

Radiosynovectomy in routine care: an old tool with modern applications

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Abstract

Objectives: Radiosynovectomy can be an effective treatment for difficult-to-treat monoarthritis resistant to systemic and local standard therapy. The objective of our study was to determine predictors of good response to radiosynovectomy in routine care and give an overview of this underused technique.

Methods: Retrospective observational study of all the patients who underwent radiosynovectomy during a 6-year inclusion period. All the procedures were ultrasound guided and the radiopharmaceutical used was chosen according to joint size. The patient was considered to have an effective response to radiosynovectomy if the attending physician reported a positive outcome and there was no need to increase local and or systemic treatment due to arthritis in the affected joint during the next 12 months following the procedure.

Results: We included 67 patients who underwent radiosynovectomy in the knee (73.1%), wrist (16.4%), and elbow (10.5%). Overall, 44 (65.7%) procedures were considered effective. In the multivariate analysis, infiltration of wrists (odds ratio=0.192; confidence interval=0.046–0.79) and pigmented villonodular synovitis (odds ratio=0.13; confidence interval=0.021–0.82) were independently associated with a noneffective response. No patients experienced complications associated with radiosynovectomy during follow-up.

Conclusion: Infiltrations of wrists with joint damage seem less likely to have a response to radiosynovectomy. In pigmented villonodular synovitis, radiosynovectomy as an adjuvant therapy for relapse might not be effective when performed more than 6 months after surgery. Overall, radiosynovectomy is an effective and safe treatment for persistent monoarthritis.

Keywords: radiosynovectomy, ultrasound

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Introduction

Synovectomy is a local treatment for diarthrodial joints, which is based on eliminating the inflamed synovial membrane. It has proven useful as a local treatment for chronic inflammatory joint diseases that are refractory to standard treatment. The three types of synovectomies are chemical synovectomy, surgical synovectomy, and radiosynovectomy (RSV). RSV requires the application of β -emitting radionuclides to treat the chronic inflammation of the joints. It selectively destroys the hypertrophic synovial membrane using

ionizing radiation. The procedure is performed by means of an intra-articular injection of radionuclides suspended in colloids, such as yttrium-90 silicate/citrate, rhenium-186 sulfide, and erbium-169 citrate.^{1–3}

The concept underlying joint radiation was first described in 1924.⁴ However, the first study on the use of RSV as treatment for chronic synovitis was published in 1952.⁵ It was not until 1963 that the first clinical trial was performed with radioactive colloidal gold-198 for treatment of persistent

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joint effusion in the knees of patients with rheumatoid arthritis (RA).⁶ Finally, in 1968, Delbarre *et al.*⁷ first used the term ‘synoviorthesis’ and the technique was properly established.

The choice of radionuclide depends on its energy and depth of penetration needed, being those with the lowest depth of penetration used mainly for small joints and the most potent ones for larger joints. Erbium-169 citrate (particle size: 1000–2000 nm, half-life: 9.4 days, max. beta energy: 0.35 MeV, gamma energy: 0, penetration: max. 1, mean 0.3 mm) is used for small joints and rhenium-186 sulfide (particle size: 50–300 nm, half-life: 3.7 days, max. beta energy: 1.07 MeV, gamma energy: 137 keV, penetration: max. 3.6, mean 1.2 mm) for medium-sized joints. Both of these are low-energy radionuclides. Due to its high energy, yttrium-90 citrate (particle size 2000 nm, half-life: 2.7 days, max. beta energy: 2.26 MeV, gamma energy: 0, penetration: max. 11, mean 3.6 mm) is used for large joints. The maximum activity for adults should not exceed 370 MBq in a single intra-articular delivery.^{8,9}

RSV is an overall safe technique. Radionuclide colloids cannot cross the joint capsule or be absorbed by lymph or blood vessels, thus restricting the ionizing radiation energy to the synovial membrane. Similarly, it cannot permanently bind to other intra-articular elements such as cartilage or bone. The synovial hypertrophy and inflammation are treated with a dual approach. Phagocytosis of the radiopharmaceutical by the macrophages eventually blocks the inflammatory process. At the same time, synovial fibrosis is directly caused as a reaction to the radiopharmaceutical.³ It is used in chronic arthritis with few radiological abnormalities that has not improved with standard systemic or local treatment, being RA the most common indication.^{1,8}

