Original Article

Yttrium-90 Synovectomy in Hemophilic Arthropathy: An Institutional Experience for 15 Years

Abstract

Objective: The objective of this study is to assess the efficacy of Yttrium-90 (Y-90) radiation synovectomy in decreasing the recurrent bleeding episodes in hemophilic joints. **Subjects and Methods:** A retrospective analysis of patients who had Y-90 synovectomy from January 2001 to January 2016 was done. Among them, patients with minimum follow-up of 6 months were selected. The response in terms of decrease in the number of bleeding episodes was evaluated. **Results:** A total of 167 patients (243 joints) with hemophilia had radiation synovectomy over 15 years. Those with a minimum follow-up of 6 months were 155 joints (115 patients). The age ranged from 5 to 43 years and included 113 male and two female patients. Data for 11 joints were unavailable as these patients were lost to follow-up. The assessment of response for the remaining 144 joints was done based on the data available for different follow-up periods. They were divided into the following – 7 months to 2 years (89 joints), 3–5 years (6 joints), 6–10 years (39 joints), and above 11 years (10 joints). Overall, 37.4% of the joints had complete response, 56% had partial response, and 6% of the joints had no response. **Conclusion:** Radiation synovectomy is a noninvasive and effective modality which decreases the bleeding episodes in hemophiliac joints and improves the quality of life remarkably.

Keywords: *Bleeding episodes, hemophilic joints, yttrium synovectomy*

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Introduction

Background

Hemophilia A and Hemophilia B are common X-linked inherited coagulation factor deficiencies of factor VIII and factor IX, respectively. These cause life-long bleeding disorders. Hemophilia A affects 1 in 5000 male births and four times more common than Hemophilia B.[1] According to the World Hemophilia Foundation, it is estimated that 43% of the world's Hemophilia population lives in Asian countries of China, Bangladesh, India, and Indonesia, of which only 12% have been diagnosed.[2]

Factor VIII or factor IX concentrations may be expressed as percentages of normal pooled plasma (defined as 100%), with normal levels ranging between 50% and 150%. They are classified into three groups based on their severity: severe, moderate, and mild. Those with severe hemophilia have no measurable factor VIII or factor IX (<1%) and may bleed spontaneously without preceding trauma. In patients with moderate hemophilia, the plasma factor VIII or factor IX concentration is 2%–5%, and in mild hemophilia, it is 6%–40%. Excessive bleeding usually occurs after trivial trauma, surgical, or dental procedures.[3]

Even though the availability of factor replacement products has significantly improved health care, effective and optimal management remains a challenge. This is primarily because of the variable pattern and severity of bleeding. It is imperative to reduce the complications of hemophilia at an early stage. Integrated care should be initiated as soon as hemophilia is diagnosed.[4]

Hemophilic arthropathy

The pathogenesis of hemophilic arthropathy can be attributed to multiple factors. Multiple bleeds intraarticularly lead to influx of inflammatory cells, toxins, and oxygen metabolites that destroy the hypertrophied synovium. In due course of time, it results in a fibrotic and destroyed joint.[5] It is characterized by chronic pain, joint stiffness, and a severely limited

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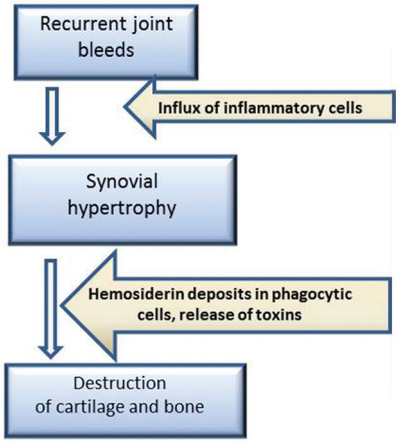


Figure 1: Pathophysiology of hemophilic arthropathy

range of motion, thus diminishing the quality of life significantly[6] [Figure 1].

Management of hemophilic arthropathy

Optimal treatment requires a multidisciplinary team which includes a hematologist, orthopedician, nuclear medicine physicians, rehabilitation physician, occupational and physiotherapist, and nurses. Effective prevention and management of hemophilic arthropathy include the use of timely factor replacement therapies, as well as elective procedures, including restorative physical therapy, analgesia, aspiration, synovectomy and orthopedic surgery.[7] The primary prophylaxis, which is also the first-line treatment, is the regular infusion of concentrates started before the age of 2 years and/or after the first joint bleed. Secondary prophylaxis, however, aims to delay the progression of hemophilic arthropathy thus improving the quality of life.[8]

