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## Clinical outcome of radiosynovectomy in haemophilia a patients with chronic knee synovitis

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### Abstract

**Aim:** There are various medical and surgical modalities available at breaking the vicious cycle of synovitis-hemarthrosis-synovitis at an early stage of synovitis in patients of haemophilia. Our study was planned to assess the short term clinical outcome in chronic knee synovitis among haemophilia A patients treated with phosphorus-32 (P-32) radiosynovectomy.

**Methods:** Fifteen haemophilia A patients with chronic knee synovitis were injected with P-32 Samarium radiocolloid into the knees. These patients were clinically assessed at time of injection, at one and at three months post procedure. The parameters evaluated are the Tegner Lysholm Score (TLS), Modified Knee Society Clinical Rating System score (MKSS) and by measuring the circumference of the knee joint pre and post injection.

**Results:** Among the fifteen haemophilia A patients studied, there was statistically significant difference in all three parameters recorded with TLS having  $\chi^2 (2) = 27.887$  and p value  $<0.001$ , MKSS scores having  $\chi^2 (2) = 27.745$  and p  $<0.001$ , and circumference of the knee joint showing  $\chi^2 (2) = 21.333$  and p  $<0.001$  at the end of one and three months follow up.

**Conclusion:** P-32 radiosynovectomy done for chronic knee synovitis among haemophilia A patients showed significant improvement in clinical parameters. Hence we suggest that this simple procedure may be added to the armamentarium of current options available for these patients.

**Keywords:** haemophilia a, chronic knee synovitis, phosphorus-32 samarium, radiosynovectomy

### Introduction

Chronic synovitis is common clinical condition treated by orthopaedic surgeons. Synovitis is associated with a number of diseases that involve joints, bones, muscles and tendons. Various diseases can cause chronic synovitis like rheumatoid arthritis, psoriatic arthritis, hemophilic synovitis, pigmented villonodular synovitis and hypertrophic pulmonary osteoarthropathy affecting various joints. Many medical and surgical modalities are available for the treatment of chronic synovitis of different etiologies. However, the goal is to slow down the inflammatory process and regress the synovial proliferation.

Haemophilic synovitis predominantly affects men as it an X-linked disease. Haemophilia A patients can experience a wide range of clinical severity according to the serum levels of factor VIII <sup>[1]</sup>. One of the most characteristic features of haemophilia is synovitis. Recurrent bleeding occurs into the joints and the lysed RBCs release hemosiderin which then leads to synovial inflammation. Such synovitis further perpetuates bleeding into the joint thus creating a recurrent cycle of synovitis-hemarthrosis-synovitis <sup>[2]</sup>.

Various modalities of therapy have been focused at breaking this vicious cycle at an early stage of synovitis. Different drugs like rifampacin, tetracycline and steroids have been used intra-articularly to prevent the synovial proliferation <sup>[3]</sup>. These therapies however are associated with an increased risk of relapse and thus have to be given repeatedly. They are also associated with various articular complications <sup>[4]</sup>.

Being minimally invasive, radiosynovectomy regresses the hypertrophic synovium, bleeding episodes and articular pain significantly. Many radioisotope molecules like Y-90, Re-186, Au-189, Er-169 and P-32 have been used for radiosynovectomy. These  $\beta$  emitting radioisotopes generate free radicals resulting in apoptosis and finally ablation of inflamed synovial membrane <sup>[5]</sup>. Moreover these molecules are safe and cause no damage to the articular surface.

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In conditions like haemophilia where factor replacement is expensive, radiosynovectomy helps by reducing the number of re-bleeds and improving not only joint function but also reduces significant economic burden to the patients [6]. With this background, this study was done to assess the short term clinical outcome of chronic knee synovitis among haemophilia A patients post P-32. Radiosynovectomy

### Materials and Methods

A prospective clinical study was done with chronic knee synovitis among haemophilia A patients attending a tertiary care hospital at Pondicherry, India. The study was over a period of 18 months. The study was approved by the Institute Scientific Advisory committee and Institute Ethics Committee for human studies.

