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ORIGINAL ARTICLE

Magnetic Resonance Imaging Changes and Clinical Response in Chinese Haemophilic Joints Treated with Yttrium 90 Radiosynoviorthesis

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ABSTRACT

Objectives: *Radiosynoviorthesis has been shown to be effective in decreasing bleeding frequency, reducing pain, and improving quality of life in haemophilic patients. The aim of this study was to evaluate the clinical response and magnetic resonance imaging (MRI) changes in Chinese haemophilic joints after Yttrium 90 (Y-90) radiosynoviorthesis.*

Methods: *We retrospectively reviewed Chinese haemophilic patients treated by Y-90 radiosynoviorthesis between 2004 and 2011. A total of nine joints in six patients (all males; mean age, 17 years; age range, 5-27 years) with recurrent joint bleeding were studied. The joints consisted of three knees, three elbows, two ankles, and one hip. The frequency of bleeding episodes, pain, and MRI features of pre-synovectomy (within 1 month before the procedure) and post-synovectomy (12-18 months after the procedure) were compared. Presence of effusion / haemarthrosis, synovial hypertrophy, haemosiderin, subchondral cysts / erosion and cartilage loss on MRI were evaluated. The Denver MRI scales before and after synovectomy were also compared.*

Results: *Clinically, all joints showed improvement in frequency of bleeding episodes ($p < 0.001$) and pain. The majority (89%, 8/9 joints) of the joints showed a decrease in effusions / haemarthrosis and synovial thickening / enhancement while more than half (56%, 5/9 joints) of the joints yielded a decrease in the extent of haemosiderin deposits. Only one joint (11%) showed progression of subchondral cyst / erosion and cartilage loss while the rest (89%, 8/9 joints) of the joints had no worsening of degenerative changes. The difference in Denver MRI scores showed no statistically significant changes in scores before and after synovectomy (median pre-score: 9 vs. post-score: 10; $p = 0.347$).*

Conclusion: *Clinical together with MRI improvements in terms of effusions / haemarthrosis, synovial hypertrophy, and haemosiderin were found in majority of haemophilic joints treated by Y-90 radiosynoviorthesis. Majority of joints also showed no further worsening of joint degeneration (including subchondral cysts / erosions and cartilage loss) though none of above-mentioned changes were considered reversible or important for ultimate joint function.*

Key Words: *Hemarthrosis; Hemophilia A; Magnetic resonance imaging; Synovitis; Yttrium radioisotopes*

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中文摘要

血友病華籍患者以90釔放射治療關節滑膜炎後出現的磁共振影像學變化和臨床反應

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目的：放射治療血友病患者關節滑膜炎已被證實可降低其出血頻率、減輕痛楚及改善生活質量。本研究目的是評估血友病華籍患者以90釔（Y-90）放射治療關節滑膜炎後所出現的臨床反應和磁共振影像學（MRI）變化。

方法：本研究回顧了2004至2011年期間接受Y-90放射治療關節滑膜炎的血友病華籍患者。研究對象為6名男性血友病患者（共9例關節），他們介乎5至27歲，平均年齡17歲，全部患者均有關節反覆出血的情況，關節部位為膝關節3例、肘關節3例、踝關節2例和髖關節1例。比較滑膜切除術前1個月及術後12至18個月的出血頻率、疼痛程度和MRI特徵。然後評估患者MRI影像有否出現關節積液/積血、滑膜增生肥厚、含鐵血黃素沉積、軟骨下囊腫/侵蝕和軟骨缺失。同時比較滑膜切除術前及術後關節MRI表現的Denver評分。

結果：臨床方面，所有關節在出血頻率（$p < 0.001$）及疼痛程度方面都有改善。大部份關節（89%，8例）減少出現積液/積血及滑膜增厚/強化，超過一半關節（56%，5例）含鐵血黃素沉積程度亦減輕了。只有1例（11%）的軟骨下囊腫/侵蝕和軟骨缺失有惡化情況，而其餘（89%，8例）關節的退行性變並無惡化跡象。滑膜切除術前及術後關節MRI表現的Denver評分差異並不顯著（得分中位數：術前為9，術後為10；$p = 0.347$）。

