Therapy Response of the Yttrium-90 (Y-90) Colloid and Rhenium-186 (Re-186) Sulphur Colloid Radiosynovectomy in Hemophilic Arthropathy

Kamalia Kamarulzaman¹,², Lee Boon Nang¹, Ibrahim L. Shuaib², Faraizah Abdul Karim³, Wan Mohd Nazlee Wan Zainon⁴, and Norazlina Mat Nawi⁵

Abstract

Introduction: Radiosynovectomy (also known as radiosynoviorthesis) is a local form of radiotherapy that is used in chronic hemophilic synovitis in the absence of radiological evidence of extensive joint damage and in patients that have failed conservative therapy with clotting factor replacement and physiotherapy.

Objectives: To evaluate the effectiveness of the Yttrium-90 (Y-90) colloid and Rhenium-186 (Re-186) sulphur colloid radiosynovectomy in hemophilic arthropathy in terms of bleeding frequency, pain score, range of motion and performance score.

Methodology: This was a prospective cohort trial. A total of 68 hemophilic arthropathy patients who had been treated with radiosynovectomy for knee, ankle, elbow and hip joint were included in this study. Patients were followed up to assess their bleeding frequency, pain score, range of motion of the affected joint and Karnofsky or Lansky performance scale at pre and 6 months post therapy.

Result: A marked decrease (80–100%) in bleeding frequency was seen in 66.2% of patients, 14.7% of patients had moderate decrease (51–79%) and mild decrease (30–50%) was seen in 14.7% of patients. The frequency of intraarticular bleeding and pain score were significantly reduced at 6 months follow up (p<0.005). The Karnofsky and Lansky performance scales were also improved at 6 months follow up (p<0.005). There was no significant difference between percentage of range of motion measured before and after the therapy (p>0.005).

Conclusion: Radiosynovectomy is a safe and effective procedure in limiting bleeding frequency, reducing pain and increasing performance scale.

Keywords
bleeding frequency, range of motion, radiosynovectomy, rhenium-186, yttrium-90

Introduction

Hemophilia is a rare inherited bleeding disorder characterized by the absence of one of the coagulation factors which is factor VIII in hemophilia A and factor IX in hemophilia B. The average prevalence of hemophilia in the world is approximately 1 per 10,000 of the population. Stonebrake, J.S et al. reported that in Malaysia, in 2006, the prevalence (per 100,000 males) of patients with hemophilia A was 6.6. The type of inheritance is sex linked (chromosome X) and recessive. The occurrence of Hemophilia A is five times more common than Hemophilia B with the incidence of Hemophilia A is 1 in 5000 live male births.

¹Department of Nuclear Medicine, Hospital Kuala Lumpur, Malaysia
²Advanced Medical & Dental Institute, Universiti Sains Malaysia, Penang, Malaysia
³National Blood Centre, Kuala Lumpur, Malaysia
⁴Hospital Universiti Sains Malaysia, Universiti Sains Malaysia, Kota Bharu Kelantan, Malaysia
⁵Department of Nuclear Medicine, Oncology and Radiotherapy, School of Medical Sciences, Universiti Sains Malaysia, Kota Bharu, Malaysia

Corresponding Author:
Norazlina Mat Nawi, Department of Nuclear Medicine, Oncology and Radiotherapy, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian 16150, Malaysia.
Email: norazlina@usm.my
and 1 in 25,000 live male births in Hemophilia B (National Hemophilia Federation, 2006).

The clinical presentation of Hemophilia A and B is similar depending on their amount of factor VIII and IX in the blood. The patient is graded according to the percentage of coagulation factor in their blood: severe (<1% of the normal amount of factor), moderate (1–5% of the normal amount of factor) and mild (>5% of the normal amount of factor). Generally, the less the percentage of coagulation factor is, the greater the risk of hemorrhagic complication.

The major complication of hemophilia is intra-articular bleeding, in which majority of bleeding (80%) occurs in ankles, knees, elbows and shoulders. The remaining 20% of bleeding takes place in central nervous system and other organ system. This explains the great interest of orthopedic surgeon in hemophilia patient. In children, hemarthrosis frequently starts early in life, with a 10-years-study suggesting that children with hemophilia typically experience their first joint bleed before the age of 2 years. In this group, evidence shows that musculoskeletal dysfunction and associated pain may affect their quality of life, performance and normal activities of daily living, for example avoidance of sports participation.

