Original Article

Effects of intraarticular ^{32}P colloid in the treatment of hemophilic synovitis of the knee

A short term clinical study

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Abstract

Background: Chronic synovitis is a consequence of recurrent intraarticular hemorrhage in patients with hemophilia. Eventually, synovitis leads to degeneration of the articular cartilage, with serious consequences that impact the quality-of-life in hemophiliacs. The aim of our study was to investigate the short term clinical effects of intraarticular injection of the radionuclide preparation ^{32}P colloid (^{32}P-labelled colloidal chromic phosphate suspension) on recurrent intraarticular hemorrhages in patients with hemophilic synovitis of the knee.

Materials and Methods: Patients who met the inclusion criteria ($n = 22$) were enrolled in an open-label study between October 2011 and September 2012. ^{32}P colloid was injected into the knee joint and patients were followed up over 6 months after treatment. Hemorrhage frequency, visual analog scale pain score, hospital for special surgery knee score, knee circumference, upper knee circumference, knee diameter, and knee range of motion (ROM) were compared before and after treatment with intraarticular ^{32}P colloid injection.

Results: In 24 knees evaluated in 22 participating patients, there was a significant reduction in the number of hemorrhages after ^{32}P colloid treatment, along with significant pain relief. However, there were no statistically significant changes in the degree of joint swelling, degree of muscle atrophy and knee ROM between the pre and post treatment evaluations.

Conclusion: The frequency of joint hemorrhage in patients with hemophilic knee synovitis can be significantly reduced and local symptoms can be improved in the short term by intraarticular injection of ^{32}P colloid.

Key words: ^{32}P colloid, hemophilia, intraarticular injection, radiosynovectomy, synovitis
MeSH terms: Knee joint, hemophilia, synovia, synovitis, radionuclides

Introduction

Recurrent intraarticular hemorrhage in patients with hemophilia leads to chronic synovitis and eventually causes degeneration of the articular cartilage. Subsequently, this leads to arthritis, ankylosis and so on, which seriously inconveniences patients and affects their physical and mental health. Therefore, early treatment of hemophilic synovitis has become a focus of management in haemophilia. Many institutions use arthroscopic techniques to treat the synovitis of hemophilia and significant clinical benefits have been achieved with these techniques. However, for hemophiliacs, arthroscopic treatment still requires infusion of large amounts of coagulation factors to prevent intraarticular hemorrhages resulting from the surgical trauma.

We have obtained good clinical results in the treatment of hemophilic synovitis with intraarticular injections of ^{32}P colloid (^{32}P-labelled colloidal chromic phosphate

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Access this article online	
Quick Response Code:	Website: www.ijoonline.com
	DOI: 10.4103/0019-5413.173507

How to cite this article: Zhang WQ, Han SQ, Yuan Z, He YT, Zhang H, Zhang M. Effects of intraarticular ^{32}P colloid in the treatment of hemophilic synovitis of the knee: A short term clinical study. Indian J Orthop 2016;50:55-8.

suspension), a pure β-particle emitting, nonabsorbable radionuclide preparation. ^{32}P is selected in the study because it is cheap, easy to obtain and is safe.[1,2] As it reduces tissue trauma, this treatment not only reduces medical costs, it also permits joint function to recover quickly. We studied the effect of intraarticular injections of ^{32}P colloid in haemophilic synovitis of knee at our institution between October 2011 and September 2012.

Materials and Methods

^{32}P colloid suspension

^{32}P colloid was produced by Chinese Research Institute of Nuclear Industry. The preparation used was a green colloidal suspension with a pH of 6.0–8.0 and 60% of the colloidal particle size was in the range 20–50 nm. Its radiochemical purity was over 98% and its half-life was 14.3 days.

Patients studied

Twenty-two patients with hemophilic synovitis of the knee were referred to our hospital for treatment between October 2011 and September 2012. All were male and age range was from 7 to 42 years, with an average of 22.3 years. Nineteen patients had hemophilia A and 3 had hemophilia B. All participants provided informed, written consent. Ethical Committee approval for the study was obtained. All patients were asked to record the number of bleeding episodes in 6 month just before treatment.

The patients' basal coagulation factor VIII or factor IX activity was determined to be 0.5–4.0%, and no anti clotting factor VIII or IX antibody was found in any of the patients prior to treatment. All patients were treated with recombinant coagulation factor VIII or factor IX injection. On the day of the treatment, all patients in the study received a dose of recombinant coagulation factor VIII or factor IX aimed at attaining a plasma level of 30% of normal and a second injection was given 8–12 h later.

