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Short communication

Our first clinical experience with radiosynoviorthesis by means of ^{166}Ho-holmium-boro-macroaggregates

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Abstract:

BACKGROUND: In this paper, we evaluate the therapeutic and adverse effects of the application of 166-holmium-boro-macroaggregates (HMBA) in radiosynovectomy (RSO) of the knees. We assessed the efficacy and safety of ^{166}Ho-HBMA in a prospective clinical trial in patients suffering from chronic synovitis.
MATERIAL AND METHODS: An effective component of radiopharmaceutical ^{166}Ho-boro-macroaggregates is radionuclide ^{166}Ho which has both β-emission and γ-emission. The physical half-life time of ^{166}Ho is 26.8 hours. After application of the radiopharmaceutical into a joint cavity, the effect of β-emission causes radiation necrosis of pathologically changed (inflamed) synovial membrane. From 15th April 2005, we have started RSO of knees by means of new radiopharmaceutical ^{166}Ho-boro-macroaggregates in patients with gonarthrosis, rheumatoid arthritis, chronic synovitis, psoriatic arthritis, gout arthropathy. Seventeen intra-articular injections were performed in fifteen patients receiving a mean activity of 972 MBq (range: 904–1057 MBq) ^{166}Ho-HMBA. The patients were hospitalized for three days. Side effects were evaluated during hospital stay and after 6–8 weeks. Static scintigraphy of knee joints and measurements of blood radioactivity were performed. Therapeutic effects were evaluated after 6–8 weeks.
RESULTS: In 2 hours and 2 days after application, we proved, by means of knee and inguinal scintigraphy, only insignificant radiopharmaceutical leakage from the joint cavity to the inguinal lymph nodes in four patients. In treated patients, no serious adverse effects occurred. Nine patients were without complaints; 4 patients had slight knee exsudation and 2 patients had great exsudation. Therapeutic effects after 6–8 weeks were as follows: 2 patients were without pain, 9 with lower pain, 3 with the same pain and 1 patient with increased pain. Joint motion was improved in 7 patients, remained the same in 7 patients and was impaired in 1 patient. Analgesics consumption was lower in 5 patients, the same in 9 patients and greater in 1 patient. Knee exsudation was absent in 2 patients, lower in 4 patients, the same in 6 patients and greater in 3 patients.
CONCLUSIONS: We proved only insignificant radiopharmaceutical leakage from the joint cavity to the inguinal lymph nodes. Six patients had early slight or great radiation synovitis. The possible cause could be rather high applicated activity. One can take into consideration its reduction. Therapeutic effects can be precisely evaluated after a longer time interval than was possible for us (6–8 weeks after RSO). ^{166}Ho-boro-macroaggregates can extend the scale of clinically used radiopharmaceuticals for RSO.
This paper is presented in the scope of the first stage of clinical evaluation of synovectomy application of holmium-boro-macroaggregates.
Key words: radiosynoviorthesis, radiation synovectomy, radionuclide synovectomy, holmium-166, ^{166}Ho-boro-macroaggregates, adverse effects, therapeutic effects, chronic synovitis

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Introduction

We present our first experiences with radiosynovectomy (RSO) of knees utilising ^{166}Ho-boro-macroaggregates (HMBA). We evaluated the adverse and therapeutic effects of applied HMBA in a prospective clinical trial in patients suffering from chronic synovitis.

Material and methods

^{166}Ho-HMBA Preparation

Radiopharmaceutical ^{166}Ho-boro-macroaggregates have been produced in the Nuclear Physics Institute of the Czech Academy of Science in Řež, near Prague, Czech Republic [1]. Main production steps of ^{166}Ho-boro-macroaggregates are shown in Table 1. The structure of Ho-macroaggregates is shown in Figure 1, and the spectrum of microsphere size distribution in Figure 2. Organ biodistribution studies with ^{166}Ho-boro-macroaggregates were carried out in rats [1]; the results are shown in Table 2.