結論：大部份血友病患者接受Y-90放射治療滑膜炎後，臨床及MRI均顯示關節積液/積血、滑膜肥厚、含鐵血黃素沉積等現象有改善。儘管上述任何病變均是不可逆的，或者說對最終的關節功能並無重要影響，但絕大部份患者的關節退行性變（包括軟骨下囊腫/侵蝕和軟骨缺失）無進一步惡化。

INTRODUCTION

Haemarthrosis is a hallmark of severe haemophilia and is the major cause of disability.[1] Repeated bleeding into the same joint can lead to chronic synovitis and progressive arthropathy. Radiosynovectomy is one of the treatment options for chronic haemophilic synovitis and has been shown to be effective in decreasing bleeding frequency, reducing pain, and improving quality of life in haemophilic patients. Nuss et al[2,3] discussed the early and late magnetic resonance imaging (MRI) appearances of the changes in haemophilic joints treated with radiosynoviorthesis. These MRI changes were also compared with the clinical response but the correlation was weak.[2,3]

All the previous studies of MRI changes after radiosynoviorthesis were performed among non-Chinese. Our institution is one of the few referral centres of haemophiliacs in Hong Kong and has pioneered the radiosynoviorthesis treatment for patients who were poor responders to conventional treatment of factor VIII/IX supplements. In this study, we sought to evaluate the MR features and clinical outcomes following radiosynoviorthesis in this pilot haemophiliac cohort. To the best of our knowledge, this is the first study to evaluate MRI changes in Chinese haemophilic joints before and after Yttrium 90 (Y-90) radiosynoviorthesis.

METHODS

Study Group

We retrospectively reviewed all Chinese haemophilic patients treated by Y-90 radiosynoviorthesis between 2004 and 2011 in the Prince of Wales Hospital, Hong Kong. Each patient had a diagnosis of severe haemophilia and a history of recurrent bleeding into the target joint. All patients in this series had three or more than three haemarthroses in the same joint within 1 year and a clinical or radiological (MRI) diagnosis of active synovitis. Exclusion criteria were the presence of oncological disease, active infection, pregnancy or breast-feeding, and advanced arthropathy for which surgical treatment was indicated. Six patients (5 with

severe haemophilia A and 1 with severe haemophilia B) were included. There were a total of nine joints in these six patients (all males; mean age, 17 years; age range, 5-27 years); the joints were three knees, three elbows, two ankles, and one hip.

Ultrasound-guided Synovectomy

Prior to the radiosynoviorthesis, these patients were all treated with their appropriate factor concentrates to avoid bleeding. The dose of the Y-90 was 5 mCi for the knee, 1.2-2 mCi for the elbow, and 2 mCi for the ankle or hip. The synovectomy was performed using ultrasound-guided injection of 1.5-5 mCi Y-90 into the target joint via 20G spinal needle. The intra-articular location of the needle was confirmed by ultrasound. Joint fluid and blood was evacuated before the injection. Y-90 was then injected intra-articularly through the same needle. After the injection, the needle was flushed with 2 ml saline. Direct pressure was then applied to the injection site for 5 minutes. The skin was scanned by the Geiger-Müller counter to detect any trace of radiation. The joint was immobilised in a compression bandage for 1 day.

Pre- and Post-synovectomy Magnetic Resonance Imaging Assessment

One month before the procedure, a pre-synovectomy was performed and the post-synovectomy assessment was performed between 12 and 18 months post-procedure. The pre- and post-procedure MRIs were compared. All MRIs were performed using either a 1.5-T (Sonata; Siemens Medical Solutions, Erlangen, Germany) or 3.0-T (Achieva TX-series, Philips Medical Systems, Best, Netherlands) whole-body scanner. The MRIs entailed T1-weighted coronal sequences, T2-weighted axial and sagittal sequences, T2-weighted fat-suppressed sagittal sequences, sagittal fat suppressed 3D gradient echo sequences or fast-field echo sequences and post-gadolinium T1-weighted sagittal and axial sequences. The presence of effusion / haemarthrosis, synovial hypertrophy, haemosiderin, subchondral cysts / erosions and cartilage loss were assessed and compared. The Denver MRI scale scores before and after synovectomy were also compared (Table 1). All the above MRI features and scorings were based on the consensus of two radiologists (years of experience: 6 and 20).

