Radiosynoviorthesis in Haemophilia: How Safe?

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SUMMARY

One of the best procedures to prevent haemarthrosis in haemophilia has been radioactive synovectomy (radiosynoviorthesis). Since 1976 we have performed 119 radiosynoviortheses in 110 patients, aged from 3 to 40 years (mean 10), and of whom 71 were under 12 years of age. The knees were injected in 71, elbow in 29, ankles in 16, and shoulders in 3 cases. Clinical results of the procedure gave excellent results 80% of patients with no further bleeding. In the case of failure a reinjection can be given in the same joint at a 6 month interval. One of the criticisms against this method is possible chromosomal damage. In our centre, 4 studies have been made in order to see whether these changes are permanent, but all have demonstrated that chromosomal changes are reversible. Radioactive material used in 2 studies was Au-189. In 1978, 354 metaphases were studied with 61 ruptures, with 17.23% non-premalignant and 6 structural changes considered premalignant (1.69%). Further study was done in 1982, in the same group of patients with the result of 21 ruptures (3.34%) and no structural changes. The third study was performed in 13 patients that sustained radiosynoviorthesis with Re-186 in 1991. We compared the chromosomal study before and 6 months after the radioactive material injection and the results confirmed that changes appeared equally in non-irradiated and radiated patients and disappeared with time, never reaching the dangerous zone of 2%. In the group treated with Re-186 we studied an additional number of 130 metaphases with identical results and no structural changes. A study performed before and after radiosynoviorthesis with Y-90 revealed no premalignant changes. It seems than radiosynoviorthesis is safe and highly beneficial to haemophilic patients.

Keywords: synoviorthesis; radionucleoid; haemarthrosis; haemophilia

INTRODUCTION

Haemarthrosis

Haemarthrosis is the most frequent bleeding episode in haemophilia occurring in 83% of patients. This abnormal bleeding originates from the subsynovial venous plexus underlying the capsule where a lack of thromboplastic activity has been demonstrated [1], thus being an intracapsular episode. If this episode is not correctly treated, the produced contracture becomes fixed, leading to more difficult treatment; such abnormal position results in mechanical alterations, recurrent bleeding and progressive destruction of the joint. Thus, it is important to apply early and correct treatment.

The aim of treatment in haemophilic haemarthrosis is not just to treat acute cases, but also, most importantly, to prevent chronic haemophilic arthropathy produced by recurrent haemarthrosis [2].

Treatment of recurrent haemarthrosis

In order to prevent haemarthrosis we must act directly on the synovial membrane either by surgical resection, synovectomy [3-6] or, better, by producing fibrosis of the synovium and subsynovial plexus: synoviorthesis [7-13]. The synoviorthesis can be done chemically with osmic acid, which is very painful, or better by Rifampicin, that acts due to its fibrotic and antifibrinolytic action producing sclerosis of the synovia, thus strangling the bleeding vessels. Oxitetracycline clorhydrate (Emicine®) has been recently substituted by Rifampicin as synoviorthesis material.

Nevertheless, the use of radioactive colloid continues to be the material of choice for synoviorthesis.

Different centres utilize different classification for the indication of synoviorthesis. For practical purposes we classified haemophilic arthropathy in four degrees or stages depending on the clinical severity of the arthropathy facilitating the indication of radioactive synoviorthesis:

- Grade I: Transitory synovitis with no after bleeding sequel. The joint goes back to pre-bleeding stage once the haemarthrosis has subsided. In these cases synoviorthesis is indicated preventively when there are more than 3 haemarthroses in 6 months;
- Grade II: Permanent synovitis with joint enlargement, synovial thickening and limitation of movements. In these cases synoviorthesis is elective;
- Grade III: Chronic arthropathy when, besides the symptoms of grade II, there are axial deformities and muscle atrophy. Synoviorthesis is of recourse;
- Grade IV: Osseous or fibrous ankylosis. Synoviorthesis is not recommended.