Table 1. Main production steps of ^{166}Ho-macroaggregates

1. Preparation of non-radioactive Ho-macroaggregates particles
Reaction of the $Ho(NO3)_3$ solution with the NaBH4 in 0.2 M NaOH
Washing and drying of precipitated particles
Milling & micro sieving
2. Irradiation in the nuclear reactor
3. Preparation of particles suspension in saline (0.9% NaCl solution)
4. Steam sterilisation
5. Distribution to the hospital
Radionuclide purity > 99% Radiochemical purity > 90%

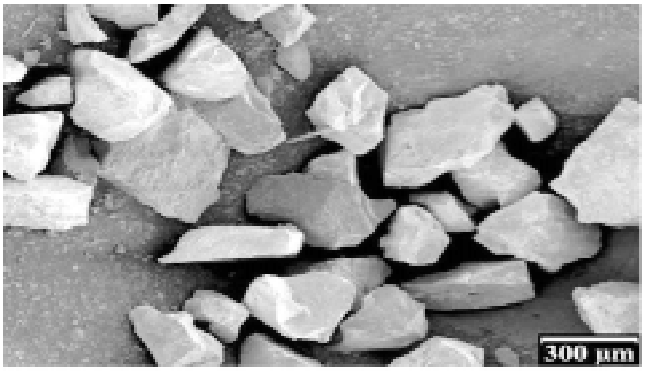

Figure 1. Structure of Ho-macroaggregates. Electron microscope scan: particles before sieving, inorganic compound, 50–60%w of Ho incorporated.

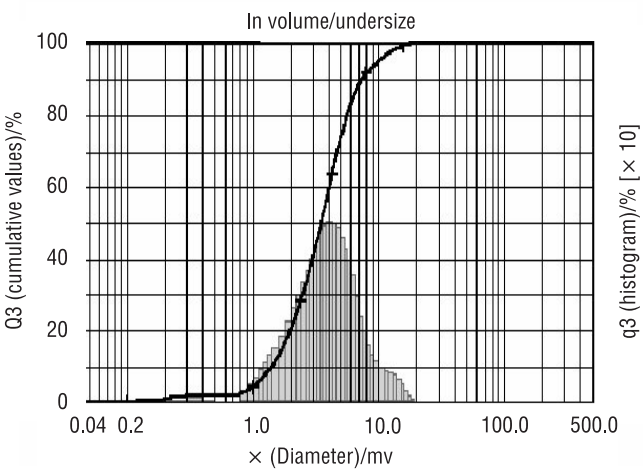

Figure 2. Structure of Ho-macroaggregates. Laser Particle Size Analyser CILAS: spectrum of microspheres size distribution in suspension after sieving.

Table 2. Organ radioactivity measurement in rats

Organ	Radioactivity
Blood	0.001%
Lung	0.003%
Spleen	0.001%
Kidney	0.001%
Liver	0.033%
Left knee joint	99.961%

Patients and procedure

On 15th April 2005, we started RSO of the knees by means of a new radiopharmaceutical, ^{166}Ho-boro-macroaggregates. All patients gave their informed consent to the treatment protocol. We treated 17 knees in 15 patients with chronic synovitis (8 men, 7 women, average age 49.6 yrs; seven patients with gonarthrosis, 6 patients with rheumatoid arthritis, one patient with psoriatic arthritis and one patient with gout arthropathy) with a mean activity of 972 MBq (range: 904–1057 MBq) of ^{166}Ho-HMBA. Patients' inclusion to the study was based upon criteria shown in Table 3. The patients were hospitalized for 3 days. Adverse effects were evaluated during hospitalization and after 6–8 weeks. Scintigraphy of knee joints was done at 2 and 48 hours after RSO by means of dual-head SPECT camera E.CAM (Siemens, Erlangen, Germany). Scans were performed in anterior and posterior projections of knees and inguinal areas, 5 minutes acquisition time per projection. Measurements of blood radioactivity were performed 4 and 24 hours after RSO (activity of 1 ml of blood measured in a well scintillation detector). Therapeutic effects were evaluated after 6–8 weeks. The project had the approval of the Local Ethical Committee.

Results

Radiopharmaceutical leakage

Two hours after application, we observed a homogenous distribution of radiopharmaceutical in the knee cavity on scintigrams (Figure 3) and we did not prove any accumulation in the inguinal lymph nodes. Two days after application, we proved only insignificant radiopharmaceutical accumulation in the inguinal lymph nodes in four patients (leakage accounted to < 1% of the total activity) (Figure 4). In 11 patients, no leakage was detected (Figure 5).

Blood activity

Activity measurement in 1 millilitre of blood, 4 hours after application, was 102–1802 counts/minute, average 650 counts/min. 24 hours after application it was 56–1079 counts/min, average 443 counts/min.

