# Radiation Synovectomy of the Ankle with 75 MBq Colloidal $^{186}$Rhenium-Sulfide: Effect, Leakage, and Radiation Considerations

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*ABSTRACT.* ***Objective.*** In a retrospective study we evaluated the effect, duration of effect, and safety of radiosynoviorthesis of the ankle in patients with persistent synovitis, refractory to disease modifying antirheumatic drugs (DMARD) and intraarticular glucocorticoid injections. We estimated leakage and dose to target and non-target organs.

***Methods.*** Radiation synovectomy was performed by injection of 75 MBq $^{186}$rhenium colloid and 20 mg triamcinolone-hexacetonide mixed in a volume of about 1.5 ml. About 24 hours after injection, leakage of the radionuclide was measured with a single-head gamma camera, with views of the ankle joint, regional (inguinal) lymph nodes, and liver. Leakage was expressed as counts in the target region of interest corrected for background relative to total counts corresponding with percentage of injected dose. The effect of radiosynoviorthesis was scored into 3 categories: (1) No effect, i.e., persistent synovitis or only minimal reduction of swelling and/or pain, or the need of intraarticular glucocorticoid injection within 3 months or arthrodesis of the treated joint within 6 months. (2) Moderate effect, i.e., significant reduction of swelling, pain, and improvement of function. (3) Good effect, i.e., complete or almost complete remission of synovitis.

***Results.*** The mean age of patients (28 women, 12 men) at the time of treatment was 58 years (range 33–76); 54 consecutive procedures in ankles of the 40 patients were evaluated. No effect was found in 12 of 54 (22%) treated joints; moderate effect in 12 (22%), with a mean duration of effect of 34 months (range 12–49); and good effect in 30 (56%), with a mean duration of effect of 41 months (range 21–75). Mean effect-duration did not differ significantly between the moderate and good effect groups. Mean leakage did not differ significantly between the effect groups.

***Conclusion.*** Radiation synovectomy of the ankle is a safe and effective treatment in persistent synovitis, although all patients eventually experienced recurrence of arthritis. (J Rheumatol 2004;31:896–901)

*Key Indexing Terms:*
RADIOSYNOVIORTHESIS RADIATION SYNOVECTOMY ANKLE
COLLOIDAL $^{186}$RHENIUM-SULFIDE RHEUMATOID ARTHRITIS LEAKAGE

Chronic rheumatic inflamed joints resistant to therapy with nonsteroidal antiinflammatory drugs (NSAID), disease modifying antirheumatic drugs (DMARD), and intraarticular glucocorticoid injections may be controlled with synovectomy. Three types of synovectomy are known: chemical, surgical, and radiation.

Osmic acid is the most frequently used agent for chemical synovectomy. The results are variable, but satisfactory disease control can be achieved[1-3]. Osmic acid etches the synovial intimal lining cells, inducing atrophy of the synoviocytes and reduction of inflammation[4,5].

Surgical synovectomy is successful in 40–90% of treated patients, although the duration of remission varies from a relatively short period up to many years[6-10]. Surgical synovectomy has evolved from open to arthroscopic techniques. A new technique is arthroscopic laser synovectomy that reduces bleeding of the synovium. However, not all joints are accessible for arthroscopic synovectomy. Surgical synovectomy in addition has the drawback that a long revalidation period is necessary after surgery.

Radiation synovectomy or radiosynoviorthesis has been used for decades. Intraarticularly injected small particles labelled with ß-emitting isotopes are phagocytized by macrophage-like synoviocytes and by phagocytizing inflammatory cells in the subsynovial connective tissue[11]. Radiation of the synovium results in necrosis of the synoviocytes and inflammatory cells, and cell proliferation

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is inhibited. Temporarily, the cycle of synovitis and joint damage can be halted[12]. Satisfactory control of synovitis is achieved in 40–80% of patients after one year, with a decline over time[13-18].

Estimation of the effect of radiation synovectomy or radiosynoviorthesis is mainly based on studies of knee joints. Studies on other joints are rare; the ankle (tibiotalar) joint has been investigated in only a few studies. To our knowledge, only 4 articles in the English literature include results of radiosynoviorthesis of the ankle[16,19-21], besides some studies of hemophilic ankle arthropathy[22,23]. In our retrospective study we evaluate the size and duration of the effect and safety of radiation synovectomy of the ankle. For this latter purpose, leakage to non-target organs and dose to target and non-target organs was measured.