The patients having haemophilic synovitis of knee joint of more than three months duration and age more than seven years attending the outpatient department were included in the study. Patients who had local skin infection, patient with prior knee surgery, infectious arthritis of knee joint, advanced knee arthritis of any cause around knee, neuropathic joint were excluded from the study.

Clinical evaluation of knee was done and baseline clinical parameters were noted before doing radiosynovectomy. Clinical Parameters by Tegner Lysholm scoring scale [7] which is a subjective scoring scale. The objective assessment was done using Knee Society Clinical Rating System [8] and the joint circumference measured just above the upper margin of the patella.

Tegner Lysholm scoring scale (TLS) being a patient-based assessment questionnaire designed to assess knee symptoms primarily with ligamentous injuries, patella femoral pain, meniscal tears, and knee osteoarthritis. The maximum score is 100 points.

Modified Knee Society Clinical Rating System (MKSS) is an objective Knee Scoring system that is based on clinical parameters. Scoring points include for pain, stability and range of motion and deduction scores for extension lag, flexion contracture and malalignment after clinical examination of affected knee. The maximum Knee Score is 100 points.

The joint circumference was measured just at the upper margin of patella with knee extension or permissible minimum flexion deformity in centimetre scale with non-expandable measuring tape. All the three clinical parameters were measured at pre-P 32 injection, one month and three month follow-up.

**Factor VIII injection required calculation [9]:** All haemophilia patients underwent factor VIII replacement during the procedure. Routine Prophylaxis of factor VIII was given according to patient weight (kg) and percentage of desired levels pre and post radiosynovectomy is calculated by the following formula.

$$\text{Factor VIII (units)} = \frac{\text{Weight (kg)} \times \text{desired factor level}}{\text{increase} \times 0.5}$$

(Desired factor level increase was taken as: Pre injection as 40% of normal and Post injection (Day1) as 30% of normal) P-32 Samarium radiocolloid was supplied to the institute by Board of Radiation and Technology, Mumbai. The administered activity of P-32 samarium colloid ranged from 10 to 40 MBq depending on the age and knee joint size for therapy. In adults the dose administered is 37MBq and in case

of children's the dose would be 40-50% of the adult dose.

**Technique of radiosynovectomy:** Under all aseptic precautions, patient is made to lie supine with knee gently flexed by an underlying cushion. Cleaning and draping of knee region was done. Patients were injected P-32 Samarium colloid radioisotope to knee joint under local anaesthesia. With the fingers of the left hand the patella is pushed slightly lateral, so that the left thumb can easily palpate the place between the lateral upper border of the patella and the insertion of the rectus femoris tendon. Then slightly posterior to the patella, the needle is inserted. The first drops of the local anaesthetic are injected subcutaneously. Synovial fluid aspirations were done but not complete aspiration, so that sufficient distribution volume is left. If there is lack of effusion, instillation of about 10-30 ml of saline was done, to provide a sufficient distribution of volume. Complete blood aspiration was done before injection, if any. The radioisotope P-32 samarium colloid was administered; then needle is flushed with 1 ml triamcinalone simultaneously by insulin syringe withdrawing the needle from the knee joint. The injected joint were passively flexed and extended five times to distribute the P-32 evenly [10]. The distribution of radiotracer of P-32 colloid in the joint was confirmed under gamma camera next day (post therapy distribution scan). The procedure was done with one day admission basis and patients were sent home next day. The patients were advised to keep the injected joint immobilized for three days with Plaster of Paris slab. Mild local pain was treated using analgesics. Patient was reviewed after three days for wound inspection. Follow up at one and three months for clinical evaluation was done using the same scores.

### Data entry and statistical analysis

Data was entered using Microsoft Excel and analyzed using IBM SPSS Version 20. Continuous variables like age and scores (TLS score, MKSS score, USG) were expressed using median (IQR). Categorical variables like sex and factor levels were expressed using proportions. Friedman test was used to see for significant difference in scores at different time periods and post hoc tests were run using Wilcoxon signed rank test. Statistical significance was set at p value less than 0.05 and 0.017 as cut off for post hoc tests.