The aim of this study is to determine the effectiveness of radiosynovectomy in bleeding frequency, pain score, range of motion and performance scale in hemophilic arthropathy and also to compare the bleeding frequency, pain score, range of motion and performance scale of different types of joint in hemophilic arthropathy.

**Methodology**

This was a prospective cohort study. Study period was 6 months which is from the time of radiosynovectomy to the time of 6 months post therapy assessment. Location of research was at Nuclear Medicine Department, Hospital Kuala Lumpur. Inclusion criteria include:

i) Patient with Hemophilia A or B with more than 1 bleed per month in target joint. Patient could be from either group since there is no difference in their clinical presentation. Target joint is defined as 3 or more spontaneous bleeds into the same joint in a 6 month time period.

ii) Chronic synovitis (patient had painless swelling of the target joint)

**Definition of Variables**

i) Bleeding frequency was evaluated by comparing the bleeding frequency of target joint before and 6 months after the procedure. The changes in the incidence of hemarthrosis of the treated joint were classified as follows: marked improvement—where the decrease of 80%–100% was seen in the number of hemarthrosis; moderate improvement—a 51%–79% decrease in the number of hemarthrosis; mild improvement—a 30%–50% decrease in the number of bleedings; and, no improvement—less than 30% decrease in the number of hemorrhathrosis. This can be objectively determined by the frequency of coagulation factor being administered per month.

ii) Range of motion (ROM) –measurement done during the physical examination. Normal adult range of motion values were used—ankle dorsiflexion (12 ± 4°), ankle plantar flexion (54 ± 6°), knee flexion (134 ± 9°), knee extension (−1 ± 2°), elbow flexion (141 ± 5°) and elbow extension (0 ± 3°). Normal pediatric range of motion values were used—ankle dorsiflexion (13 ± 5°), ankle plantar flexion (58 ± 6°), knee flexion (144 ± 5°), knee extension (−2 ± 3°), elbow flexion (145 ± 5°), elbow extension (1 ± 4°), hip flexion (123 ± 6) and extension (7 ± 7).

The worsening of range of motion is defined as reduction in range of motion by at least 5%. The improvement of range of motion is defined as an increment by at least 5%.

iii) Pain—any unpleasant sensory or emotional experience associated with actual or potential tissue damage.

Pain finding (0–3)

0= no pain, no analgesia used except with acute hemorrhathrosis

1= mild pain, does not interfere with occupation, daily activities that occasionally require analgesia

2= moderate pain, partial or occasional interference with occupation or activities of daily living

3= severe pain, interferes with occupation or activities of daily living, frequent use of analgesics

For Pediatric cases, Wong-Baker Faces Pain Rating Scale was used Figure 1.

iv) Performance scale: Both Karnofsky Performance Status Scale (KPS) and Lansky Scale were designed to measure the level of patients’ activity and medical care requirements (Table 1). The KPS was designed for recipients aged 16 years and older, and the Lansky Scale was designed for recipients less than 16 years old. Both KPS and Lansky Scale were used as a global indicator of the functional status of patients with chronic disease to assess overall physical status. It can be used as an objective measure although it does not seem to reflect variations in psychological well-being, other than those associated with physical disability.

**Statistical Analysis**

All the collected data was analyzed using IBM SPSS Statistic Version 19. A paired-samples t-test was conducted to compare the mean score of bleeding frequency, pain scale, range of motion and performance scale at pre and 6 months post radiosynovectomy for overall assessment of the joints. A p-value of less than 0.05 was considered significant and confidence interval (CI) was set at 95%. Wilcoxon signed ranked test was used to test the significance of differences between pre and post therapeutic variables.

**Results**

Out of 68 patients with hemophilic arthropathies, 31 patients underwent radiosynovectomy for elbow joint, 15 patients for knee joint, 21 patients for ankle joint and 1 hip joint. Majority of the patients (28 patients) were aged from 5 to 14 years. Among the patients, 38 of them were Malays while 30 of them were non-Malays. The non-Malay consisted of 18 Chinese, 9 Indian and 3 others.