Radionuclide synovectomy

The indication for a synoviorthesis or synovectomy is chronic synovitis causing recurrent bleeds, which are refractory to hematological treatment. It involves the intraarticular injection of a certain material to cause fibrosis of the synovial hypertrophy, thus decreasing the intensity and frequency of hemarthroses. There are two basic types, namely chemical and radiation synoviorthesis. On an average, the efficacy of the procedure ranges from 76% to 80% and can be performed at any age.[9] It is a safe, potent and cost-effective method.[9]

Mechanism of action

The most commonly used are colloidal solutions of Yttrium-90 (Y-90), Rhenium-186 and Erbium-169. They differ in the range, radiation energy, and tissue penetration.[10]

Y-90 has an energy of 2.26 MeV, a half-life of 2.7 days with maximum and mean tissue penetration of 11 mm and 3.6 mm, respectively. It is mostly used for injection into larger joints such as shoulders, hips, wrists, knees, and ankle joints.

The range of diameter of the injected colloid of Y-90 is between 2 and 5 μm. This size is optimal because it is small enough to be phagocytized and does not enter the bloodstream through capillary fenestrations.[11] Following the intraarticular injection, it is captured in the synovial membrane after phagocytosis by synovial macrophages. By the production of reactive oxygen species, the β-radiation of the radionuclides causes cell apoptosis.[10] This subsequently leads to necrosis and fibrosis of the hypertrophied synovial membrane, thereby decreasing the inflammatory responses and bleeding episodes. The range of the β-radiation for Y-90 is around 10 mm. This ensures that most of the radiation is absorbed by the synovium and superficial layers of cartilage, sparing the subchondral bone.[9]

Procedure

The triphase bone scintigraphy was not done before radiation synovectomy for all the patients. The application of local anesthetic under aseptic precautions is done. Following aspiration of the joint effusion, careful intraarticular injection of the Y-90 colloid is administered. The large joints receive a dose of 5 mCi and small joints are treated with 3 mCi. After the procedure, the treated joint must be immobilized for 48–72 h to reduce the risk of leakage to paraarticular tissues. Although bremsstrahlung imaging can be employed to confirm the intraarticular distribution of radiopharmaceutical up to 24 h after injection, it was not done for all patients in our study.

Efficacy

A significant decrease in the frequency of the bleeding episodes was noted in various studies following Y-90 synovectomy.[12] However, the response rates were not studied in our population. Hence, this study was carried out to assess the therapeutic efficacy of Y-90 synovectomy in hemophilic joints in our institution for a study period of 15 years.

Subjects and Methods

All patients with hemophilic arthropathy from January 2001 to January 2016 were retrospectively analyzed. Those referred to the nuclear medicine department for yttrium synovectomy with a minimum follow-up period of 6 months were included in the study. They were followed up in the hematology and physical medicine and rehabilitation outpatient clinic.

A total of 167 patients (243 joints) underwent yttrium synovectomy. Of these, 115 patients (155 joints) had a minimum follow-up of 6 months, of which 140 joints had a single injection and 15 joints had a repeat injection.

Response to the yttrium synovectomy was ascertained based on the decrease in the frequency of bleeding

episodes and symptomatic improvement. The bleeding episodes ranged from 6 to 4 episodes in a month. "Partial" response was defined as a reduction in the frequency to <3 episodes/month. It was termed as "Complete" when there were no further bleeding episodes and "Nil" when there was no improvement.

Results

Of the total 243 joints (167 patients) received the Y-90 synovectomy, those with a minimum follow-up of 6 months were 155 joints (115 patients). There were 113 male and two female patients. The age distribution was as follows – 74 patients were below the 20 years, 38 in the age group of 20–40 years, and three patients were above 40 years. Among the 155 joints that were injected, 6 were shoulder joints, 45 were elbow joints, 1 hip joint, 91 knee joints and 12 ankle joints, 140 joints had a single injection, and 15 joints had a repeat injection [Tables 1 and 2].

Of the 155 joints with follow-up for 6 months, data for 11 joints were unavailable as they were lost to follow-up. The assessment of response for the remaining 144 joints was done based on the data available for different follow-up periods. They were divided into the following – 7 months–2 years (89 joints), 3–5 years (6 joints), 6–10 years (39 joints), and above 11 years (10 joints) [Flow chart 1].

It was found that at the 6-month follow-up period – of the 155 joints, 61 (39.3%) had complete response, 87 (56.5%) had partial response, and 7 (5%) had no response. Eighty-nine joints had follow-up ranging from 7 months to 2 years. Of these, 33 (37%) had complete response, 51 (57.3%) had partial response, and 5 (5.6%) had no response. There were six joints with data available for the follow-up period of 3–5 years, of which there were two joints each in the complete, partial, and nil response groups. Thirty-nine joints had follow-up ranging from 6 to 10 years. Of these, 12 (30.8%) had complete response, 22 (56.4%) had partial response, and 5 (12.8%) had no response. Only ten joints had follow-up data beyond 11 years. Of these, four joints had complete response and six had partial response [Table 3]. Overall, 37.4% of the joints had complete response, 56.6% had partial response, and 6% of the joints had no response.