## MATERIALS AND METHODS

*Patients.* In the Medical Centre Alkmaar, a 913-bed non-university teaching hospital, patients with persistent synovitis refractory to DMARD and at least one intraarticular glucocorticoid injection (20 mg triamcinolone-hexacetonide) are referred to the nuclear medicine department for radiation synovectomy. In the period 1990 to 1996 all 54 consecutive procedures in ankles of 40 patients could be evaluated. The characteristics are summarized in Table 1. The mean age of the patients at the time of treatment was 58 years (range 33–76 yrs). The female:male ratio of the 40 patients was 28:12. In 10 patients both ankles were treated, and in 3 patients (in one, both ankles) a second radiosynoviorthesis in the same joint was performed. The underlying disease causing synovitis was rheumatoid arthritis (RA) in 49 cases, psoriatic arthritis in 3, posttraumatic arthritis in one, and reactive (Yersinia) arthritis in one.

From the patient's chart the following data were obtained: age, sex, rheumatic disease causing the synovitis, global opinion from the treating physician, and if available, inflammatory joint measures (pain, swelling/hydrops, and range of motion) and side effects (needle tract burn, radiation induced flare of synovitis).

The effect of radiosynoviorthesis was scored into 3 categories: (1) No effect, i.e., persistent synovitis or only minimal reduction of swelling and/or pain, or the need of an intraarticular glucocorticoid injection within 3 months or arthrodesis of the treated joint within 6 months (Group 1). (2) Moderate effect, i.e., significant reduction of swelling and pain, and improvement of function (Group 2). (3) Good effect, i.e., complete or almost complete remission of synovitis (Group 3). The patients' radiographs were reread by the first author and scored according to the radiological Steinbrocker classification[24]. The duration of the effect was defined as the interval until clinical recurrence of synovitis, considerable worsening of the joint inflammatory indicators, or the need for an intraarticular glucocorticoid injection.

*Radiosynoviorthesis procedure.* Radiation synovectomy was performed under sterile conditions. After puncture of the tibiotalar joint (ankle), synovial fluid was aspirated if present. Aspiration was performed to avoid back-flushing due to high hydrostatic pressure and to confirm correct intraarticular needle positioning. If needed, local anesthesia with 2% lidocaine was given. Arthrography with small amounts of x-ray contrast medium was performed to confirm intraarticular needle position just before injection of 75 MBq $^{186}$rhenium colloid (RE-186-MM-1; CIS Bio International, Gif sur Yvette, France) and 20 mg triamcinolone-hexacetonide mixed in a volume of about 1.5 ml. In our institution, glucocorticoids are coadministered to avoid radiation induced flare of synovitis and to bridge the lag phase of the onset of effect of radiosynoviorthesis. Further, glucocorticoids can reduce inflammation of the synovium and thus vascularization, diminishing leakage of the radiopharmaceutical to non-target organs. The syringe was flushed with 0.9% NaCl before withdrawal, to minimize the chance of "needle tract burn" (a ß-radiation induced skin lesion or fistula caused by backflushing of the radioisotope through the needle tract). The ankle was immobilized by a bandage for 72 hours.

*Table 1.* Characteristics of 54 synovectomies in 40 patients.

| | |
|---|---|
| Mean age, yrs (SD, range) | 58 (11, 33–76) |
| F/M (% female) | 36/18 (67) |
| Right/left ankle (% right) | 35/19 (65) |
| Diagnosis: n (%), ankles | |
| Rheumatoid arthritis | 49 (91) |
| Psoriatic arthritis | 3 (6) |
| Posttraumatic arthritis | 1 (2) |
| Reactive (Yersinia) arthritis | 1 (2) |

*Leakage measurements.* Roughly 24 hours after the injection, leakage of the radionuclide was measured with a single-head gamma camera. Views of the ankle joint, regional (inguinal) lymph nodes, and liver were obtained with the following acquisition variables: time 150 s, peak 1: 140 keV with a window of 15%; peak 2: 62 keV with a window of 20% (for measuring Brehmmstrahlung), matrix 256 × 256. Regions of interest (ROI) were drawn around target areas and background areas. Leakage was expressed as counts in the target ROI corrected for background relative to total counts corresponding with percentage of injected dose.