Pre- and Post-synovectomy Clinical Assessment

The frequencies of bleeding episodes and joint pain pre- and post-synovectomy were retrospectively reviewed via the electronic patient history system. The frequency of bleeding episodes was assessed based on the bleeding episode per month before and after the synovectomy. The post-synovectomy pain assessment was categorised as improved, unchanged, or worse. The pre-synovectomy clinical assessment was performed 1 to 3 months before the procedure while the post-synovectomy clinical assessment was performed 12 to 24 months after the procedure, which coincided with the MRI scanning schedule.

Table 1. The Denver magnetic resonance imaging (MRI) scoring scheme (maximum score, 10) in which different stages of pathological development are classified in relation to the most severe findings.

Stage of pathological development	Denver MRI score
Normal joint	0
Effusion / haemarthrosis	
Small	1
Moderate	2
Large	3
Synovial hypertrophy / haemosiderin	
Small	4
Moderate	5
Large	6
Cyst / erosion	
One cyst or partial surface erosion	7
More than one cyst and full surface erosion	8
Cartilage loss	
<50%	9
≥50%	10

Statistical Analysis

The Wilcoxon signed rank test was used to compare the frequency of bleeding episodes and Denver MRI scales before and after the synovectomy. Two-sided p values of less than 0.05 were defined as significant.

RESULTS

Magnetic Resonance Imaging Assessment

The majority (89%, 8/9 joints) of joints showed a decrease in effusions / haemarthroses and synovial thickening / enhancement (Figures 1 and 2), while more than half (56%, 5/9 joints) of the joints yielded decreases in the extent of haemosiderin deposits (Figure 3). All the joints had already had some form of degenerative changes before synovectomy. Only one joint (11%, 1/9 joints) showed progression of subchondral cysts / erosion and cartilage loss while the rest (89%, 8/9 joints) showed no significant change. There was no statistically significant difference in the Denver MRI scores before and after synovectomy (median values: 9 vs. 10, p = 0.347; Table 2).

