluid. Posterior administration of the corticosteroid facilitated the distribution of the radiopharmaceutical within the articular cavity. Thereafter, a compressive bandage was applied, recommending 48 h of rest with the leg raised to avoid leakage of the radiopharmaceutical from the articular cavity via the administration site or by absorption of the adjacent lymphatic system. The patients were also informed about radioprotection norms of bathroom hygiene to avoid the contamination of risk groups.

The following clinical data are described in Table 2: age, sex, etiology of the synovitis, history of previous surgical interventions, previous imaging tests (3-phase bone scintigraphy or ultrasonography performed or radiology or magnetic resonance (MR) studies which allow evaluation of the presence of joint inflammation, as well as the possible presence of Baker cysts in the same and their possible rupture or septums including radiological evolution by conventional radiography. The radiographic findings were interpreted based on the Kellgren-Lawrence (KL) scale of osteodegenerative changes and were grouped as absent, doubtful or mild (KL grades 0/1/2, respectively) and moderate or advanced (KL grades 3/4, respectively) as shown in Fig. 1.

The 3-phase bone scintigraphy findings were considered to indicate synovitis if presenting early flow, a pool phase with an increase in periarticular vascularization and increased uptake in the bone phase, irregular thickening of the synovial membrane and contrast enhancement visualized in the MR, and the presence of hypoechoic synovial thickening in the ultrasonography, with an increase in vascularization in the Doppler mode.

Table 2
Description of the patients included.

	Sex	Age	Disease	Previous surgical synovectomy	Previous radiography	Previous ultra-sonography	Previous scintigraphy	Previous magnetic resonance	Complication post-synoviorthesis with ^{90}Y	Evolution	Duration of improvement	Radiological evolution	Posterior treatments
1	Male	42	Seronegative oligoarthritis	No	No	Yes	No	No	No	Improvement	More than 2 years		Infiltrations
2	Male	54	Osteoarthritis	No	No	Yes	No	No	No	No improvement			
3	Male	47	Osteoarthritis	No	No	No	No	Yes	No	No improvement			Infiltrations
4	Male	67	Psoriatic arthritis	No	No	Yes	No	No	No	Improvement	Between 1 and 2 years		Infiltrations
5	Male	46	Osteoarthritis	No	Yes	Yes	No	No	No	No improvement		Stable (3)	Infiltrations
6	Male	49	Psoriatic arthritis	No	Yes	Yes	No	No	No	Improvement	More than 2 years		Infiltrations
7	Male	68	Psoriatic arthritis	No	No	Yes	No	No	No	Improvement	More than 2 years		Infiltrations
8	Female	71	Osteoarthritis	No	No	Yes	No	No	No	No improvement		Stable (1)	Infiltrations
9	Female	55	Post-traumatic arthrosis	No	Yes	Yes	No	No	No	Improvement	More than 2 years	Progression (3–4)	Prosthesis
10	Male	67	Undifferentiated arthritis	No	Yes	Yes	No	No	No	Improvement	More than 2 years		
11	Male	39	Psoriatic arthritis	No	Yes	No	No	Yes	No	No improvement		Stable (3)	
12	Male	55	Osteoarthritis	No	Yes	No	No	Yes	No	No improvement		Stable (3)	Surgical synovectomy and prosthesis
13	Female	58	Calcium pyrophosphate cristal arthritis	No	Yes	Yes	No	Yes	No	Improvement	Less than 1 year		Infiltrations
14	Female	75	Rheumatoid arthritis	No	Yes	Yes	No	No	No	No improvement			Infiltrations
15	Female	35	Psoriatic arthritis	No	No	No	Yes	No	No	Improvement	Less than 4 months		Infiltrations
16	Male	42	Psoriatic arthritis	No	Yes	Yes	No	Yes	Yes	Improvement	Less than 1 year	Stable (1)	Infiltrations
17	Female	58	Psoriatic arthritis	No	Yes	Yes	No	No	Yes	Improvement	Less than 1 year		
18	Male	34	HLAB27 negative spondy-loarthritis	No	No	Yes	No	No	No	No improvement			
19	Male	34	Idiopathic juvenile arthritis	No	No	No	No	Yes	No	Improvement	Between 1 and 2 years		
20	Male	34	Idiopathic juvenile arthritis	No	No	No	No	Yes	No	Improvement	Between 1 and 2 years		