The absolute contraindications for RSV are the presence of a ruptured Baker’s cyst, active infection (cutaneous, joint, or systemic), and ongoing pregnancy or breastfeeding. Likewise, there are relative contraindications, being mainly extensive joint instability with bone destruction (Steinbrocker stages III and IV) or fractures, evidence of significant cartilage loss within the joint, less than 2 weeks after a previous arthrocentesis and no response to two previous radiosynovectomies.^{1,8,10} As a noteworthy consideration, RSV should only be used in children and young patients (<20 years) if the benefit of treatment is

likely to outweigh the potential risks.¹ Adverse effects are unusual in adult patients, the most common being synovitis triggered by administration of the radionuclide, followed by septic arthritis, local tissue necrosis, rupture of a Baker’s cyst, and a flu-like syndrome. These usually appear as short-term complications.^{8,11}

Despite the use of ionizing radiation, overall exposure is low and there is no evidence of an increase in cancer risk when compared with the general population in adult patients.¹² Immobilization of the treated joint for 2–3 days after injection reduces the rate of release of the radiopharmaceutical from the joint by up to 1%.^{2,3}

The reference departments for this technique are the Nuclear Medicine Department and the Rheumatology Department, with the ideal approach being a multidisciplinary one involving both specialties. At our center, it has been a technique done with the collaboration of both departments for over 20 years. Our objective is to determine predictors of good response to RSV in routine care and bring attention to this technique that has been underused in the last decade.

Materials and methods

Patients and data collection

We designed a retrospective observational study including patients consecutively treated with RSV between 31 May 2013 and 31 October 2019. We reviewed the medical records and collected demographic data (sex, age), diagnosis, time since diagnosis, joint infiltrated, presence of a Baker’s cyst in knees, radiopharmaceutical used, systemic treatment received at the time of infiltration (corticosteroids, synthetic and biological disease-modifying antirheumatic drugs), changes in treatment during the 12 months before and after treatment (including new infiltrations with corticosteroids or RSV), and complications associated with RSV during the following 12 months after the procedure. The study was approved by the Ethics Committee of H. G. U. Gregorio Marañón, Madrid, Spain (RS-2013/19). The reporting of this study conforms to Strengthening the reporting of observational studies in epidemiology (STROBE) statement.¹³

Technique

Radiopharmaceuticals were prepared, administered, and stored at the Nuclear Medicine

Department facilities in accordance with the recommendations for radiologic protection approved by the Nuclear Safety Council in Spain. All RSV procedures were done with ultrasound-guided arthrocentesis and as outpatients. According to protocol, patients underwent a clinical and ultrasound evaluation between 1 and 3 weeks before the procedure to confirm the presence of synovitis and select the appropriate radiopharmaceutical [yttrium-90 citrate for knees (185 MBq) and rhenium-186 sulfide for elbows and carps (74–111 MBq)]. Ultrasound was performed using a Mylab Twice device (Esaote, Genoa, Italy) with a linear probe (up to 15 MHz) from May 2013 to May 2019 and an Acuson NX3 Elite (Siemens) with a linear probe (up to 12 MHz) from June 2019. All patients signed a patient consent before the procedure. RSV was done under strict local antiseptic conditions.

Confirmation of joint effusion by ultrasound was the first step of the procedure. The most appropriate access point was determined, and the radiopharmaceutical was then administered using ultrasound as guidance, followed by 1 ml of triamcinolone acetonide (40 mg) and 1–5 ml of 0.9% saline solution. Once the infiltration was complete, joint movements – both active and passive – were avoided for at least 5 min in order to guarantee an even distribution of the radionuclide in the joint cavity. At discharge, the patient was instructed to rest the joint for 24–48 h and to avoid contact with pregnant women and children for at least 2 weeks (equal to $10 \times$ isotope half-life, when it can no longer be detected on the joint).¹²

Ultrasound guidance varied depending on the joint: in the case of knees, the approach was lateral via the suprapatellar recess with an intramuscular needle (18G); in elbows, it was approached medially via the olecranon fossa using an intramuscular needle (18G); and in wrists, the approach was dorsal – both medial and lateral, depending on whether the distal radiocarpal joint or radioulnar joint was involved – using a subcutaneous needle (15G).