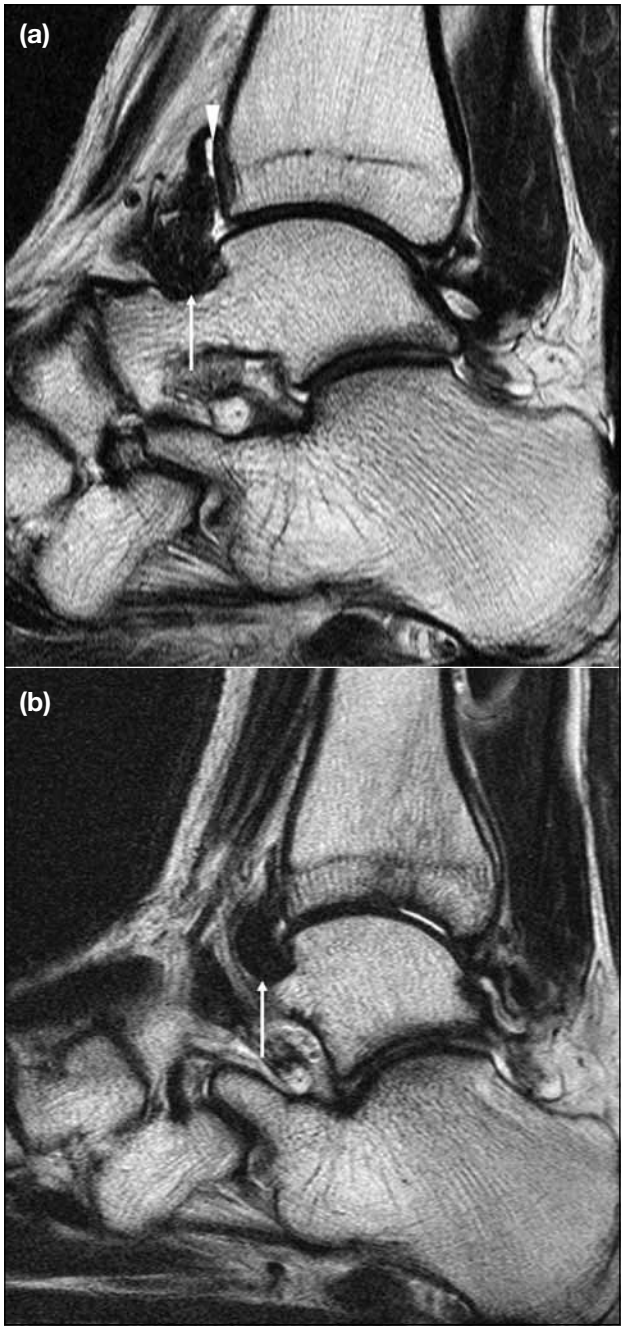

Figure 1. Sagittal T2-weighted magnetic resonance imaging ankle (a) before synovectomy shows severe synovial thickening in the anterior recess of the ankle (white arrow); this is associated with mild ankle joint effusion (arrowhead), and (b) 12 months after synovectomy shows decrease in synovial thickening in the anterior recess of the ankle (white arrow); the mild ankle joint effusion has largely resolved.

Figure 2. Post-gadolinium sagittal T1-weighted magnetic resonance imaging ankle (a) before synovectomy shows moderate synovial thickening and enhancement in the subfibular region of the ankle joint (white arrow), and (b) 12 months after synovectomy shows reduction of synovial thickening and enhancement in the subfibular region of the ankle joint (white arrow). This suggests a good response.

Clinical Assessment

All joints manifested clinical improvement in terms of frequency of bleeding episodes. The median monthly frequency of bleeding had decreased from six prior to the procedure to one after the procedure ($p < 0.001$) [Table 2]. All patients reported subjective improvement in terms of pain; none experienced an increase in pain. No patient endured complications such as skin atrophy due to extravasation of the radionuclide.

DISCUSSION

Intra-articular haemorrhage is the most common

clinical manifestation of haemophilia.[4] Even trivial trauma can trigger intra-articular haemorrhage.[4] Acute synovial inflammation occur in the first few bleeding episodes.[4] However, recurrent haemarthroses lead to chronic synovitis which eventually results in articular damage through synovitis-mediated cartilage destruction (chondrolysis) or a direct harmful effect of blood on cartilage physiochemical balance.[4,5] The articular damage results in impaired function, anatomic alterations, and pain.[6]

Medical and surgical methods are used to stop joint bleeding and post-haemorrhagic synovitis.[6] Medical treatment with clotting factor concentrate is the first-line strategy to prevent bleeding.[1] However, for those with pre-existing joint damage, prophylaxis may not sufficiently reduce the frequency of haemarthrosis and subsequent arthropathy and may warrant synovectomy.[1] The types of synovectomy include open, arthroscopic, chemical, and radio-isotopic. Invasive methods of synovectomy include open and arthroscopic resection while newer methods of synovectomy include using chemical and radioactive agents which have been proven to be efficient regardless of the type of isotope used.[6] Chemical synovectomy (such as osmic acid, oxytetracycline chlorohydrate and rifampicin) have been used in a relatively small number of subjects. Global result of treatment with these chemicals seems to be less favourable than with radionuclides.[6] The late effects of chemical synovectomy are not known.[6] Open excision is associated with arthrofibrosis and loss of range of motion as well as longer postoperative rehabilitation, and therefore, is rarely performed nowadays.[5] Arthroscopic synovectomy is the treatment of choice if surgical synovectomy is indicated.[5] The indications of different types of synovectomy are still unclear.