The fibrosing of synovium by a radioactive material applied in haemophiliacs was first performed by Ahlberg in 1971 [7]. This procedure has the advantage of a minimal requirement of AHF (30 % of above coagulation level for 48 hours), can be performed in an ambulatory base, several cases can be performed in one sitting and, being a non-aggressive procedure, never gives the restriction of movement range. In regard to results, these are similar to those reported for surgical synovectomy, with 80% of successful outcome [2, 9, 10, 12-15]. It is performed through an intra-articular injection of radioactive colloid that will cause fibrosis of the synovial membrane thus strangling the subsynovial venous plexus and preventing haemarthrosis. It is

Table 1. Physical properties of the radiocolloids used in our center

Properties	Au-198	Re-186	Y-90
Beta radiation	Yes	-	-
Gamma radiation		Rare	No
Penetration	3.6 mm	Soft tissue	2.7 mm
	0.9 mm	Cartilage	1.0 mm
Energy	0.96 Mev	0.98 Mev	-
Size	300 Å	10 Å	3,000-10,000 μ
Half-life	2.7 days	3.7 days	2.7 days

done on an ambulatory bases and can be done as many as 16 cases in one sitting. It requires very low AHF coverage to raise factor to 15% for 72 hours. The method used in our Unit consists in a Tc-99m previous control in order to obtain the objective status of the inflamed joint, raise AHF to 15% and then perform an intra-articular injection under local anaesthesia followed by the injection of the radioactive colloid, immobilization with plaster of Paris for 4 days and in the case we used a colloid with gamma waves (Au-189) gammagram and scintilogram to confirm the material is confined to the injected joint.

We perform periodical controls every 6 months; clinically, Tc-99m control to compare the diminution of inflammation in the joint and evaluation of recurrence, AHF requirements and days of treatment. Finally, a chromosomal study is done to see the presence or absence of chromosomal damages [9, 10, 11].

The radioactive materials used at our centre were Au-198, Re-186 and Y-90 (Table 1).

RESULTS

Diminution of haemarthrosis occurred in 88% of cases; with none in 30 (60%) and less in 14 (28%), with only 5 failures (knees) that sustained surgical synovectomy in a future stage, with a diminution of requirement of AHF that dropped from 67% to 94.5% less AHF required. When recurrent haemarthrosis was present, it subsided just with local means such as ice or compression. The days of treatment required for haemarthrosis after synoviorthesis was performed 1 to 4 days with a previous mean of 8 with a maximum of 25 days of treatment.

Chromosomal studies

Since the first report by Ahlberg [7] and Tezanos Pinto [15], a concern arose on possible permanent chromosomal damage that may induce malignancy. In order to assess the safety of radioactive synoviorthesis, a series of chromosomal studies were done at our Centre, by means of banding and fluorescence techniques in non-irradiated haemophiliacs, 1, 2, 5 and 6 years after the radioactive synoviorthesis was performed.

The first study was performed in 1978 on 354 metaphases (mp) after synoviorthesis with Au-198, where breakage lesions appeared in 61 mp (17.23%) and fragmented chromosomes in 13 mp and only 6 premalignant lesions (1.6%) (2 dicentrics, 2 markers, 1 triradius and 1 segregated chromosomes). The second study was performed in 1982 on the same irradiated haemophiliacs, studying 649 mp. At this occasion breakages occurred in 21 cases (13.24%) segregated in 1 and fragmented in 1, with no premalignant lesions. These premalignant lesions presented in the first study had completely disappeared. We also performed a third study in non-irradiated haemophiliacs on 282 mp obtaining 1 breakage (1.2%) and 2 acrocentric segregation (2.32%) with no premalignant lesions. Therefore we can conclude that all chromosomal changes that could be attributed to radioactive material injected, disappeared after few years of treatment and were thus transitory. These findings are similar to those found after other type of drug therapy such as NSAID, aspirin etc., and some infectious diseases (virus, etc.) (Table 2).

Chromosomal studies performed after radioactive synoviorthesis with Re-186 showed no premalignant chromosomal abnormalities such as markers, seggregations, triradiates and others, different to previous studies with Au-189. These studies consisted of 2 groups; Group A of 12 haemophiliacs before radioactive injection and Group B of 7 of these haemophiliacs 5 to 7 months after radioactive Re-186 (Table 3).

Lately we performed 2 further studies in patients who had Y-90 as the radiocolloid, before and after the injection. In neither of the 2 studies any premalignant chromosomal change appeared.

Of the 3 radiocolloid used Au-198, Re-186 and Y-90, only in those that used Au-198 we detected some premalignant chromosomal damage, below the dangerous limit of 2%, but all disappeared in the second study of these patients. Physical difference among the 3 radiocolloids is the presence in Au-198 of gamma radiation, rare in Re-186 and non-existent in Y-90.