*Dosimetry.* For radiation synovectomy, the dose $D_{syn}$ in the synovium can be determined using the equation:

$$D_{syn} = \frac{A_{syn} F}{\lambda_n S_{syn}} \quad (1)$$

where $A_{syn}$ = total activity in the synovium, $\lambda_n$ = nuclear decay constant of the radionuclide, and F = absorbed dose constant (in Gy cm$^2$ MBq$^{-1}$ s $-$ 1)[25]. For ankle joints $S_{syn}$ = 44 cm$^2$ (surface of the synovium of the ankle)[26].

Given the distribution of the radionuclide in the body, it is possible to calculate the dose to the whole body as well as to different organs. As $^{186}$Re emits γ- and ß-radiation, each should be considered separately.

The tissue penetration of ß-radiation (electrons) is within the range of millimetres. Assuming that organs are larger than the average range $r^{\beta}_{avg}$ of electrons, the dose $D^{\beta}_{org}$ is given by:

$$D^{\beta}_{org} = 1.6*10^{-10} \frac{A_{org} \sum y_i E_i}{\lambda_n m_{org}} \quad (2)$$

in which $A_{org}$ = total activity in the organ, $y_i$ = fraction of energy $E_i$ in the decay spectrum, $\lambda_n$ = the nuclear decay constant, and $m_{org}$ = the mass of the organ. In situations where the biological decay constant $\lambda_{biol}$ is small compared to the nuclear decay constant $\lambda_n$, the effective decay constant $\lambda_{eff} = \lambda_n + \lambda_{biol}$ should be used instead:

$$D^{\beta}_{org} = 1.6*10^{-10} \frac{A_{org} \sum y_i E_i}{\lambda_{eff} m_{org}} \quad (3)$$

As $r^{\beta}_{avg}$ for $^{186}$Re is around 1.2 mm, the assumption holds for all organs, except for lymph nodes.

As the diameter of a lymph node is within the (average) range of an emitted electron, a correction is necessary. Assuming that continuous slowing down approximation holds, the fraction of the dose deposited in a small organ follows from:

$$D^{\beta}_{lymph} = D^{\beta}_{org} \frac{r_{lymph}}{r^{\beta}_{avg}} \quad (4)$$

with $r_{lymph}$ the (average) radius of the lymph node.

Compared to ß-radiation, γ-radiation (photons) has much greater tissue penetration. Indeed, the whole body can be seen as the target and consequently, dose will be deposited over the whole body. Given the localization of the radionuclide (in the ankle) and the energy of this γ-radiation (137 keV), the resulting dose in the lower trunk (first localization to find organs at risk) can be estimated. Very important for this dose is the transmission through the leg, which can be calculated as:

$$I_d = I_o e^{-\mu d} \quad (5)$$

where $I_o$ = initial intensity, $I_d$ = intensity after d cm of tissue with an absorption coefficient μ. For a leg with a length of 70 cm, the transmitted portion of radiation is < 0.01%. Therefore, the contribution of γ-radiation from the ankle to the trunk can be ignored.

For the smaller portion of leaked radionuclide (e.g., = 5% to the liver), the contribution to the dose of the organs at risk can also be neglected. This means, that for this particular situation (radiation synovectomy of the ankle), the contribution of γ-radiation to the dose of the organs at risk can be ignored.

The equivalent body dose $E_{body}$ can be calculated with the tissue weight factor $w_T$ as defined by the International Commission on Radiological Protection (ICRP) and the tissue dose $D_T$ using[27]:

$$E_{body} = \sum w_T D_T \quad (6)$$

According to this ICRP model, liver and ankle do have a contribution to the equivalent body dose, but solitary lymph nodes have no contribution. With the equivalent body dose $E_{body}$ it is possible to estimate the total risk of the treatment.