**Distribution of Number of Patient with Improvement in Joint Bleed**

45 patients had marked improvement (80–100% decrease in number of bleedings) within 6 months post therapy. There were 10 patients who had moderate improvement and 10 patients who with mild improvement. 3 patients had no
improvement; 2 with ankle joint, 1 with knee arthropathy. There were 26 patients with complete cessation of bleeding after the therapy. The best therapeutic outcome was found in elbow joint in which 100% reduction was seen in 14 out of 21 patients in 6 months after the treatment. As shown in Table 2, 80.6% of elbow joints, 61.9% of ankle joints and 40% of knee joints had marked improvement after the therapy. The paired T test was conducted to look at mean score of bleeding frequency of the overall joints. It was 17.03 (14.63) within the last 6 months in the pretreatment evaluation. After the treatment, the mean score of bleeding frequency decreased to 2.56 (3.38). The mean score for bleeding frequency between pre and post radiosynovectomy was significantly different (p < 0.001, 95% CI 10.98, 17.96). Wilcoxon signed rank test proved that, in each type of joint, the difference in bleeding frequency was statistically significant between pre and post treatment.

**The Comparison Between Pre and 6 Months Post Radiosynovectomy Response on Pain**

Table 3 showed a marked improvement in pain score. The patients with no pain before the procedure had increased from 39 to 63 patients after the procedure, this include the improvement of all patients with moderate pain score and 16 patients with mild pain score at pretherapy assessment. As the values in different types of joint were too small, \( p \)-value cannot be derived. Paired T test was conducted to compare the mean difference of overall pain score before and after the intervention. There was a significant difference in the score for pre therapy 0.54 (0.70) and post therapy 0.07 (0.26) (\( p < 0.001, 95\% CI 0.29, 0.65 \)). The pain score reduced from 0.54 (0.70) to 0.07 (0.26). The difference was also statistically significant in each type of joint between pre and post therapy assessment.

**The Comparison Between Pre and 6 Months Post Radiosynovectomy Response on Range of Motion**

Based on Table 4, 23 patients had improvement in range of motion and 19 patients had similar range of motion at 6 months post therapy. However, there were 22 patients with worsening of the range of motion seen at 6 months interval. The remaining 4 patients that were not included in the category had similar 100% range of motion before and after 6 months post procedure. The overall mean score for range of motion between pre and post radiosynovectomy was not
significantly different (p = 0.39, 95% CI = 2.96, 7.52). The mean score for range of motion reduced from 79.34 (16.18) to 77.06 (19.41). The Wilcoxon signed rank test showed that the difference in percentage range of motion was not statistically significant in each different type of joints.

The Comparison Between Pre and 6 Months Post Radiosynovectomy Response on Karnofsky/Lansky Performance Scale

Karnofsky Performance Scale (16 Years and Above). Table 5 showed that the percentage of patients with score of 80–100 had increased from 69.4% to 97.2% in 6 months post therapy and the percentage of patients with score of 50–70 before radiosynovectomy had decreased from 30.6% to 2.8% after the therapy. The mean score of Karnofsky performance scale between pre and post radiosynovectomy was significantly different (p < 0.001, 95% CI = −11.41, −5.25). The Karnofsky performance score had increased from 76.94 (8.89) before the procedure to 85.28 (5.59) at 6 months post therapy.

Lansky Performance Scale (Less than 16 Years Old). Table 6 showed marked improvement in the performance score. 16 patients that were presented with mild to moderate restriction (score between 50 and 70) prior to treatment had improved their condition to being able to carry on normal activity (score between 80 and 100) at 6 months post therapy. Patients with the score of 80–100 had increased from 40.6% to 90.6% at 6 months post therapy and the patients with score of 50–70 had decreased from 59.4% to 9.4%.

The mean score for Lansky performance was 74.69 (6.21) within the last 6 months in the pretreatment evaluation. After the treatment, the mean score for Lansky performance increased to 81.88 (7.80) at the end of the follow up period. The mean score for Lansky performance between pre and post treatment was significantly different (p = 0.39, 95% CI = −2.96, 7.52). The mean score for Karnofsky performance reduced from 79.34 (16.18) to 77.06 (19.41). The Wilcoxon signed rank test showed that the difference in percentage range of motion was not statistically significant in each different type of joints.