### Results

Among the 15 male patients followed up median (IQR) age was 20 (10 to 23) years. The minimum age was 8 years and maximum 30 years. Six (40%) were under the age of 15 years and nine (60%) were above the age of 15 years. Among the 15 patients, four of them had estimated factor levels of 1%, eight of them had factor levels between 1% and 5%, whereas three of them had factor levels of more than 5%.

Friedman test showed that there was a statistically significant difference in TLS score at pre P32 injection, one month and three month follow up with  $\chi^2(2) = 27.887$  and p value  $<0.001$ . There was also statistically significant difference in MKSS Scores at pre P32 injection, one month and three month follow up  $\chi^2(2) = 27.745$ , p  $<0.001$ . Similarly, a statistically significant difference was noted in the circumference of the knee joint at the level of supra patellar region at pre P32 injection, one month and three month follow up with  $\chi^2(2) = 21.333$ , p  $<0.001$ . Post hoc analysis with Wilcoxon signed-rank tests is shown in table 1. Both TLS and MKSS scores and also the circumference of knee joint at the level of suprapatellar region showed that the clinical

improvement is more in the last two months compared to the first month as shown by the difference in the median scores as

shown in table 1.

**Table 1:** Subjective and objective assessment of clinical improvement in chronic knee synovitis among Hemophilia A patients post P-32 radiosynoviorthesis (N=15)

Parameter	Time period	Median (IQR)	p value*
Tegner Lysholm Score	Pre-operative	23 (19 to 27)	0.011*
	One month	27 (23 to 35)	
	One month	27 (23 to 35)	0.001*
	Three month	36 (29 to 41)	
	Pre-operative	23 (19 to 27)	0.001*
	Three month	36 (29 to 41)	
Modified Clinical Knee Society Scoring System Scores	Pre-operative	53 (37 to 57)	0.001
	One month	59 (44 to 70)	
	One month	59 (44 to 70)	0.003
	Three month	74 (49 to 79)	
	Pre-operative	53 (37 to 57)	0.001
	Three month	74 (49 to 79)	
Circumference of the knee joint at the level of supra patellar region	Pre-operative	36 (27 to 39)	0.003
	One month	35.5 (26.5 to 37)	
	One month	35.5 (26.5 to 37)	0.018
	Three month	34 (29 to 36)	
	Pre-operative	36 (27 to 39)	0.004
	Three month	34 (29 to 36)	

\*Wilcoxon Signed Rank test

## Discussion

Radiosynovectomy a novel method of treatment used for chronic synovitis in Haemophilic patients. It causes radio synovial ablation and halts progression of synovitis. Among all the radioisotopes we have evaluated P-32 radioisotope in hemophilic synovitis and various inflammatory chronic synovitis as various literature outside India has shown successful outcomes in chronic synovitis and also easy availability of this radioisotope in our Institution.

The present study was designed to evaluate the early clinical outcomes of radiosynovectomy in hemophilic synovitis. We choose P32 radionuclide for the study. P-32 being a pure beta emitter with half-life of 14 days, 3-5 mm penetration and particle size between 6-20 microns is currently the agent of choice in United States of America and Canada<sup>[11]</sup>.

Among the patients studied, all of them were followed up for three months after P-32 radiosynovectomy. All showed clinical improvement in both TLS (subjective sore) and MKSS (objective sore) and circumference of knee joint at the suprapatellar region measurements. Among the various studies conducted, the clinical improvement was shown to be in the range between 60% to 80% across various joints in nine studies published between 1982-1991 by Deutsch *et al.*<sup>[12]</sup>. The follow up time in different studies ranged between one month to five years.

The difference in the rates of clinical improvement across studies can be attributed to various factors. Firstly, clinical outcomes were measured using different scoring systems. Secondly, we have assessed short term outcomes (i.e., at one and three months) compared to other studies which have assessed outcomes after a longer period of time. Thirdly, our study population had all patients who were aged less than thirty years compared to different age groups across other studies. Fourthly, the current study evaluated on only knee joint unlike others who had studied different joints and use of different radio isotopes in the study. As ours was a time bound study we could not had long follow up and more cases.