*Statistics*. The one-sample Kolmogorov-Smirnov test was used to test continuous data for normal distribution and the Kolmogorov-Smirnov Z test was used to test the distribution of groups. Continuous data (leakage and response time) of groups were tested for statistically significant difference with analysis of variance (ANOVA) or 2-sample T tests in case of normal distribution of the data and otherwise with Mann-Whitney U tests. Ordinal data like Steinbrocker radiological classifications were tested for statistical significance with Fisher's exact test. Statistical significance was defined as $p < 0.05$.

## RESULTS

Radiation synovectomy resulted in no effect or only minimal reduction of swelling and/or pain in 12 (22%) of the treated joints (Group 1); a moderate effect, i.e., significant reduction of swelling and pain and improvement of function in 12 (22%; Group 2); and a good effect, i.e., complete or almost complete remission of synovitis in 30 (56%; Group 3). The mean duration of effect for Group 2 was 34 months (range 12–49 mo) versus 40 months (range 21–75 mo) for Group 3. Although the duration of effect seems to be in favor of Group 3, it did not differ significantly between Groups 2 and 3. Survival curves for the moderate and good effect categories are illustrated in Figure 1. Radiation synovectomy was repeated in 3 patients 11, 14, and 36 months after the first treatment. In one patient neither synovectomy had any effect. In the other 2 patients both procedures showed a good effect; in these patients the duration of effect was longer for the second synovectomy. The duration of the first treatment in these 2 patients was 11 and 16 months and of the second treatment 25 and 36 months.

In this study no short-term side effects were recorded. Side effects in the longer term caused by leakage have not been reported, although the followup period for late effects is too short. The immobilization and hospitalization for 3 days were experienced as only slightly inconvenient by the patients. No thromboembolic events have been reported in the first 3 months after synovectomy.

At the time of treatment the Steinbrocker radiological classification was 1 or 2 in 43 (80%) joints and 3 or 4 in 11 (20%) joints. Radiation synovectomy failed in 5 (12%) of 43 treatments in joints with radiological classification 1 or 2, and in 7 (64%) of 11 treatments in joints with radiological classification 3 or 4 ($p = 0.001$), as described in Table 2.

Data on leakage (as percentage of injected dose) to lymph nodes and liver are shown in Table 3. As expected, leakage to lymph nodes occurred more often than leakage to the liver; mean leakage was higher in lymph nodes than in liver. Of all procedures, maximal leakage to a single lymph node was 4% and to the liver 5.5%. "Total leakage" was defined as the sum of leakage to lymph nodes and liver. Mean "total leakage" and variance did not differ significantly in the 3 effect groups (by ANOVA), nor was there a significant difference between radiological classification 1 or 2 and 3 or 4 (independent 2-sample T tests).

The dose to the synovium of the ankle was 3.05 Gy and lowered to 2.76 Gy in case of leakage of 9.5%. Leakage of maximal 4% to a single lymph node gives a dose of 35 Gy and maximal dose to the liver was 0.0075 Gy. Given that the tissue weight factor (a concept devised by the ICRP to translate a partial radiation dose into a whole-body dose) for both ankle and liver is 0.05, the equivalent body dose $E_{body}$ will be 0.15 mSv (no leakage) or 0.14 mSv (9.5% leakage), which means no substantial difference. Compared to a dose of 5.0 mSv received from a chest computer tomography (CT) scan, this is a low dose. It is somewhat higher than a dose of 0.01 mSv received from a radiograph of the ankle[28].

## DISCUSSION

Inflammatory joint diseases, most commonly RA, generate high costs. The clinical effect of radiation synovectomy, using different isotopes, has been studied for decades. Deutsch, *et al* summarized the results of 64 studies. In these mainly retrospective studies, good effect after one year is achieved in 40–90% of subjects[15]. To our knowledge, in the English literature only 4 studies have described results of radiation synovectomy of the ankle[16,19-21]. In some studies results of different joint are presented, but the effect of radiation synovectomy of the ankle has not been described separately[29-31]. In the 4 studies above, radiosynoviorthesis was effective in 90% (9 out of 10)[19], 17% (4/23)[16], 53% (8/15)[20], and 62% (19/26)[21] of subjects. In 2 studies colloidal $^{186}$rhenium-sulfide was used[20,21], in one $^{32}$P-colloidal chromic phosphate[19], and in one $^{90}$yttrium colloid[16]. In our study moderate or good effect was achieved in 78% (42 out of 54) of the procedures. There is a difference in effect rate