Discussion

The treatment of synovial hypertrophy using radionuclides such as Y-90 is an effective and safe procedure. Several studies in the past that have studied the efficacy of radionuclide synovectomy have produced similar results.

In our study, we found that overall 94% had either partial or complete response to the treatment. In some cases, the therapeutic efficacy was found to last up to 10 years and beyond. The quality of life was also improved to a great extent.

Table 1: Age and Gender distribution

Age (years)	Male	Female
<20	74	-
20-40	36	2
>40	3	-
Total	113	2

Table 2: Joints injected

Joint injected	*n*=155 joints
Shoulder	6
Elbow	45
Hip	1
Knee	91
Ankle	12

Heim *et al*. had studied the same in 115 patients with recurrent hemarthroses.[13] The median age at the time of the initial injection of Y-90 ranged between 11 and 15 years, with a median follow-up period of 11 years. More than 80% of the patients reported a reduction in the number of hemarthroses, and 15% had no further bleeding episodes. The efficacy of this therapy was documented in all age groups.

A study done in Spain by De la Corte-Rodriguez *et al*. in 104 joints highlighted that following yttrium synovectomy, the improvement was markedly noted as decrease in the amount of bleeding (70%) and in the level of pain experienced.[14] Synovial hypertrophy as assessed clinically and by imaging techniques also showed a reduction of 30% and 39%, respectively. Muscle strength also improved in flexion and extension by 7.9% and 8.2%, respectively.

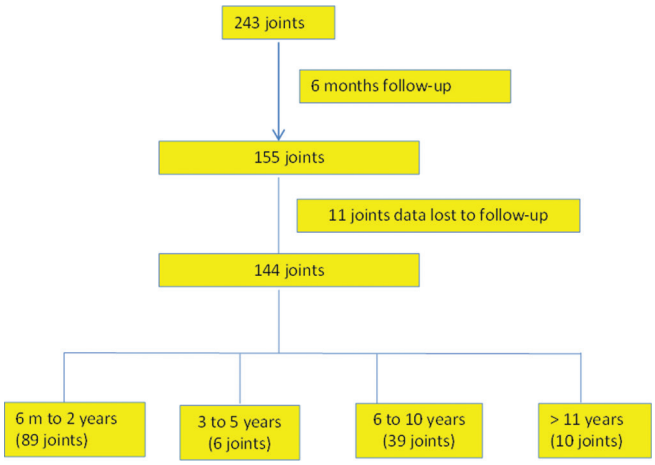
These studies demonstrated that the overall efficacy of yttrium synovectomy is independent of the severity, type of hemophilia and age of the patient. It is not influenced by the presence of a circulating inhibitor, prior hematologic intervention, level of patient activity, and the presence of previous arthropathy. Repeat injections were acquired in knee joints compared to smaller joints and in those with more severe synovitis.[14]

It is also worthy to note that there are no major side effects reported. Alioglu *et al*. in 2010 revealed that there are no major complications requiring secondary treatments after performing yttrium synovectomy in 18 joints.[15] Thomas *et al*. in 2011 reported similar results with no adverse effects in 245 joints with chronic hemophilic synovitis following yttrium injections.[16]

Similar results were reported in a review by Rodriguez-Merchan *et al*. in synovectomies in 443 joints (345 patients) with chronic hemophilic synovitis. On average, the frequency of hemarthroses reduced by 64.1%, pain reduced by 69.4%, the degree of synovitis reduced by 31.3%, and the World Federation of Hemophilia score improved by 19% with minimal complications of 0.9%. In

Table 3: Response assessment at follow up

Time of follow up	No of joints	Complete response (%)	Partial response (%)	Nil response (%)
Upto 6 months	155	61	87	7
≤2 yrs	89	33	51	5
3-5 yrs	6	2	2	2
6-10 yrs	39	12	22	5
>11 yrs	10	4	6	0



Flow Chart 1: Timeline of follow up of patients

6.3% of the joints, total knee replacement or arthroscopic synovectomy was ultimately required on follow-up.[17]

In our institutional study which included patients who received the synovectomy over 15 years, we found a significant reduction in the frequency of bleeding episodes and in the pain experienced by the patient and reaffirm the results of these previous studies.

Conclusion

Yttrium synovectomy is a safe and easy procedure that is performed on an outpatient basis. The simple, cost-effective procedure with minimal side effects can significantly reduce the morbidity and chronic debilitation of relatively young patients. This remarkably improves the quality of life for a long period of time.

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Conflicts of interest

There are no conflicts of interest.

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