Side effects

In our group of patients no serious unwanted effects occurred. Nine patients were without complaints, 4 patients had slight knee exsudation and 2 patients had great knee exsudation.

Treatment effect

Therapeutic effects after 6–8 weeks were as follows: 2 patients were without pain, 9 with lower pain, 3 with the same pain

Table 3. Inclusion and exclusion criterions

Inclusion criterions	Exclusion criterions
Age 18–60 years	Drug allergy
Joint affections:	Gravidity, lactation
RA	Infection or febrile conditions last 4 weeks
Osteoarthrosis	Infectious knee or bone affections
Psoriatic arthropathy	Knee RSO last 6 months
Other	X-ray knee irradiation last 6 months
Repeated hydrops	Intra-articular knee application of corticoids last 2 months
Informed consent	Significant destruction of knee
	Positive HIV, HCV, HBsAg
	Significant deviation of laboratory tests
	Participation in other clinical study last 6 months
	Inability of co-operation
	Foreigner
	Disabled patient
	Person performed military service or in prison

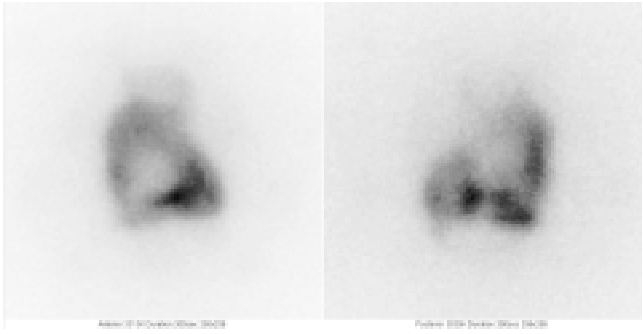

Figure 3. Distribution of radiopharmaceutical in knee cavity after 2 hours after RSO.

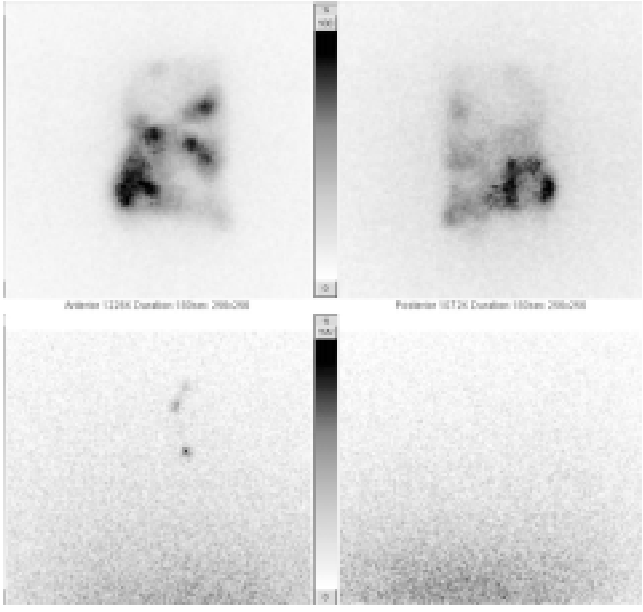

Figure 4. 48 hours after application: distribution of radiopharmaceutical in knee cavity and insignificant radiopharmaceutical leakage from the joint cavity to the inguinal lymph nodes.

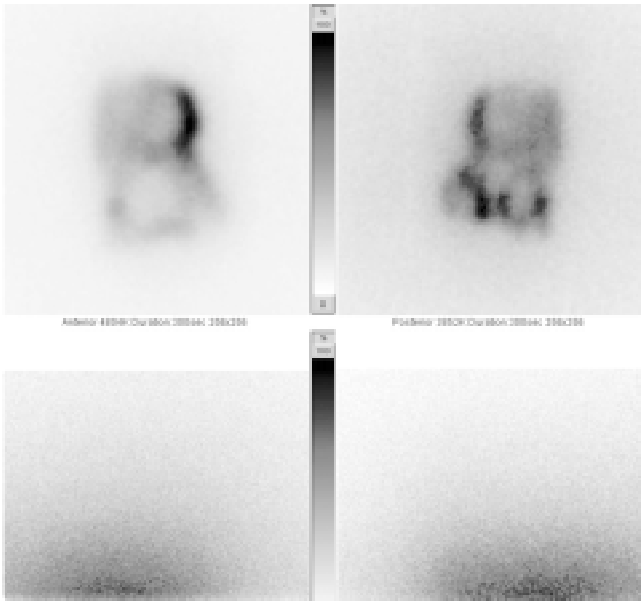

Figure 5. 48 hours after application: distribution of radiopharmaceutical in knee cavity without leakage to the inguinal lymph nodes.