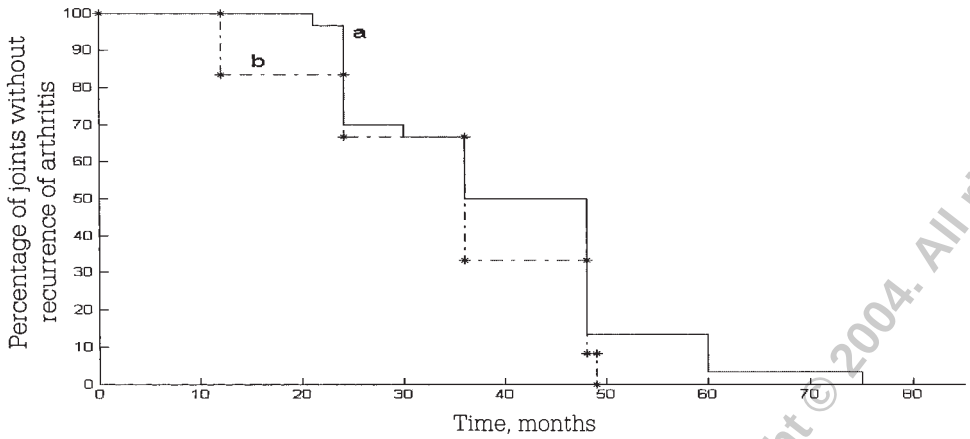


*Figure 1*. Survival curves for the effect categories moderate and good effect; percentage of joints with persistent effect in time. Line a: good effect group; line b: moderate effect group. The duration of effect did not differ significantly between the good and moderate effect categories.

between our study (78%) and the 2 studies using colloidal $^{186}$rhenium-sulfide, with an effect rate of 53% and 62%, respectively[20,21]. The explanation of this difference could be that one study did miss patient data in 42% (11 out of 26) of treatments[20], and in the other study 31% (8 of 26) did not have RA compared to 9% (5 of 54) in our study[21]. In patients with RA, 78% (14 of 18) of the treated joints did show moderate or good effect[21].

In other reports the duration of the effect of radiosynoviorthesis is scarcely described and data for the ankle are not available. In one study the mean duration of remission in knee joints was 21 months (range 1–95 mo)[17]. In our study the mean duration of effect in ankle joints was 34 months in the group with moderate effect and 40 months in the group with good effect.

Surgical, especially arthroscopic, synovectomy followed by radiation synovectomy 4 to 6 weeks postoperatively should theoretically give a more radical reduction of inflammatory activity, resulting in a higher success rate and a longer disease-free period, although to our knowledge no studies have been performed to confirm this.

Leakage from the treated joint is one drawback of radiation synovectomy and can lead to radiation especially of lymph nodes. No late clinical effects of radiation synovectomy have been described in previous reports, although they have not been studied systematically, probably because such a study would extend over many decades. However, early effects, i.e., chromosomal aberrations, after radiosynoviorthesis have been described[32,33]. In our experience little leakage is seen after radiosynoviorthesis of finger joints with $^{169}$erbium or knees with $^{90}$yttrium. In contrast, leakage

*Table 2*. Effect of synovectomy versus radiological classification.

| Effect of Synovectomy | Steinbrocker Radiological Classification 1 or 2 | 3 or 4 | Total |
|---|---|---|---|
| No or minimal | 5 | 7 | 12 |
| Moderate or good | 38 | 4 | 42 |
| Total | 43 | 11 | 54 |

Fisher exact test p = 0.001.