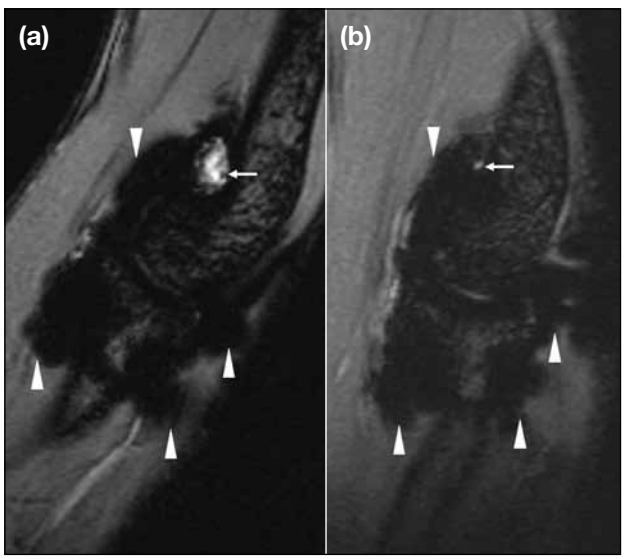

Figure 3. Sagittal fast-field echo magnetic resonance imaging elbow (a) before synovectomy shows severe blooming artefact around the radiocapitellar articulation (white arrowheads). Small amount of elbow joint effusion is also present (white arrow), and (b) 15 months after synovectomy shows moderate decrease in the haemosiderin around the radiocapitellar articulation (white arrowheads). There is also a decrease in elbow joint effusion (white arrow). Features suggest a good response to synovectomy.

The first radiosynovectomy was performed in 1971.[4] Nowadays, radioactive synoviorthesis becomes a common therapeutic option for chronic haemophilic synovitis. Its advantages over other methods include easier to perform, less costly (<5% compared to surgical synovectomy), less invasive, safer, shorter immobilisation, and reduced bleeding tendency.[6] The procedure can be performed in an outpatient setting with minimal factor coverage and substantial cost-benefits.[4] The radioactive synovectomy can be repeated in case of primary or secondary failure, or relapse.[4] After injection of the radioisotopes into the joint, the radionuclide-loaded colloidal particles are rapidly phagocytised by the superficial cells of the synovium.[7] The absorbed radionuclides emit beta-irradiation which induces highly reactive free radicals and causes fibrosis of the subsynovial connective tissue associated with closure

Table 2. Denver scores before and after the synovectomy.

Joints	Denver score		Frequency of bleeding	
	Pre-synovectomy	Post-synovectomy	Pre-synovectomy	Post-synovectomy
1 (hip)	9	10	4	0
2 (elbow)	9	9	5	0
3 (elbow)	9	9	6	1
4 (elbow)	9	9	5	1
5 (ankle)	10	10	5	0
6 (ankle)	10	10	6	1
7 (knee)	8	8	7	2
8 (knee)	10	10	7	2
9 (knee)	10	10	8	2

or occlusion of some vessels, thus helping to decrease the repetitive bleeding and secretary activity.[4] The free radicals can also remove the biochemical substances that trigger the cartilage damage.[5,7]

To the best of our knowledge, this is the first study to evaluate both clinical and MRI changes of patients with haemophilia among Chinese patients after Y-90 radiosynovectomy, while the current available studies were performed on non-Chinese. We described a marked decrease in the number of haemarthrosis after treatment, which was independent of the type of joint, and there was a significant reduction in joint pain among Chinese haemophilic patients. These findings were similar to the results of studies performed on non-Chinese patients.[8-13] In this study, all patients required one injection. However, repeated injection can be given in the same joint at 6-monthly intervals.[2] In most of the patients who used radiosynovectomy, one to three intra-articular injections are enough to stabilise the hyperactive synovia.[2]

MRI has been shown to be more effective than plain radiography in assessment of joint damage.[14-24] Therefore, it is commonly used to assess early post-radiosynoviorthesis changes. It was previously thought that the changes in the synovium might predict the clinical outcomes. However, Nuss et al[2] showed that the synovial hyperplasia was generally unchanged 6 months post-procedure though there was significant clinical improvement. They concluded that the MRI findings in the early post-radiosynoviorthesis period, particularly synovial hyperplasia and haemosiderin deposits, were not predictive of clinical response.[2]