In a publication of our group on the same subject (10) we summarized our studies on the safety of radiosynoviorthesis. Thus, we performed studies on chromosomal structural changes (CSC) by conventional lymphocyte cultures

Table 2. Chromosomal studies

Study	Year	Feature	Non-specific structural changes	Chromosomes*
I	1978	After 1-2 years	61 (17.23%)	6 (1.69%)
II	1982	After 5-6 years	21 (3.24%)	0 (0%)
III		Non-irradiated	2 (2.32%)	0 (0%)

* pre-malignant lesions

Table 3. Chromosomal abnormalities of 431 metaphases in 11 patients treated with Re-186

Group	Number of metaphases	Abnormal cells number	Number of aneuploidy	Number of breakages	Frequency of abnormal cells
A (11)*	272	13 (4.77%)	13 (4.77%)	-	4.7***
B (7)**	159	19 (11.94%)	17 (10.69%)	2 (1.25%)	11.94***

* pre Re-186; ** post Re-186; *** no pre-malignant chromosomal abnormalities

and banding techniques in 79 haemophiliacs treated by radioactive synoviorthesis, 31 untreated haemophiliacs and 110 non-hemophiliacs matched by age and sex as a control group. In 14 patients treated with Au-198, premalignant CSC and non-specific CSC were found in 1.69% and 17.23% of metaphases, respectively. The former disappeared, but 1.7% of non-specific changes persisted for 2 years. In 31 patients treated by Re-186, CSC were not found previous to radioactive synoviorthesis, but were present as non-specific changes in 1.25% of metaphases 6 months afterwards, disappearing 1 year after the injection. In 39 patients treated by Y-90 CSC were not found previous to the injection but were present as non-specific changes in 0.89% of metaphases after 6 months and also disappeared after one year. In non-irradiated patients 0.79% only non-specific changes were found.

CONCLUSION

Chromosomal studies performed on haemophilic patients who underwent radioactive synoviorthesis, regardless of the radiocolloid isotope used demonstrated no pre-malignant chromosomal abnormalities. Also, the penetration of the radiocolloids in the articular cartilage in the haemophiliacs will never penetrate even to the growing layer of the surface cartilage, least to the epiphyseal cartilage. Therefore its cost, easiness of procedure, possibility of multiple patients performed in one session on an outpatient basis and effective clinical results, without the danger of radiation induced lasting lesions, recommend this procedure as the one of choice in the treatment of recurrent haemarthrosis in haemophilia.

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Радиосиновиортеза код болесника с хемофилијом: колико је безбедна?

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КРАТАК САДРЖАЈ

Један од најбољих поступака за спречавање хемартрозе код особа оболелих од хемофилије је радиоактивна синовијектомија (радиосиновиортеза). Од 1976. године урадили смо 119 радиосиновиортеза код 110 болесника старости од три године до 40 година (просечно 10 година), од којих је 71 болесник био млађи од 12 година. Давањем инјекције код 71 болесника су лечена колена, код 29 лактови, код 16 глежњеви, а код три болесника рамена. Клинички резултати поступка били су одлични код 80% болесника, а даљег крварења није било. У случају неуспеха, поновили бисмо давање инјекције у исти зглоб након шест месеци. Критике ове методе указују на могућа оштећења хромозома. У нашем центру изведена су четири истраживања да би се утврдило да ли су хромозомске промене трајне, међутим, показало се да су реверзибилне. У два истраживања коришћен је радиоактивни материјал злато (^{189}Au). Године 1978. испитивали смо 354 метафазе са 61 руптуром, 17,23% непредмалигних и шест структурних промена које су се сматрале предмалигним (1,69%). Следеће истраживање је изведено 1982. године на истој групи болесника; резултат је био 21 руптура (3,34%) без структурних промена. Треће истраживање је обављено 1991. године на 13 болесника под одржаваном радиосиновиортезом са ренијумом (^{186}Re). Спровели смо упоредно истраживање хромозома шест месеци пре и после примене радиоактивног материјала који је дат инјекцијом; резултати су потврдили да су се јавиле исте промене и код неозрачених и код озрачених болесника, које су се временом повукле а да никада нису досегле опасну зону од 2%. У групи испитаника који су лечени са ^{186}Re испитивали смо додатни број од 130 метафаза; добили смо исте резултате без структурних промена. Испитивањем изведеним пре и после радиосиновиортезе итријумом (^{90}Y) нисмо уочили предмалигне промене. Изгледа да је радиосиновиортеза метода која је безбедна и даје веома повољне резултате у лечењу болесника с хемофилијом.

Кључне речи: синовиортеза; радионуклеоид; хемартроза; хемофилија

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