*Table 3*. Leakage (as percentage of injected dose) to lymph nodes, liver, and total leakage (defined as sum of leakage to lymph nodes and liver) in the different effect groups.

| | No Effect, Group 1 | Moderate Effect, Group 2 | Good Effect, Group 3 | For All 54 Treatments |
|---|---|---|---|---|
| Leakage to lymph nodes | | | | |
| Mean (SD) | 2.6 (3.1) | 2.1 (3.2) | 2.4 (2.9) | 2.4 (3.0) |
| Range | 0–9.6 | 0–8.8 | 0–9.5 | 0–9.6 |
| Leakage to liver | | | | |
| Mean (SD) | 1.6 (2.3) | 0.5 (0.2) | 0.9 (1.7) | 0.8 (1.7) |
| Range | 0–5.5 | 0–0.7 | 0–5.5 | 0–5.5 |
| Total leakage | | | | |
| Mean (SD) | 4.2 (2.9) | 2.1 (3.2) | 3.3 (3.2) | 3.2 (3.2) |
| Range | 0–9.6 | 0–8.8 | 0–9.5 | 0–9.6 |

is more often seen in radiosynoviorthesis of other joints with $^{186}$rhenium, despite arthrographic control, and using the least traumatic injection technique and immobilization for 72 hours.

Particle size is an important factor in leakage: bigger particles show fewer tendencies to leakage. The appropriate size is considered to be 2 to 5 µm[34]. In Europe, 3 products are commercially available. The size of colloidal $^{186}$rhenium-sulfide is 50–300 nm, $^{90}$yttrium colloid 200 nm, and $^{169}$erbium 2000–3000 nm (CIS Bio International), or 100 nm for $^{90}$yttrium colloid (Amersham Healthcare, Little Chalfont, Buckinghamshire, UK). Radioactive gold particles of 20 nm size did show leakage to lymph nodes in 30%, whereas particles of 300 nm did not show leakage to lymph nodes[35-38]. In some reports a maximal leakage of 48% to lymph nodes has been described, although the smallest particles were not designed for radiation synovectomy[35]. In some studies other agents (not commercially available) with larger particle sizes than above have been used. Maximal leakage varied from 3% for $^{153}$samarium hydroxyapatite, with particle sizes 16–22 µm, to 9% for $^{165}$dysprosium hydroxide macroaggregate, with particle sizes 2–5 µm[39,40]. In another study with $^{166}$holmiun polymeric microspheres (particle sizes 2–13 µm), minimal retention in the joint was 95% of the injected dose, i.e., leakage to non-target organs was less than 5%[41].

Dosimetry, using theoretical models, gives a fairly good impression of the radiation dose and risk. Using the equivalent body dose ($E_{body}$), it is possible to determine the risk of death or the loss of years because of the use of radiation. The risk of dying from radiation is currently set to $10^{-2}$/Sv, which means the risk of dying is 1% when receiving an equivalent body dose of 1 Sv. For radiosynoviorthesis of the ankle the equivalent body dose is around 0.15 mSv, leading to risk of $1.5 \times 10^{-6}$ of death through radiation. As the averaged loss of years is 13 years for each case of death, an equivalent body dose of 0.15 mSv results in 0.002 years (= 0.7 day) loss of life, which can be ignored. The same conclusion can be drawn comparing the risk of radiosynoviorthesis of the ankle with the normal risks of life and of a CT examination of the chest and a radiograph of the ankle (Table 4).

*Table 4.* Risk of radiosynoviorthesis compared to other activities.

| | Risk (death per 10,000 per year) |
|---|---|
| Smoking 10 cigarettes per day | 18 |
| Traffic | 2.3 |
| Housework | 1.6 |
| CT chest examination | 0.5 |
| Radiosynoviorthesis of ankle joint | 0.02 |
| Radiograph of ankle | 0.0001 |

Retrospective studies have several limitations, in particular, how are criteria on which improvement is made derived? It is preferable to assess outcome measurements on validated criteria such as proposed by the American College of Rheumatology. Such outcome assessment is not necessarily available in retrospective studies and is a major limitation. Clinical judgment of the treating physician is subject to bias. Therefore in our study complementary to this we used the more objective criteria "need of an intraarticular glucocorticoid injection within 3 months" and "arthrodesis within 6 months" for no effect, and "time to next intra-articular corticosteroid injection" as duration of effect.

Despite the limitations of our study we suggest radiation synovectomy of the ankle is safe and effective but temporary treatment in persistent synovitis refractory to DMARD and intraarticular glucocorticoid injection.

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