Treatment procedure

The prerequisite of intervention is that the patients' coagulation factor VIII or factor IX activity had increased to a level of 30%. A hollow needle was inserted into the joint and haematoma was aspirated and 5 mci of ^{32}P colloid fluid was injected into the joint. This was followed by an intraarticular injection of 1 mg betamethasone. The site was covered with a sterile dressing. 5–7 days after treatment, a full range of joint motions was performed 3–5 times daily. Supplementary coagulation factor VIII or factor IX infusions were given intravenously to maintain the level at 30% and the factor VIII or IX treatment is over 2 days.

The frequency of intraarticular hemorrhages was recorded at the 6th month, along with a visual analog scale (VAS) pain scores, hospital for special surgery (HSS) knee scores, the degree of knee swelling, quadriceps muscle atrophy (as measured by the lap circumference), knee range of motion (ROM) and the patients' level of activity. The degree of knee swelling was quantified by measuring the midline of the patella on joint extension and the upper patellar circumference. Data obtained before and at 6-month after treatment were analyzed statistically by the rank sum test (Wilcoxon signed-rank test).

Results

In 22 patients who participated in the study, a total of 24 knees were treated. Results for the 24 knees are shown in Tables 1 and 2. The number of hemorrhages in the 6-month period after treatment was significantly less than the number of hemorrhages in 6-month period just before treatment. Comparisons of pre and post treatment parameters were analyzed by the Wilcoxon Signed Ranks Test, Which showed statistically significant differences in the frequency of intraarticular hemorrhages over 6-month ($P < 0.01$), VAS pain scores ($P < 0.01$), HSS scores ($P < 0.01$), knee circumferences ($P < 0.01$), lap circumferences ($P < 0.01$), and knee ROM ($P < 0.05$) [Table 2]. However, there was considerable variation in the frequency of intraarticular hemorrhages and VAS scores over 6-month posttreatment. No instances of local necrosis were seen during followup of our patients.

Discussion

Recurrent spontaneous hemorrhage in hemophiliac joints leads to local synovial hyperplasia and edema, which eventually leads to synovial hypertrophy. As hypertrophy of the synovial joints makes them more prone to impact injury, hemorrhage is more likely and a vicious circle is created. Persistence of these factors leads to chronic hemophilic synovitis. Persistent swelling of a joint over 3 months indicates that the patient's condition has progressed to chronic synovitis. The clinical manifestations of chronic synovitis are persistent joint swelling, synovial hyperplasia and articular cartilage damage.[3] Inflammation persisting for more than 6 months can cause degenerative changes of the joint and further development of the disease will result in fibrosis of peripheral articular tissue, progressive joint degeneration and diminished joint function and ultimately lead to serious consequences that impact the quality-of-life.[4]

Recurrent spontaneous joint bleeding in hemophiliacs has mainly been treated by supplementary coagulation factors,

Table 1: Data recorded in the 24 knees evaluated before and after ^{32}P colloid treatment

Knee	Before treatment						After treatment					
	No. of times haemorrhages	VAS pain scores	HSS scores	Knee circum-ference (cm)	Lap circum-ference[a] (cm)	ROM degree (°)	No. of times haemorrhages	VAS pain scores	HSS scores	Knee circum-ference (cm)	Lap circum-ference[a] (cm)	ROM degree (°)
1	10	4	85	30.3	42.2	140	3	1	90	30.2	43.0	140
2	9	3	75	38.1	47.0	133	0	0	80	37.9	47.0	135
3	7	4	75	41.2	50.0	140	1	0	85	40.8	50.0	142
4	12	4	48	39.5	47.6	45	4	2	53	39.6	47.8	45
5	8	4	80	30.3	35.5	142	2	1	85	28.6	35.5	142
6	10	3	66	35.5	46.3	110	4	1	71	35.0	46.6	110
7	4	1	80	38.1	46.0	105	0	0	85	36.7	47.0	106
8	12	4	55	36.2	45.5	90	4	2	60	36.3	46.1	90
9	5	1	85	44.3	54.4	125	0	0	90	42.9	54.6	125
10	8	4	70	28.1	40.0	80	1	0	85	28.2	40.0	80
11	11	3	65	40.0	48.2	80	2	1	70	40.0	48.1	80
12	10	4	75	36.3	47.0	95	2	2	80	35.5	47.0	95
13	18	4	30	35.1	40.4	30	4	1	45	34.3	41.1	30
14	13	4	76	44.2	53.2	100	3	2	85	42.8	53.4	110
15	5	3	80	42.0	52.2	75	1	1	85	42.0	52.1	75
16	14	3	55	39.0	50.4	80	6	1	70	39.0	50.4	80
17	10	3	66	34.0	45.7	85	3	1	75	34.0	46.1	85
18	16	2	30	33.7	41.4	30	1	0	50	33.5	41.4	35
19	8	2	76	41.0	51.3	110	1	1	80	40.0	51.4	110
20	7	3	75	39.3	50.4	100	0	0	80	38.5	51.2	100
21	12	4	75	38.6	50.4	112	0	0	80	37.9	50.4	115
22	13	1	80	40.0	51.2	145	3	0	90	40.0	52.1	145
23	11	2	60	38.2	49.6	80	3	0	75	37.6	50.2	80
24	5	1	85	36.0	48.4	150	0	0	90	36.0	48.3	150