The Comparison Between Pre and 6 Months Post Radiosynovectomy Response on Karnofsky/Lansky Performance Scale

Karnofsky Performance Scale (16 Years and Above). Table 5 showed that the percentage of patients with score of 80–100 had increased from 69.4% to 97.2% in 6 months post therapy and the percentage of patients with score of 50–70 before radiosynovectomy had decreased from 30.6% to 2.8% after the therapy. The mean score of Karnofsky performance scale between pre and post radiosynovectomy was significantly different (p < 0.001, 95% CI = −11.41, −5.25). The Karnofsky performance score had increased from 76.94 (8.89) before the procedure to 85.28 (5.59) at 6 months post therapy.

Lansky Performance Scale (Less than 16 Years Old). Table 6 showed marked improvement in the performance score. 16 patients that were presented with mild to moderate restriction (score between 50 and 70) prior to treatment had improved their condition to being able to carry on normal activity (score between 80 and 100) at 6 months post therapy. Patients with the score of 80–100 had increased from 40.6% to 90.6% at 6 months post therapy and the patients with score of 50–70 had decreased from 59.4% to 9.4%.

The mean score for Lansky performance was 74.69 (6.21) within the last 6 months in the pretreatment evaluation. After the treatment, the mean score for Lansky performance increased to 81.88 (7.80) at the end of the follow up period. The mean score for Lansky performance between pre and post treatment was significantly different (p = 0.39, 95% CI = −2.96, 7.52). The mean score for Karnofsky performance reduced from 79.34 (16.18) to 77.06 (19.41). The Wilcoxon signed rank test showed that the difference in percentage range of motion was not statistically significant in each different type of joints.

The Comparison Between Pre and 6 Months Post Radiosynovectomy Response on Karnofsky/Lansky Performance Scale

Karnofsky Performance Scale (16 Years and Above). Table 5 showed that the percentage of patients with score of 80–100 had increased from 69.4% to 97.2% in 6 months post therapy and the percentage of patients with score of 50–70 before radiosynovectomy had decreased from 30.6% to 2.8% after the therapy. The mean score of Karnofsky performance scale between pre and post radiosynovectomy was significantly different (p < 0.001, 95% CI = −11.41, −5.25). The Karnofsky performance score had increased from 76.94 (8.89) before the procedure to 85.28 (5.59) at 6 months post therapy.

Lansky Performance Scale (Less than 16 Years Old). Table 6 showed marked improvement in the performance score. 16 patients that were presented with mild to moderate restriction (score between 50 and 70) prior to treatment had improved their condition to being able to carry on normal activity (score between 80 and 100) at 6 months post therapy. Patients with the score of 80–100 had increased from 40.6% to 90.6% at 6 months post therapy and the patients with score of 50–70 had decreased from 59.4% to 9.4%.

The mean score for Lansky performance was 74.69 (6.21) within the last 6 months in the pretreatment evaluation. After the treatment, the mean score for Lansky performance increased to 81.88 (7.80) at the end of the follow up period. The mean score for Lansky performance between pre and post treatment was significantly different (p = 0.39, 95% CI = −2.96, 7.52). The mean score for Karnofsky performance reduced from 79.34 (16.18) to 77.06 (19.41). The Wilcoxon signed rank test showed that the difference in percentage range of motion was not statistically significant in each different type of joints.

The Comparison Between Pre and 6 Months Post Radiosynovectomy Response on Karnofsky/Lansky Performance Scale

Karnofsky Performance Scale (16 Years and Above). Table 5 showed that the percentage of patients with score of 80–100 had increased from 69.4% to 97.2% in 6 months post therapy and the percentage of patients with score of 50–70 before radiosynovectomy had decreased from 30.6% to 2.8% after the therapy. The mean score of Karnofsky performance scale between pre and post radiosynovectomy was significantly different (p < 0.001, 95% CI = −11.41, −5.25). The Karnofsky performance score had increased from 76.94 (8.89) before the procedure to 85.28 (5.59) at 6 months post therapy.

Lansky Performance Scale (Less than 16 Years Old). Table 6 showed marked improvement in the performance score. 16 patients that were presented with mild to moderate restriction (score between 50 and 70) prior to treatment had improved their condition to being able to carry on normal activity (score between 80 and 100) at 6 months post therapy. Patients with the score of 80–100 had increased from 40.6% to 90.6% at 6 months post therapy and the patients with score of 50–70 had decreased from 59.4% to 9.4%.