Clinical outcome

The primary outcome was to evaluate the clinical response according to the underlying disease and the type of joint infiltrated. RSV was considered effective if the patient met all of the following requirements: a positive response from the attending physician's evaluation, no need to increase

systemic treatment due to arthritis in the infiltrated joint nor need to receive new infiltrations during the next 12 months. The secondary outcome was to evaluate the safety profile of RSV, changes in systemic treatment, and the need of subsequent infiltrations after 6 and 12 months.

Statistical analysis

Data were analyzed using SPSS, Version 24.0. Qualitative variables used absolute and relative values and quantitative variables used median and interquartile ranges. Between groups comparisons were made with univariate and multivariate analyses. Chi-square test was used for qualitative variables and *T*-student distribution for continuous variables. Multivariate analysis was done with a binary logistic regression. *p* values <0.05 were considered significant.

Results

We evaluated 67 joints from 49 patients seen at our center during the study period (Table 1). All of the patients had arthritis that was refractory to standard treatment as indication for RSV. Median age was 53.3 years [interquartile range (IQR), 43.4–67.1 years], 44 patients (65.7%) were women, and the mean disease duration was 12.5 years. Radiopharmaceuticals were infiltrated in the knees [49 (73.1%)], wrists [11 (16.4%)], and elbows [7 (10.5%)].

In all joints, RA was the most frequent diagnosis with 30 (44.7%) patients. Out of these, 16 received RSV in the knees and 13 (81.2%) achieved an effective response although no statistical significant differences were found. The presence or absence of a Baker's cyst had no statistical significance between effective and noneffective responses [11 (61.1%) *versus* 7 (38.8%), $p=0.63$]. In the elbows, an effective response was achieved in all of them, and 6 (85.7%) of these had RA as diagnosis. With a statistical significance, elbows were more likely to have an effective response to RSV [7 (100%) effective, $p=0.04$]. However, in the wrists, even when 9 (81.1%) patients had RA, a noneffective response was observed with statistical significance [7 (63.7%) noneffective; $p=0.02$]. This may be explained due to the fact that out of these 6 (85.7%) had previous joint damage, which is a known factor for a less effective response to RSV. In contrast, out of the effective wrists, only 2 (50%) had joint damage.

Table 1. Patient characteristics and univariate analysis.

	Total 67 (100%)	Effective 44 (65.7%)	Noneffective 23 (34.3%)	<i>p</i>
Demographics				
Women (%)	44 (65.7)	29 (65.9)	15 (34.1)	0.95
Age (median, IQR)	53.3 (24.3)	56 (51.4–69.4)	44.7 (39.3–60.8)	0.06
Mean disease duration (years; median, IQR)	12.5 (14.8)	13.5 (7.3–24.6)	8.5 (4.7–15.5)	0.01
Radiopharmaceuticals				
Yttrium (%)	49 (73.1)	35 (71.4)	14 (28.6)	0.1
Renium (%)	18 (26.8)	9 (50)	9 (50)	0.1
Joints				
Knees (%)	49 (73.1)	33 (67.3)	16 (32.7)	0.6
Wrists (%)	11 (16.4)	4 (36.3)	7 (63.7)	0.02
Elbows (%)	7 (10.5)	7 (100)	0 (0)	0.04
Diagnosis				
Inflammatory joint diseases (RA + PsA + SpA + JIA) (%)	52 (77.6)	37 (71.1)	15 (28.9)	0.07
Rheumatoid arthritis (RA) (%)	30 (44.7)	21 (70)	9 (30)	0.5
Psoriatic arthritis (PsA) (%)	6 (9)	4 (66.6)	2 (33.3)	0.9
Spondyloarthritis (SpA) (%)	9 (13.4)	8 (88.8)	1 (11.1)	0.1
Juvenile idiopathic arthritis (JIA) (%)	7 (10.4)	4 (57.1)	3 (42.8)	0.6
Pigmented villonodular synovitis (%)	8 (11.9)	2 (25)	6 (75)	0.01
Nonspecific monoarthritis (%)	3 (4.4)	3 (100)	0 (0)	0.23
Arthrosis + calcium pyrophosphate deposition disease (%)	4 (5.9)	2 (50)	2 (50)	0.49
IQR, interquartile range.				