Table 2
(*Continued*)

	Sex	Age	Disease	Previous surgical synovectomy	Previous radiography	Previous ultra-sonography	Previous scintigraphy	Previous magnetic resonance	Complication post-synoviorthesis with ^{90}Y	Evolution	Duration of improvement	Radiological evolution	Posterior treatments
21	Male	20	Idiopathic juvenile arthritis	No	No	Yes	No	No	No	Improvement	Less than 1 year		
22	Male	44	Psoriatic arthritis	No	No	Yes	No	No	Yes	Improvement	Less than 1 year		
23	Male	22	HLA B27 positive spondy-loarthritis	No	Yes	No	No	Yes	No	Improvement	Less than 4 months		
24	Male	41	Psoriatic arthritis	No	No	No	No	Yes	Yes	Improvement	Less than 1 year		
25	Female	59	Osteoarthritis	No	Yes	No	No	Yes	No	No improvement		Stable (3)	Prosthesis
26	Female	70	Rheumatoid arthritis	No	Yes	Yes	No	No	No	No improvement			Infiltrations
27	Male	61	Rheumatoid arthritis	No	Yes	No	Yes	Yes	No	Improvement	More than 2 years	Stable (1)	
28	Female	56	Villonodular synovitis	No	Yes	No	Yes	Yes	No	Improvement	Less than 4 months	Progression (3–4)	Prosthesis
29	Male	46	Villonodular synovitis	No	Yes	No	Yes	Yes	No	Improvement	Between 1 and 2 years		Surgical synovectomy
30	Male	41	Villonodular synovitis	Yes	Yes	No	Yes	Yes	No	Improvement	Less than 4 months	Stable (3)	iPACK block and radiofrequency
31	Female	41	Villonodular synovitis	No	Yes	No	Yes	Yes	No	Improvement	Less than 4 months	Progression (1–4)	Surgical synovectomy
32	Male	52	Villonodular synovitis	No	Yes	No	Yes	Yes	No	Improvement	Between 1 and 2 years	Stable (3)	Infiltrations
33	Male	59	Rheumatoid arthritis	No	Yes	No	No	Yes	No	Improvement	Less than 1 year		
34	Male	57	Osteoarthritis	No	Yes	No	Yes	No	No	Improvement	Less than 4 months		

Figure 1. Grade of osteodegenerative changes according to the Kellgren-Lawrence scle: 0 absent, 1 doubtful, 2 mild, 3 moderate, 4 advanced.

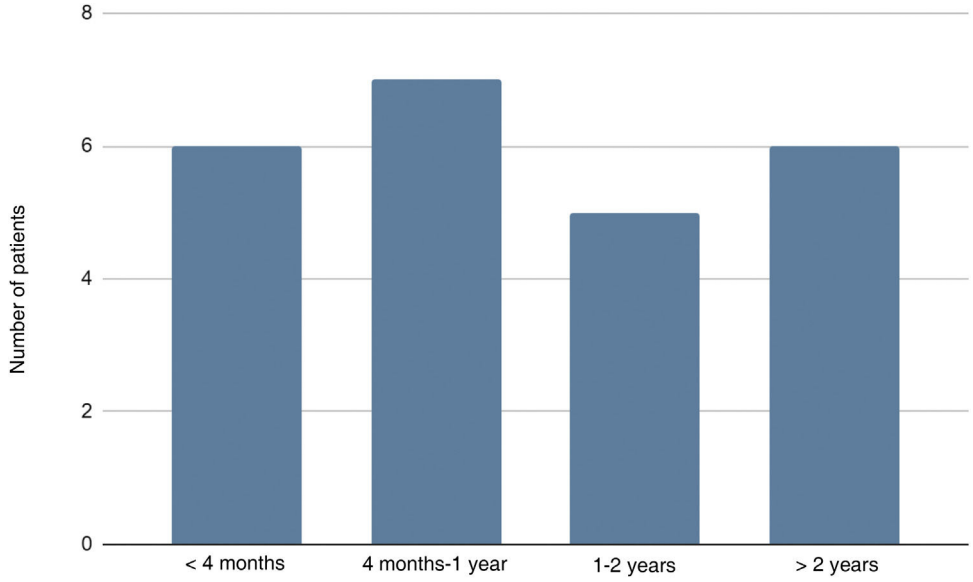

Figure 2. Duration of subjective improvement reported by the patients.