The mean score for Lansky performance was 74.69 (6.21) within the last 6 months in the pretreatment evaluation. After the treatment, the mean score for Lansky performance increased to 81.88 (7.80) at the end of the follow up period. The mean score for Lansky performance between pre and post treatment was significantly different (p = 0.39, 95% CI = −2.96, 7.52). The mean score for Karnofsky performance reduced from 79.34 (16.18) to 77.06 (19.41). The Wilcoxon signed rank test showed that the difference in percentage range of motion was not statistically significant in each different type of joints.
Table 6. Therapy Response on Lansky Performance Scale ($n = 32$).

| Variables                  | Pre-score mean (SD) | Post-score mean (SD) | Mean score difference (95% CI) | t-statistic (df) | p-value |
|----------------------------|---------------------|----------------------|--------------------------------|------------------|---------|
| Bleeding frequency         | 17.03 (14.63)       | 2.56 (3.38)          | 14.48 (10.98, 17.96)           | 8.28 (67)        | $<0.001$|
| Pain score                 | 0.54 (0.70)         | 0.07 (0.26)          | 0.47 (0.29, 0.65)              | 5.37 (67)        | $<0.001$|
| Range of motion            | 79.34 (16.18)       | 77.06 (19.41)        | 2.28 (-2.96, 7.52)             | 0.868 (67)       | 0.39    |
| Karnofsky performance score| 76.94 (8.89)        | 85.28 (5.59)         | -8.33 (-11.41, -5.25)          | -5.49 (35)       | $<0.001$|
| Lansky performance score   | 74.69 (6.21)        | 81.88 (7.80)         | -7.19 (-9.82, -4.56)           | -5.58 (31)       | $<0.001$|

Changes of Mean Scores of Different Variables Before and After Intervention of Overall Joints ($n = 68$).

Table 6 showed the overall summary of the changes in mean scores of different variables before and after radiosynovectomy. There was a statistically significant difference in bleeding frequency, pain and performance score at pre and post radiosynovectomy. However, there was no significant statistical difference in range of motion between pre and post radiosynovectomy.

Discussion

Therapy Response on Bleeding Frequency

In this study, 45 patients (66.2%) had marked improvement (80–100% decrease in number of bleedings) at 6 months post therapy, 10 patients (14.7%) had moderate improvement and another 10 patients (14.7%) had mild improvement. This was comparable to the study by curnev et al. who reported a marked decrease in 75% of joints, a moderate decreased in 1% of joints, a mild decrease in 13% of joints and no improvement in 13% of joints. There were 26 patients (38%) who had a complete cessation of bleeding after the therapy. This finding was good as the study by Heim only showed complete cessation of bleeding episodes in 15% of patients, although another study done by Das et al. showed complete cessation in about 60% of patients. There was a statistically significant difference in the mean score of bleeding frequency between pre and 6 months post radiosynovectomy ($p < 0.05$) in which there was an improvement of 85% in bleeding frequency after the radiosynovectomy. This improvement was seen in each different types of joint. The result was underlined by the data from Peter et al. 2005 and Tena et al. who reported good to excellent results for radiosynovectomy in 60–80% of patient with hemarthrosis. Similar result was found in the study by Martinez, who reported a significant decreased in bleeding frequency in 70–80% of patient. Rate of bleeding frequency was the only variable used to determine treatment failure, hence the need of further radiosynovectomy. Patient who had 2 or more bleeding episodes in the 6 months post therapy period was subjected for further radiosynovectomy. The similar procedure is to be followed as described for the first radiosynovectomy. This discrepancy in term of the need to repeat radiosynovectomy is due to the fact that, in developed country, most of the patients are readily on prophylactic coagulation therapy. On the contrary, many hemophilic athropathy patients in Malaysia are on on-demand coagulation treatment. In this study, 16 (23.5%) patients were resubjected for further radiosynovectomy at 6 months post therapy. There were 19.3% of patients from elbow group (3 of them from the aged of 5–14 years), 33.3% of patients from knee group (3 of them from the aged of 25–44 years) and 23.8% of patients from ankle group (3 of them from the aged of 15–24 years old). This result was comparable with the study done by Hortensia et al. 2013 which found that 19% of the hemophilic patient needed further radiosynovectomy at 6 months interval Hortensia et al. 2013. Study done by Van Vulpen et al. showed patients who have undergone radiosynovectomy for knee joints require repeated treatment in case of severely thickened synovium. The risk of failure after the first therapy was attributed to persistent chronic synovitis where it cannot be adequately ablated by a pure beta emitting radiocolloid. It is due to short penetration of this radiocolloid, between 2.2 and 2.8 mm in the thickened synovium in the later course of the disease. In the case of thick synovium, it may be necessary to perform several consecutive procedures. In addition to that, children and young adult were at risk of treatment failure due to their active lifestyle. Based on this study, knee joint contributed to the highest number of repeated procedure (33%). This could be due to the fact that, being the most active hinges joint, it is more susceptible to being over stretched compared to others.
Therapy Response on Pain Score