Despite not finding any statistical differences when comparing individual immune-mediated chronic inflammatory joint disease [RA, psoriatic arthritis (PsA), spondyloarthritis (SpA), and juvenile idiopathic arthritis (JIA)], when analyzed as a group (52 patients), the response to treatment was likely to be effective, with a near statistical significance ($p=0.07$) compared with other diagnoses. Out of the eight patients with pigmented villonodular synovitis (PVNS), six (75%) had a noneffective response with statistically significant difference ($p=0.01$). All patients who had PVNS had surgical synovectomy previously and the RSV was indicated as adjuvant; however, only one

patient received RSV in the following 6 months of the surgery. We found no other differences with the remaining diagnosis studied.

In the multivariate analysis (Table 2), there was an independent negative correlation to treatment response when the diagnosis was PVNS [odds ratio (OR)=0.13; confidence interval (CI)=0.021–0.82; $p=0.03$], and when the joint was the wrist [OR=0.192 (CI=0.046–0.79), $p=0.02$] with the caveats mentioned before. There was no clear significance on mean disease duration, and the elbows had no statistical significance when analyzed with Fisher's exact test ($p=0.086$).

Table 2. Multivariate analysis.

		Total 67 (100%)	Effective 44 (65.6%)	Noneffective 23 (34.3%)	<i>p</i>	OR
Parameter with <i>p</i> < 0.05 in univariate analysis.						
Diagnosis	Pigmented villonodular synovitis (%)	8 (11.9)	2 (25)	6 (75)	0.03	0.13 (0.021–0.82)
Demographics	Mean disease duration in years (median, IQR)	12.5 (14.8)	13.5 (7.3–24.6)	8.5 (4.7–15.5)	0.5	1.02 (0.95–1.1)
Joints	Wrists (%)	11 (16.4)	4 (36.3)	7 (63.7)	0.02	0.19 (0.046–0.79)
	Elbows (%)	7 (10.5)	7 (100)	0 (0)	0.08	NA
IQR, interquartile range; OR, odds ratio.						

The joint infiltrations are shown in Table 3. As for corticosteroid infiltrations before the procedure, no differences were found between patients with an effective and noneffective response during the previous 12 months. After the procedure, 18 patients (26.8%) required infiltrations. Of these, 11 (61%) required corticosteroids due to a noneffective response between 0 and 6 months after RSV ($p < 0.0001$); the difference remained unchanged for up to 12 months after ($p < 0.01$). The remaining seven patients (38.8%) required a second RSV; of these only two (28.5%) were in the same joint due to noneffective response with the first procedure, and again, no response was achieved.

Systemic treatment 12 months after RSV in patients with effective response (Figure 1) was not intensified in 72.7% (remained unchanged in 28, was reduced in 3, and suspended in 1 due to herpes zoster infection). It was intensified in 12 (27.3%) in order to control inflammation in joints other than the one where RSV was done.

In patients with noneffective response to RSV (Figure 2), treatment remained unchanged in 12 (52.2%) and was intensified in 10 (44%) due to poor control of inflammation in the joint that underwent RSV and other joints. It was discontinued in one (4.3%) case due to prostate cancer.

In total, four patients (8.2%) required surgical synovectomy after RSV owing to poor control of inflammation in that joint (all PVNS). Among the

patients who presented an effective response, one was lost to follow-up before the 12-month mark. No patients reported complications associated with RSV during the follow-up (including one patient with a previous total knee replacement).