To evaluate the efficacy of the technique, the presence or not of subjective improvement and its duration expressed by the patient was used: less than 4 months, between 4 months and 1 year, between 1 and 2 years or greater than 2 years. According to the EANM guidelines, the recommended time for evaluating the results of the technique is 4–6 months post-radiosynovectomy.[2]

In addition, we recorded the absence or presence of adverse effects (swelling, pain, functional incapacity y redness) and the need for posterior therapeutic interventions, if necessary (infiltrations with corticosteroids, surgical synovectomy or placement of total knee prosthesis).

Statistical analysis of the efficacy of the treatment was performed with the Wilcoxon test, while the Fisher's exact test was used to relate the efficacy of the technique to the absent, doubtful or mild versus moderate or advanced osteodegenerative changes. Finally, the Pearson Chi-square test was used to analyze the relation with inflammatory etiology versus osteoarthritis. The statistical analyses were performed with the SPSS statistical program.

Results

Of the 34 knees infiltrated, 24 (70.6%) showed a subjective statistically significant improvement ($p < 0.001$). In relation to the duration of improvement, 18 cases (75%) showed improvement for more than 4 months: being from 4 months to 1 year in 7 cases (29.2%), from 1 to 2 years in 5 cases (20.8%) and for greater than 2 years in 6 cases (25%) (Fig. 2).

The etiologies present were: spondyloarthropathies in 47.1% (psoriatic arthritis, HLA-B27 +/- spondyloarthritis, idiopathic juvenile arthritis, seronegative oligoarthritis), osteoarthritis in 20.6%, villonodular synovitis in 14.7%, rheumatoid arthritis in 11.8% and the remaining etiologies were post-traumatic arthritis and uncertain. All these etiologies are shown in Fig. 3.

No improvement was reported in 10 of the 34 knees treated (29.4%), 4 of which had undergone intervention for total knee arthroplasty (while this was only necessary in 1 case of the group that reported improvement).

In regard to the results based on previously existing osteodegenerative changes, 92.3% of those presenting absent, doubtful or mild changes (KL 0-2) improved, while only 50% of those presenting moderate or advanced changes (KL 3-4) improved, showing statistically significant differences ($p = 0.03$). In fact, of the 5 knees in our sample finally requiring prosthesis implantation, all presented KL grade 3 (moderate osteodegenerative changes) in the radiography prior to the administration of the radioisotope.

The results of the technique also showed differences based on the origin of the synovitis in each case. Thus, of the total number of patients in whom the etiology of the knee synovitis was chronic inflammatory disease (spondyloarthropathies and rheumatoid arthritis), 80% (16/20) presented subjective improvement, while in those in whom the origin was osteoarthritis (degenerative), 25% (2/8) presented subjective improvement, showing statistically significant differences ($p = 0.006$).

Within the first group of patients with chronic inflammatory etiology, more than 75% of the cases presenting spondyloarthropathy