Paired T test showed the mean of pain score reduced from 0.54 (0.70) to 0.07 (0.26), which was statistically significant \( p < 0.05 \), with the percentage of improvement was 87% as compared to pre therapy score. It was also significantly reduced in all types of joints. This finding was better than that seen in a study done by H. De La Corte Rodriguez et al., as their study showed improvement of only 72%.\(^\text{15}\) 42.7% of patients had pain before the injection as compared to 7.4% 6 months into the treatment (35.3% improvement) which corresponds to the study done by Ozkan et al. which showed reduction of pain at 6 months post therapy.\(^\text{16}\) Based on this finding, radiosynovectomy was found to be an effective treatment in reducing the pain score in patient with hemophilic arthropathy. Pain in patients with chronic hemophilic arthropathy could be due to arthritic pain or acute pain of hemorrhosis in a target joint.

Therapy Response on Range of Motion

Study showed that 35.93%\(^\text{23}\) of the patients had improvement in range of motion, 29.68% (19 patients) with similar range of motion and 34.37% (22 patients) with worsening of the range of motion at 6 months post therapy. Cuneyt et al. found a similar finding in which there were 31% of patients had improved range of motion, 41% had unchanged range of motion and 28% had worsening range of motion after treatment.\(^\text{17}\) Another study done by Cuneyt et al., also found that there was no significant difference between percent joint ranges of motion as compared from normal measured before and after therapy.\(^\text{3}\) The limitation of range of motion in hemophilia patients is due to chronic bleeding into the joint that produce inflammatory response that progress over the time to produce overt hemophilic arthropathy. In severe type of hemophilia, the joint limitation is also positively associated with recent orthopedic procedure, patient with inhibitors and the frequency of bleed.\(^\text{4}\) Nuss et al. reported that based on MRI finding, the severity of synovial hyperplasia was unchanged 6 months after the procedure despite the improvement in bleeding frequency. This was due to the finding that the synovium become fibrotic and inactive rather regressing after radiosynovectomy.\(^\text{18}\)

Therapy Response on Karnofsky/Lansky Performance Scale

All patients recruited in this study had at least moderate performance score, with the lowest score for patient below aged 16 years was 70 (Lansky performance score) and for patient aged 16 and above (Karnofsky performance score) was 60. None of the patient was in severe performance score prior to the procedure. Only slight improvement was seen in performance scale in 6 months post therapy since none of them were functionally or physically affected by the disease at pre therapy state. This improvement was seen post procedure and it can be attributed to the reduce number of bleed and pain score after the therapy. No study reported an increased risk of cancer after radiosynovectomy.\(^\text{19}\) The effective dose to the whole body with Erbium-169 citrate colloid and Rhenium-186 sulphur colloid was estimated to be 30 times lower than in iodine-131 therapy of benign thyroid disease.\(^\text{20}\) If three consecutive radiosynovectomies given at 6 months interval fails, a surgical synovectomy is indicated as it is often more effective.\(^\text{15}\)

Conclusion

Radiosynovectomy should be considered as an initial procedure of choice for the treatment of patients with hemophilic arthropathy as it is simple, effective, safe and low-cost technique that can be performed in children and adult.

Acknowledgements

The authors would like to thank all the staffs from the Department of Nuclear Medicine Hospital Kuala Lumpur their cooperation and help

Author contributions

All authors managed the patient, and prepared the manuscript, edited, and approved the final draft.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

The study was approved by Human Research Ethics Committee USM (HREC), Universiti Sains Malaysia (JEPEM Code: USM/JEPEM/00,004,494) and National Medical Research Registration (NMRR-11–976-10,568).

Informed Consent

The patients were informed that their data would be submitted for publication and gave their written consent.

Trial Registration

(where applicable):

Availability of data

Data sharing does not apply to this article, as no data sets were generated or analysed.