**Clinical scores by subjective assessment done by Tegner Lysholm score consisted of total 35 points which includes**

## the following

- Pain scores which was marked after walking for less than 2 km in 12/15 patients but among them 3/12 had marked increase in walking distance of more than 2 km post radiosynovectomy suggesting decreased pain and swelling markedly reduced after severe exertion in 5/11 patients thus patients had improved ambulation.
- Limp was present in 10/15 patients in the study group of which 5/10 patients had complete remission of limp after 3 months because of remission of synovitis, pain and isometric quadriceps strengthening exercises.
- Swelling on ordinary exertion was present in 11/15 patients which improved in 3 months in 5/11 patients where as 4/15 had on severe exertion. Patients after P32 injection the number of spontaneous onset bleeds reduced markedly but post traumatic injury bleeds had no effect.
- Stair climbing was not possible in 2/15 patients and 6/15 had impaired stair climbing or was climbing with one step at a time and after P32 injection 2/6 patients of impaired stair climbing became normal at end of 3 months.
- No patient had Instability and locking in patients during the study period as recurrent hemarthrosis causes immobilisation due to pain and progressive periarticular soft tissue fibrosis and capsular contracture.
- Walking with support was for 2/15 patients among them one patient had associated secondary hip arthritis of haemophilic arthropathy and other patient with 30° fixed flexion deformity of knee (factor level <1%)
- Squatting 10/15 patients were not able to squat which improved in 4/10 patients after p32 injection at the end of 3 months.

**Objective assessment by Modified Clinical Knee Society Scoring System Scores consisted of total 100 points which includes scoring points as below:**

- Pain 12/15 had moderate pain of them 9/12 converted to mild pain and 3/12 had no pain at end of 3 months and 3/15 had mild pain and all 3 patients had no pain at end of three months.
- ROM improved in 5/15 patients because of decreases pain,

- physiotherapy and was stable in 10/15 of patients.
- c) Stability: no patient had mediolateral or anteroposterior instability at knee joint.
  - d) Extension lag 1/15 patient had extensor lag of terminal 20° which persisted after P32 injection.
  - e) Flexion Contracture 4/15 patients had flexion contracture of 20° and 1 patient had flexion contracture of 30°. P32 injection had no effect in correction of fixed flexion deformity knee.
  - f) Pain at rest, none of patient had pain on non weightbearing at rest.
  - g) None of the patient had gross malalignment of knee.

Circumference of the knee joint measured at supra patellar region in hemophilia A patients for serial assessment of synovial thickness shows significant response being delayed for about one month indicating delayed response secondary to P32 injection secondary to time elapsed in synovial destruction underlying submucosal fibrosis and decreased synovial effusion.

We had no short term clinical complications in any patients during the study. Immediate complications such as drug extravasations, superficial skin necrosis have been noted in other studies, hence intra-articular confirmation of needle before radioisotope P32 injection is absolutely mandatory. Infection in joints is very rare (one in 35000) because intense beta radiation by radioisotope kills the bacteria. Thrombosis and lymph edema may occur<sup>[13]</sup>.

The study has few strengths. Firstly, this is the first prospective clinical study in India, which evaluated short term beneficial effect of P-32 radio synovectomy. secondly, both objective and subjective scoring system was done to assess the clinical outcome in the patients. As only one investigator assessed the clinical outcomes in both subjective and objective component in all the patients there was no chance of inter-observer variability.

The study also has few limitations. We could not capture the factor VIII usage levels before and after radio synovectomy, which could have been used as a marker for clinical improvement. As this study was planned to assess short term outcomes we were not able to assess the long term outcomes of P-32 radio synovectomy.

The study also establishes a need for a standard protocol for P-32 radiosynovectomy has to be formulated in the future.

### Conclusion

P-32 radiosynovectomy done for chronic synovitis among hemophilia A patients showed significant improvement in clinical parameters. The improvement was more so in the last two months compared to the first month follow-up after treatment.

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### Declaration of conflicting interests

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