In the same study, Nuss et al[2] also showed that three of seven joints yielded decreased synovial hyperplasia in later follow-up MRIs (12 months and 24 months after synovectomy). Similar to our cohort, post-synovectomy MRIs were all performed between 12 and 18 months and most (up to 90%) of the joints showed decreases in synovial hyperplasia, synovial enhancement, and haemosiderin. Both Nuss et al[2] and our results might suggest that reduction in synovial hyperplasia appears at a later stage (after 12 months) and lags the clinical response. Possible explanations include decreased frequency of bleeding and pain was usually due to regression of active synovium, rather than immediate synovial atrophy. Thus, inactive synovium takes time to atrophy and eventually becomes visible in MRIs. However, currently there are still no studies entailing serial MRIs to monitor the changes in synovium and correlate them with the clinical response. There is also no particular imaging available to differentiate active from inactive synovium, to show better correlations with the clinical response, in the early post-synovectomy period before the synovial hyperplasia begins to cease.

Early treatment of synovitis is generally recommended to decrease the rebleeding rate.[8] The optimal time point of synovectomy recommended is Arnold-Hilgartner stage II.[4] However, Y-90 shows pain reduction in patients with all stages of arthropathy, although some authors do not recommend radiosynovectomy in damaged joints.[4]

In our cohort, the majority of joints were damaged before the synovectomy (Denver MRI scores 8-10). This was because radiosynoviorthesis was generally considered only after significant recurrent joint haemorrhage had occurred and therefore majority of joints were usually severely degenerated. An overall decrease in the frequency of intra-articular bleeding, pain reduction, and MRI evidence of cessation of progressive joint destruction were observed in all patients in our cohort. These findings were comparable with those of other studies performed at different stages of arthropathy.[1-13]

Ideal radioisotopes must have a beta ray that is sufficient to resect the proliferated synovium. The size of radioisotopes must be small enough to be engulfed by phagocytosis of synovial cells. They must have an optimal half-life to minimise biological risks, and enter the synovial membrane without eliciting an inflammatory response. Moreover, they must not leak out of synovial membrane. Y-90 is an ideal radioisotope fulfilling the above requirements. There is only very minimal gamma radiation in Y-90 and it is a pure beta particle emitter, with an average soft tissue penetration of 3.6 mm, and a physical half life of 2.7 days.[24] Y-90 has been widely used with good results.[24] According to the guidelines for radiosynovectomy of the European Association of Nuclear Medicine, Y90 has a higher profile of tissue penetration and it is therefore appropriate for treating larger joins such as the knee joint, Rhenium 186 (Re-186) is appropriate for the treatment of medium-sized joints such as elbows and ankles.[4,24] However, Re-186 carries gamma radiation which may pose an additional hazard to the patient.[4,7,24] In this study, all the joints were treated by Y-90 which has better tissue penetration than Re-186 and might explain the slightly better results of the former in terms of pain and haemarthrosis control compared

with similar studies using Re-186 to treat medium-sized joints. The main concern of Y-90 is the radiation hazard to adjacent soft tissues owing to the better tissue penetration. However, any chromosomal changes seen after radioactive synoviorthesis are usually transient,[6] and there is no evidence of disturbance in normal growth plate maturation.[4] Moreover, neither articular nor neoplastic complications have been reported in literature.[13]

One limitation of this study was that it was retrospective. Second, no objective pain scoring system was used to evaluate post-synovectomy pain reduction. Third, joint disability and deformity were not addressed. Fourth, the sample size was small partly because radiosynoviorthesis was reserved for cases resistant to conservative treatment only, and not a routine treatment of haemophilic patients. Fifth, different joints were assessed together due to the overall small cohort size. Sixth, MRI changes of different joints might differ, although overall changes seemed to be similar across different joints. Lastly, the radiographical findings or Arnold-Hilgartner staging were not compared to MRI and clinical findings in this study.

CONCLUSION

Clinical improvement together with MRI improvement (in terms of effusions / haemarthroses, synovial hypertrophy, and haemosiderin deposits) were found in the majority of haemophilic joints treated by Y-90 radiosynoviorthesis, with no further deterioration in terms of subchondral cysts / erosion and cartilage loss. In our local experience, Y-90 radiosynoviorthesis seems to be an effective treatment for Chinese haemophilic joints, which can be considered in future treatment of local haemophilic patients with early changes, in order to better preserve joint function.

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