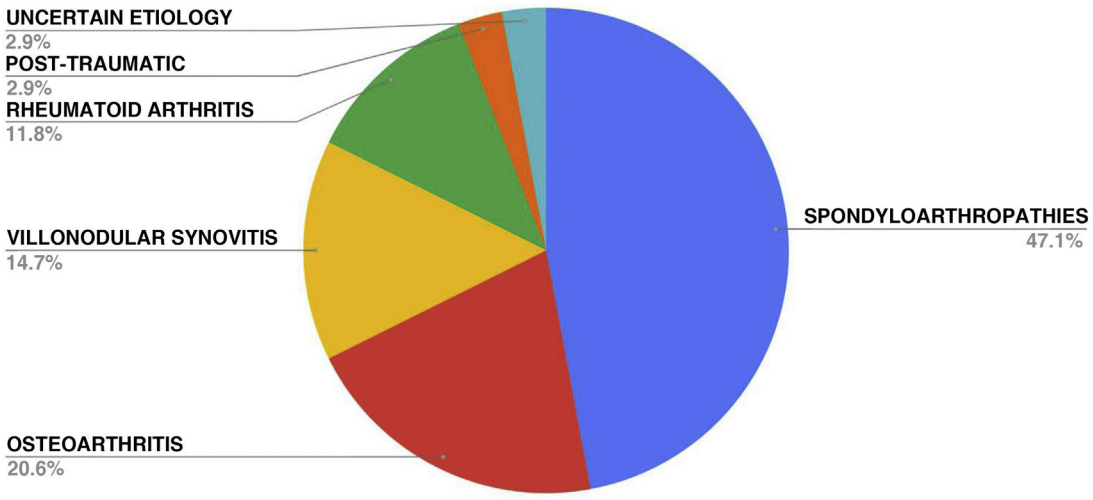

Figure 3. Etiologies of chronic synovitis of the knee in our sample.

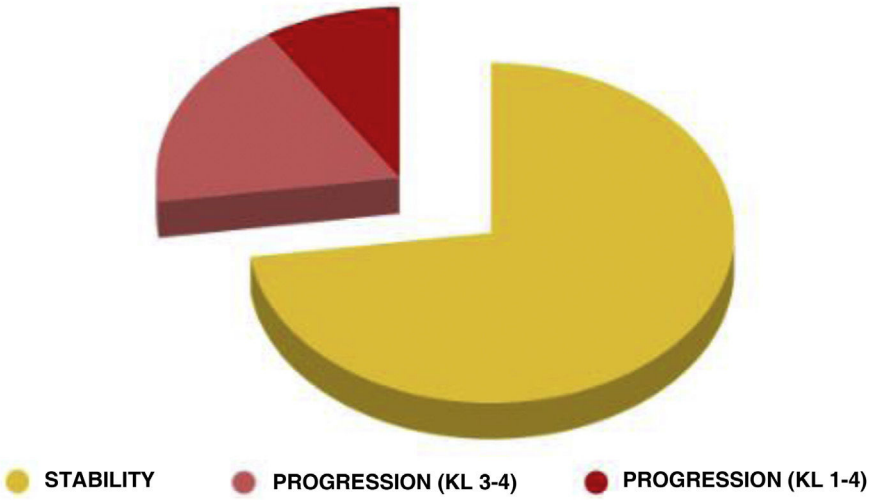

Figure 4. Radiological evolution evaluated by the changes produced according to the Kellgren-Lawrence scale in the radiographies prior to and after treatment.

improved, while only 50% of the group with rheumatoid arthritis reported improvement.

With respect to total number of patients with villonodular synovitis ($n = 5$), all improved with intraarticular administration of the radioisotope. However, in 3 cases the improvement was of less than 4 months, with surgical synovectomy later being performed in one patient, without clear improvement.

We were able to observe the radiological evolution of 12 patients who presented radiographies before and after radiosynoviorthesis. Of these, 9 presented radiological stability with a median follow-up of 43 months (mean 36.4; range 7–84), 2 progressed from KL grade 3 to grade 4 within 24 and 18 months, respectively, and 1 progressed from KL grade 1 to grade 4 in 24 months, although, as shown, there was great variability in patient follow-up due to the lack of standardization in the times to perform the intervention. The different distribution in the radiological evolution of the 12 patients is shown in Fig. 4, and the radiographic findings of 2 specific patients are shown in Fig. 5.

In regard to the adverse effects observed in our study, 4 patients presented mild and self-limiting adverse effects during the first week. All these patients presented swelling, in addition to reddening in one case and pain and incapacity in another case, and responded to treatment with rest, local cold and anti-inflammatories. All showed subjective improvement of the synovitis following radiosynoviorthesis.