Discussion

RSV is a quick, simple, safe, and inexpensive technique when compared with the more traditional surgical synovectomy. It can be repeated and does not contraindicate a subsequent surgical approach if necessary.^{14–16} While it was first described more than half a century ago, it seems to have become less prevalent since the advent of biologic therapy. Our experience shows that RSV is a useful treatment for cases of mono and oligoarthritis and should be considered in patients who are refractory to standard treatment.

In the knee, the most frequently infiltrated joint, RSV tended to be effective despite not reaching statistical significant difference in our study (possibly due to sample size and heterogeneity of diagnoses), whereas the wrists had noneffective response with statistical significance; this may be because the wrists are conformed by the three joints (radiocarpal, radioulnar, and midcarpal joint) and the most frequent diagnosis was RA which is commonly associated with increased joint damage and cartilage loss.

In PVNS, medium- and long-term efficacy seems to be poor in contrast with data from other series.¹⁷ This may be due to the fact that, in our

Table 3. Infiltrations before and after radiosynovectomy.

	Total 67 (100%)	Effective 44 (65.6%)	Noneffective 23 (34.3%)	p
Previous infiltrations (0–6 months)				
Corticosteroids in the same joint (%)	35 (52.2)	25 (56.8)	10 (43.4)	0.29
With radiopharmaceuticals (%)	3 (4.4)	3 (6.8)	0	0.2
Same joint (%)	0	0	0	–
Different joint (%)	3 (4.4)	3 (6.8)	0	0.2
Previous infiltrations (6–12 months)				
Corticosteroids in the same joint (%)	21 (31.3)	12 (27.2)	9 (39.1)	0.32
With radiopharmaceuticals (%)	1 (1.5)	0	1 (4.3)	0.16
Same joint (%)	1 (1.5)	0	1 (4.3)	0.16
Different joint (%)	0	0	0	–
Subsequent infiltrations (0–6 months)				
Corticosteroids in the same joint (%)	8 (11.9)	0	8 (34.7)	< 0.0001
With radiopharmaceuticals (%)	3 (4.4)	3 (6.8)	0	0.2
Same joint (%)	0	0	0	–
Different joint (%)	3 (4.4)	3 (6.8)	0	0.2
Subsequent infiltrations (6–12 months)				
Corticosteroids in the same joint (%)	3 (4.4)	0	3 (13)	0.01
With radiopharmaceuticals (%)	4 (5.9)	2 (4.5)	2 (8.6)	0.49
Same joint (%)	2 (2.9)	0	2 (8.6)	0.04
Different joint (%)	2 (2.9)	2 (4.5)	0	0.29

series, most of the RSV were not performed in the next 6 months after the surgery, which usually increases the effectiveness of the technique.¹⁸ This translates in a low lower likelihood of response to therapy as confirmed by the multivariate analysis. When comparing chronic inflammatory joint diseases (RA + PsA + SpA + JIA) with all other causes of arthritis, we found a tendency to a better rate of response on the former; however, it did not reach statistical significance probably due to study power and sample size. Nevertheless, the results that we obtained in chronic arthritis are consistent with those reported in the literature.^{2,14}

Considering the reports of complications with RSV, these are generally infrequent, as we also

confirmed in our study, in which no complications were reported. Ultrasound guidance is probably an important factor in reducing the possibility of complications even further and obviating the need for subsequent radiological monitoring to confirm appropriate placement of the radioisotope; however, as the follow-up time is relatively short, further monitoring is strongly advised.

Our study has several strengths, the main one being the high number of patients included compared with other single-center series,^{17–20} together with the variety of joints (large and small) and the spectrum of diagnosis, thus reflecting real-world clinical practice. In addition, our description of the ultrasound-guided technique could prove useful for other centers performing or intending