[a]Degree of muscle atrophy. HSS score=Hospital for special surgery knee score, ROM=Knee range of motion, VAS=Visual analogue scale

Table 2: Comparison of pre and post treatment parameters via Wilcoxon signed-rank test *Z* and *P*

Parameter (pre vs. post treatment)	*Z*	*P*
Haemorrhage frequency	−4.345	0.000
VAS pain score	−4.392	0.000
Knee circumference	−3.405	0.001
Upper knee circumference	−3.137	0.002
ROM diameter	−2.207	0.027

ROM=Knee range of motion, VAS=Visual analog scale

joint puncture and intraarticular haematoma aspiration.[5,6] However, as haematoma aspiration cannot reduce synovial inflammation, there will still be a high hemorrhage rate when coagulation factors have been fully metabolized. In such cases, synovectomy has been performed after arthroscopy, in order to resect the hyperplastic synovial tissue and thereby reduce bleeding. Although arthroscopic synovectomy has achieved good results, large amounts of coagulation factors are necessary perioperatively to avoid bleeding caused by the arthroscopic surgical trauma. This creates a substantial financial burden on patients, their families and the society in general. In the 1970s, Ahlberg[7] proposed the use of radionuclides in the treatment of hemophilic synovitis and reported that this type of treatment requires only a simple operation and is characterized by minimal trauma, less use of supplementary clotting factors, and only a short hospitalization time.[8-10]

Our results indicate that clinical symptoms and the frequency of hemorrhage can be significantly improved by intraarticular ^{32}P colloid injection. The degree of improvement showed no clear correlation with the patient's age, type and grade of hemophilia, or previous treatment. Overall, these results suggest that the usage of invasive treatment could significantly improve patients' subjective symptoms and the frequency of intraarticular hemorrhage.

Intraarticular injection of ^{32}P colloid may be associated with some adverse events.[11] Although local complications after radioactive synovectomy are rare, local joint swelling, and pain may occur within 6–48 h after injection. There may also be rare instances of local lymphedema or fever, but these symptoms are self-limiting and can be managed by topical application of ice packs, etc., without requiring further special treatment. More serious local complications include necrosis of surrounding skin and soft tissue caused by reflux leakage of radionuclides along the puncture needle tract. In our experience, following injection of the radionuclide into the articular cavity with an injection of

a corticosteroid can avoid the above complications, and no instances of local necrosis were seen during followup of our patients. However, there have been a few reports in the literature of needle tract ulcers and tissue necrosis surrounding joints.[12,13] To avoid these complications, it is advisable that that needle puncture should only be performed by experienced physicians, ensuring that the needle is indeed in the articular cavity.

Another potential adverse consequence of intraarticular injection of radionuclides is loss of the articular cartilage. β-rays emitted by colloidal particles are swallowed by synovial macrophage phagocytosis and become parcels, but some radiation damage of cartilage and subchondral bone is inevitable. Although studies have shown that mature cartilage is resistant to β-rays, small articular cartilage damage may still be a problem.[14,15] But, potential cartilage damage by ß-emitters is inferior to the much more damage due to the ongoing bleeding events or synovial inflammation.

It was suggested that radiosynovectomy should be considered the initial procedure of choice for the treatment of patients with hemarthrosis in hemophilia.[16] In conclusion, the treatment of hemophilic synovitis of the knee with intraarticular injection of ^{32}P colloid proved to be a simple, safe, reliable, economical and practical procedure with few complications and other joints may be treated as well.

Moreover, the limitation of our study is that the sample size is too small because the incidence of hemophilia is rare and not all of them are treated by this method. Another limitation is that followup time is too short because this treatment is symptomatic. Hemophilia treated by this method will relapse because this treatment only alleviates the symptoms of arthrosynovitis induced by bleeding.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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