Discussion

In our sample, 24 out of 34 the knees infiltrated (70.6%) presented subjective improvement, similar to the results described in the literature. For example, the metaanalysis of Kresnik et al. described mean response rates of 72.5 + 17%,[4] and in the review by Knut in 2015, the rate was between 60%–80%,[3] while the 2019 study by Miszczyk et al., 80.9% reported at least partial response to pain.[5]

However, many causes make it difficult to compare the efficacy of radioisotopic synovectomy among the different studies published in the literature and, thus, extrapolation of the results to a specific population is complicated.

Firstly, the efficacy of the technique depends on the grade of synovitis as well as the grade of arthrosis the joint presents at the time of treatment, being more effective in cases with marked inflammatory changes and mild osteodegenerative changes. The previously mentioned metaanalysis[4] concluded that joints with mild or moderate osteodegenerative changes respond better than those with more advanced changes. In our case, the response

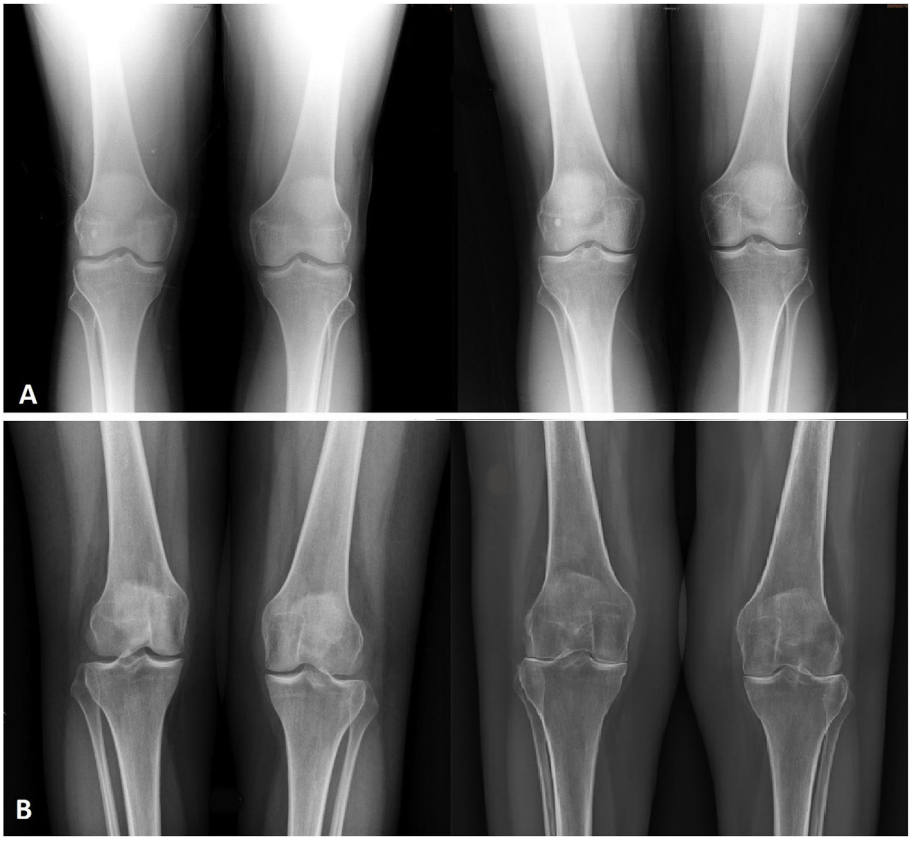

Figure 5. A. Patient with radiological stability with Kellgren-Lawrence grade 1 at two years of evolution. The image of the left was obtained prior to radiosynovectomy while the image on the right is from after the intervention. B. Patient with radiological progression with Kellgren-Lawrence grade 1 (image on the left is prior to radiosynovectomy) to 4 (image of the right after radiosynovectomy) at two years of evolution.

was lower in knees with moderate/advanced changes (KL 3-4), and thus, the indication of radiosynoviorthesis should, perhaps, be reconsidered in this group, or at least, patient selection could be improved with the support of different additional diagnostic techniques not used in the initial evaluation. In this sense, if, *a priori*, an articulation shows advanced degenerative osteoarthritic changes and mild or doubtful signs of inflammation, evaluation should be complemented with the performance of an additional diagnostic technique, such as 3-phase bone scintigraphy, MR or ultrasound study including the Doppler mode to ensure the presence of marked inflammatory changes and allow more adequate selection of patients who are candidates for radiosynoviorthesis. This additional evaluation should include special attention to knees with moderate/advanced osteoarthritic changes but without signs suggestive of synovitis. Thus, our results demonstrate the importance of referring patients at the most adequate time, and avoiding delayed treatment, which involves advanced evolutive changes and a reduction in treatment efficacy.