and 1 patient with increased pain. Joint motion was improved in 7 patients, unchanged in 7 patients and impaired in one patient. Analgesic consumption was lower in 5 patients, the same in 9 patients and greater in one patient. Knee exsudation totally withdrew in 2patients, was decreased in 4 patients, was the same in 6 patients and greater in 3 patients

Discussion

Radiation synovectomy (RSO) by intra-articular injection of beta-emitting radionuclides is a reliable and easy-to-perform therapy without harmful side effects for the treatment of inflammatory rheumatoid, as well as degenerative, joint diseases. The indication for radiation synovectomy is based on

Table 4. Radiopharmaceuticals for RSO

Radiopharmaceuticals	Radionuclide
FHMA	^{166}Ho, ^{165}Dy, ^{169}Er
Hydroxyapatit particles	^{166}Ho, ^{186}Re, ^{153}Sm
Glass microspheres	^{90}Y, ^{166}Ho, ^{153}Sm
Ho-B-MA	^{166}Ho
Ho-PLA-MS	^{166}Ho
Ho-citrate colloids	^{166}Ho
HSA microspheres	^{186}Re
Chitosan complex	^{166}Ho, ^{165}Dy, ^{169}Er, ^{153}Sm

FHMA — ferric hydroxid macroaggregates; Ho-B-MA — Ho-boro-macroaggregates; Ho-PLA-MS — Ho-polylactic acid microspheres

both clinical symptoms and on proven hyperperfusion, with active synovitis being seen on a pre-treatment three-phase bone scan.

Radiation synovectomy is the alternative way for surgical synovectomy. It is possible to repeat this therapy with similarly good results as the first therapy [2]. The most often used radiopharmaceuticals are colloids labelled with ^{90}Y [3] or ^{32}P [4] (for big joints — knees), ^{186}Re (for medium joints) [5] and ^{169}Er (for small joints) [6]. In addition to these colloids, there are many other radiopharmaceuticals suitable for RSO (Table 4) [7–10].

An effective component of ^{166}Ho-boro-macroaggregates is radionuclide ^{166}Ho, which has β-emission with maximum energy of 1.85 MeV, maximum soft tissue penetration of 8.7 millimetres and γ emission of energy 48–58 keV (9.8%), 81 keV (6.2%) and in small proportion 1379 keV. The physical half-life time of ^{166}Ho is 26.8 hours. Its daughter nuclide is ^{166}Eu (Europium) which is stable. The holmium-166 was prepared in a LWR-15 nuclear reactor (8–10 MW) by ^{165}Ho (n, γ) ^{166}Ho reaction (neutron flux 10^{13}–10^{14} neutrons.cm^{-24}.s^{-1}) [1]. After an application of the radiopharmaceutical to the joint cavity, the micro-particles, which are carriers of radionuclides, are trapped by macrophages and transported to the synovia, then the effect of β-emission causes radiation necrosis of the pathologically changed (inflamed) synovial membrane.

Conclusions

We proved only insignificant radiopharmaceutical leakage from the joint cavity to the inguinal lymph nodes. Blood activity after 4 and 24 hours was not significant. Six patients had early slight or great radiation synovitis; the possible cause could be the rather high activity applied (in average 972 MBq). One can take into consideration its reduction. Therapeutic effects can be precisely evaluated after a longer time interval than was available to us (6–8 weeks after RSO). We have planned to treat other patients with reduced activity (about 500 MBq) to decrease early adverse effects.

^{166}Ho-holmium-boro-macroaggregates can extend the scale of clinically used radiopharmaceuticals for RSO and fill the gap between ^{90}Y with high β-energy and ^{186}Re a ^{169}Er with lower energy. Energy of ^{166}Ho is suitable for large and medium joints (knees, hips, shoulders, elbows, wrists, ankles). It is also a prospective agent for RSO because ^{166}Ho is a radionuclide suitable for imaging with a gamma camera after administration to the joints.

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