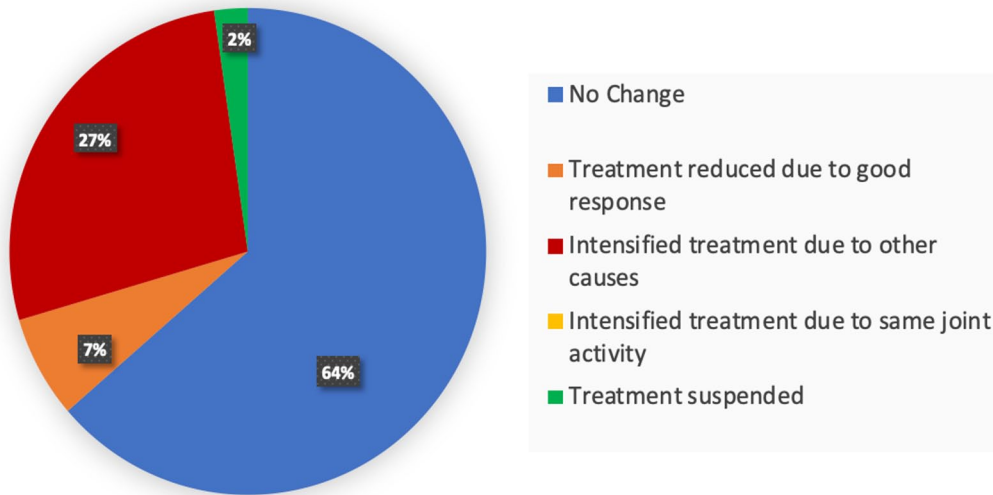


Figure 1. Systemic treatment in patients with an effective response.

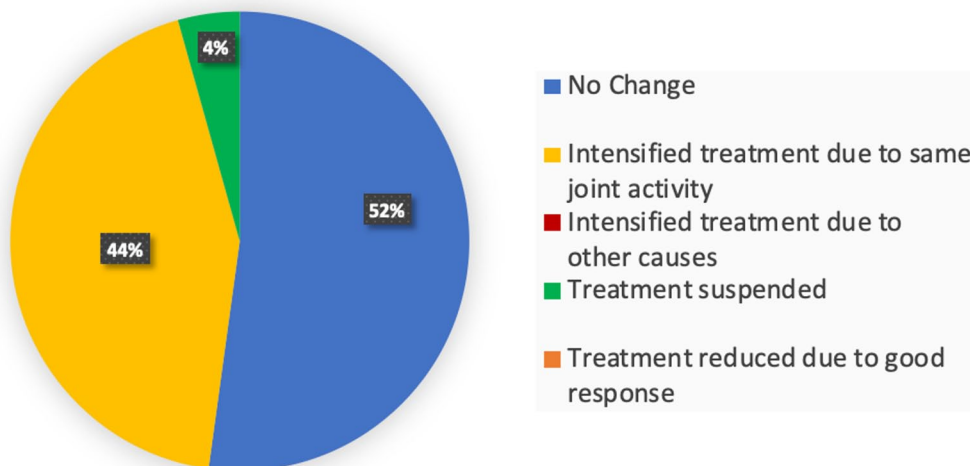


Figure 2. Systemic treatment in patients with a noneffective response.

to perform RSV. However, our study is also subject to limitations, its design was both retrospective and observational and patients come from a single center. We also chose mainly a clinical outcome as the benchmark for determining whether the procedure was effective, although we did apply additional ‘effective response’ criteria to reduce the subjectivity of the attending physician, such as maintenance or reduction of systemic treatment, no need for new infiltrations in the same joint, and no complications related to RSV, all of which offer a more objective value to the response or nonresponse.

In summary, our study shows that RSV continues to be a useful option for the treatment of persistent arthritis that is refractory to standard treatment. Furthermore, infiltration with a radiopharmaceutical in wrists, especially with joint damage, and in PVNS with a relapse to surgery seems to be associated with worse outcomes. Inflammatory arthritis seems to be more likely to have a positive response; however, we believe that a larger multicenter study with a longer follow-up will be useful to determine other indicators for an effective response, especially in the biologic and minimal invasive procedures era that is the mainstay of treatments today.

Author contributions

I want to thank the Rheumatology Department and the Nuclear Medicine Department for their collaboration, through their efforts we were able to improve the quality of life of many patients and we were able to explain our technique so that those who wish can implement it in their practice.

Conflict of interest statement

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