On the other hand, one of the main reasons why the efficacy of the technique may vary greatly is because of the lack of a reference test for evaluation. The different tools that have been used to achieve this involve from some tools which are objective, such as scales of pain and mobility, the patellar tap test, diameter of the joint, joint temperature, the need for drainage and its volume, as described in the series of Miszczyk et al.,[5,6] to the lack of need by the clinician to scale the systemic treatments or the subjective improvement reported by the patient.[7] In our study we used the latter and its duration until relapse, observing a great heterogeneity in the time until evaluation of treatment efficacy by the requesting physicians in our centers.

In addition, the most frequent etiology of refractory knee synovitis among the different groups in the literature varies greatly, making comparison among groups and extrapolation of the results difficult. For example, the most frequent etiology in the series by Miszczyk et al. was unspecific arthritis with 394 cases[5] and pigmented villonodular synovitis was the most frequent etiology in the group of Castro et al.[6] with 26 cases, while in our case spondyloarthropathies were the most frequent. In relation to etiology, better response to radiosynoviorthesis is described in cases with chronic inflammatory diseases (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, idiopathic juvenile arthritis, among others) versus degenerative etiologies (osteoarthritis).[7] The metaanalysis of Kresnik et al. concluded that this technique provides better results in rheumatoid arthritis than in osteoarthritis.[4] This was similar to what was found in our sample, in which we observed better response in the group of patients with chronic inflammatory etiology of synovitis versus cases of osteoarthritic/degenerative origin.

With respect to the group with villonodular synovitis, there is some debate in the literature on the utility of radiosynoviorthesis in these patients. While the main treatment is surgical by total synovectomy in diffuse or marginal forms, in the more localized forms, there is a high rate of recurrence, representing more than 20% of the cases, mainly among the diffuse forms.[8] Thus, adjuvant treatments, such as radiosynoviorthesis, have been studied to reduce recurrence. The metaanalysis by Mollen et al. described a significantly lower rate of recurrence in patients, who, after surgical intervention (arthroscopic or open surgery), received adjuvant treatment with radiation (external or intraarticular) compared to patients who did not receive this adjuvant treatment.[9] Other studies included in the

current European guidelines,[2] report that adjuvant radiation treatment may be used as a complementary technique to surgery in diffuse villonodular synovitis to reduce the rate of recurrence, ideally following a period of 6 weeks after the surgical intervention.[2,8,9] On the other hand, the systematic review published by Healey et al. in 2020 reported that the studies that included ^{90}Y radiosynoviorthesis as the adjuvant treatment did not observe a significant reduction in recurrences.[10] In our sample, only 20% (1/5) of the cases of villonodular synovitis underwent surgical synovectomy prior to radioisotopic therapy, despite surgery being the principle treatment, while in another case, surgery was performed after our intervention, with no clear improvement being observed. Perhaps, with the aim of improving our results, the earlier indication of surgery in these patients in our centers should be reconsidered, as should the adjuvant role of radiosynoviorthesis following synovectomy in the more diffuse forms.

The main limitations of our study include the small sample size, the etiologic variability of synovitis of the knee among the different patients and the KL grade. In addition, there was a lack of standardization in relation to both the follow-up time and the application of objective scales of clinical evaluation for studying the efficacy of the technique.

Conclusion

Radiosynoviorthesis with ^{90}Y is an effective treatment in patients with chronic refractory synovitis of the knee, especially in the presence of mild degenerative joint changes and with a chronic inflammatory origin. Adequate patient selection with a multidisciplinary approach with the use of the different diagnostic techniques available is essential and delayed referral should be avoided to ensure adequate results.

Ethical aspects

This study was approved by the Ethical Committee of Investigation with Drugs.

Conflict of interest

The authors have no conflicts of interest to declare.

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