ORCID iD

Norazlina Mat Nawi  https://orcid.org/0000-0002-0476-1398

References

1. Rodriguez-Merchan EC. Musculoskeletal complications of hemophilia. HSS J 2010; 6(1): 37–42.
2. Stonebraker JS, Bolton-Maggs PHB, Michael Soucie J, et al. A study of variations in the reported haemophilia B prevalence around the world. Haemophilia 2012; 18(3): 1–4.
3. Türkmen C, Zülfikar B, Taşer Ö, et al. Radiosynovectomy in hemophilic synovitis: correlation of therapeutic response and blood-pool changes. Cancer Biother Radiopharm 2005; 20(3): 363–370.
4. Soucie JM, Cianfrini C, Janco RL, et al. Joint range-of-motion limitations among young males with hemophilia: prevalence and risk factors. Blood 2004; 103: 2467–2473.

5. Gouw SC, Timmer MA, Srivastava A, et al. Measurement of joint health in persons with haemophilia: a systematic review of the measurement properties of haemophilia-specific instruments. Haemophilia 2019; 25(1): c1–10.

6. Drendel AL, Kelly BT and Ali S. Pain assessment for children: overcoming challenges and optimizing care. Pediatr Emerg Care 2011; 27(8): 773–781.

7. Christianson D and Rizzo D. Provision of Karnofsky performance score (KPS) versus ECOG performance score (ECOG PS) to CIBMTR. Forms Man Append L- Karnofsky/Lansky Perform Status 2009; 1: 1–5.

8. Heim M, Goshen E, Amit Y, et al. Synoviorthesis with radioactive Yttrium in haemophilia: Israel experience. Haemophilia 2001; 7(SUPPL. 2): 36–39.

9. Das BK. Role of radiosynovectomy in the treatment of rheumatoid arthritis and hemophilic arthropathies. Biomed Imaging Interv J 2007; 3(4): 2–6.

10. Schneider P, Farahati J and Reiners C. Radiosynovectomy in rheumatology, orthopedics, and hemophilia. J Nucl Med 2005; 46(1 SUPPL): 48–54.

11. Tena-Sanabria ME, Rojas-Sato YF, Castañeda-Resendiz JC, et al. Treatment with radiosynoviorthesis in hemophilic patients with and without inhibitor. BMC Pediatr 2020; 20(1): 1–6.

12. Martínez-Esteve A, Álvarez-Pérez RM, Núñez-Vázquez R, et al. Radioisotope synoviorthesis in pediatric and adolescent patients with hemophilia. Rev Española Med Nucl e Imagen Mol (English Ed) 2016; 35(1): 12–16.

13. De La Corte-Rodriguez H, Rodriguez-Merchan EC and Jimenez-Yuste V. Consecutive radiosynovectomy procedures at 6-monthly intervals behave independently in haemophilic synovitis. Blood Transfus 2013; 11(2): 254–259.

14. van Vulpen LFD, Thomas S, Keny SA, et al. Synovitis and synovectomy in haemophilia. Haemophilia 2021; 27(S3): 96–102.

15. De La Corte-Rodriguez H, Rodriguez-Merchan EC and Jimenez-Yuste V. Radiosynovectomy in hemophilia: quantification of its effectiveness through the assessment of 10 articular parameters. J Thromb Haemost 2011; 9: 928–935.

16. Özkam E. Radionuclide pain palliation treatment and radiosynovectomy. United Kingdom: Intech Open, 2017.

17. Turkmen C. Safety of radio synovectomy in hemophilic synovitis: it is time to re-evaluate. J Coagul Disord 2009; 1(1): 29–36.

18. Nuss R, Kilcoyne RF, Rivard GE, et al. Late clinical, plain X-ray and magnetic resonance imaging findings in hemophilic joints treated with radiosynoviorthesis. Haemophilia 2000; 6(6): 658–663.

19. Vuorela J, Sokka T, Pukkala E, et al. Does yttrium radiosynovectomy increase the risk of cancer in patients with rheumatoid arthritis? Ann Rheum Dis 2003; 62(3): 251–253.

20. Manil L, Voisin P, Aubert B, et al. Physical and biological dosimetry in patients undergoing radiosynoviorthesis with erbium-169 and rhenium-186. Nucl Med Commun 2001; 22(4): 405–416.