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ORIGINAL ARTICLE

Efficacy of radiosynoviorthesis and its impact on chosen inflammatory markers

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Abstract Radiosynoviorthesis is used for the local treatment of recurrent joint effusions and leads to synovium necrosis after radionuclide administration. This procedure provides opportunity to full recovery of normal synovium function after local corticosteroids and systemic modifying drugs failure.

Keywords Radiosynoviorthesis · Radionuclides · Chronic inflammatory joints disorders

Introduction

Radiosynoviorthesis (RS) has established position in rheumatology, and it is usually used in rheumatoid arthritis (RA) and inflammatory spondyloarthropaties (SPA). The primary indication for RS is treatment of recurrent joint effusions among patients who obtained general improvement after systemic therapy but one or a few joints stay resistant to this treatment. Nowadays RS is an alternative method toward synovectomy, and it supports disease modifying anti-rheumatic drugs (DMARDs) therapy [1–3].

In the presence of last clinical research results conducted in vitro on human chondrocytes and in vivo on animals chondrocytes which indicated harmful influence of RS on articular cartilage, we have evaluated concentration of chosen bone and cartilage turnover markers and acute phase proteins in around procedure period in RA and SPA patients [4].

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Groups and methods

Seventy-one patients were included in this research; we divided all of them into two groups. Forty-three patients with RA (43 knee joints) aged 22–68 (on average 50, 1 year) and 19 SPA patients (19 knee joints) aged 20–70 (on average 42, 6 years) were treated with RS and then observed during 6 months. Among 19 SPA patients, 8 were treated due to ankylosing spondylitis (AS), 4 due to psoriatic arthritis (PsA), and 7 due to undifferentiated inflammatory spondyloarthropaty.

On the basis of knee X-rays taken not longer than 1 month before RS, considering those pictures, 23 knee joints patients with RA were classified as I grade according to Steinbröcker staging, 18 knee joints patients with RA as II grade, and 2 knee joints patients with RA as III anatomical grade.

Indication for RS was moderate or severe, persistent knee joint effusion that was recurrent in spite of local corticosteroid injections (minimum of 3 given in 4–6 weekly intervals) and optimal systemic treatment of disease with modifying drugs in a stable dose for a period not shorter than 4 weeks before RS. Intraarticular injection with corticosteroid was prohibited within 4 weeks before RS. Patients were assigned randomly to the therapeutic appropriate procedure, and DMARDs were sustained in stable doses for 6-month observation period after RS. Any DMARDs dose change or intraarticular corticosteroid injection within 6 months after RS excluded patient from

further observation. Those patients were treated as RS failure.

Each patient signed an informed consent form before any study related procedure and further observation after therapy. The written approval for conducting the study and obtaining an informed consent form was given by the Independent Ethics Committee of the Medical University in Lublin, Poland.

Technique of radiosynoviorthesis

The procedure was performed as follows. The knee joint was punctured with 20 G needle and inflammatory fluid was evacuated, then 1 ml of sterile suspension of ^{90}Yttrium isotype (^{90}Y, CIS Bio International Company) with activity of 185 MBq (5 mCi) and 1 ml of 40 mg triamcynolon (Polcortolon 40 Jelfa Company) were injected. The procedure ended flushing channel of needle with 4 ml of 0.9% saline. RS was performed in aseptic conditions. After injection of all substances and dressing the wound, three passive movements for homogenic isotype distribution in joint space were performed; afterward joint was stabilized for 48 h to avoid radionuclide molecules migration to peripheral lymph nodules [3].

Three-phase bone scintigraphy of knee joints

The three-phase bone scintigraphy was performed before and 6 months after RS behind assistance of gamma camera Varicam (Elscint, Haifa, Izrael).

The three-phase bone scintigraphy was performed after intravenous injection of 740 MBq metylbiphosphonian MDP-99mTc above knee joint in antero-posterior and postero-anterior projection in all phases of examination. The third phase of knee joints scintigraphy was estimated in semi-quantitive ROI (Region of Interest) method. We calculated J/B (Joint/Bone) ratio by dividing average number of pixels in treated region knee joint by average number of pixels in a distal part of the femoral bone body on the treated joint side.

We evaluated cured joints after 24 weeks of RS in the scope of tissue blood supply and metabolism and compared it with the state before therapy according to the procedure described above.

Effusion evaluation of knee joint

The efficacy of procedure was evaluated on the basis of physical examination taking into account the presence of effusion before procedure and then in the first and sixth month after RS according to the placed scheme:

1) joint free of effusion—very good result
2) mild effusion (trace of patella balloting)—good result
3) moderate effusion (marked patella balloting)—lack of improvement
4) severe effusion (in up-right knee position and muscle relaxation articular capsule tense)—lack of improvement or deterioration

Biochemical and serological designations

Following were taken from each of patients: erythrocyte sedimentation rate (ESR, normal range: 0–15 mm/h), C-reactive protein level (CRP, normal range 0–5 mg/l) immunoturbidymetric method and osteoprotegerin level (OPG, normal range: 1.7–5.4 pmol/l), hialuronic acid (HA, normal range: 0–75 ng/ml) and serum amyloid A (SSA, normal range: 10–270 ng/ml) ELISA method in serum, directly before RS (1st period), then 4 (2nd period) and 24 weeks (3rd period) after procedure.

Statistical analysis

Statistical analysis of results was conducted with usage of computer program STATISTICA 6.0 StatSoft company. We calculated average arithmetic (M) for quantitative features and standard deviation (SD).

Shapiro–Wilk W test was used for analysis of schedule of evaluated features. Mann–Whitney U test was used to estimate the differences between researched groups. We estimated differences between analyzed features using Spearman's correlation test, Anova Friedman test, Kendall's ratio of correspondence, Wilcoxon's couples correspondence, and chi square test. We accepted for statistically important differences for $P < 0.05$.

Results of research

Patients with moderate or severe knee effusion were qualified for RS. Physical examination which evaluated presence of knee effusion in the joint treated was of primary importance of treatment efficacy.

We observed very good results in 25 patients with RA (58.1%)—lack of effusion, in 10 patients good result—mild effusion (23.3%), lack of improvement in 8 patients (18.6%). Very good and good results all together satisfied 35 patients (81.4%).

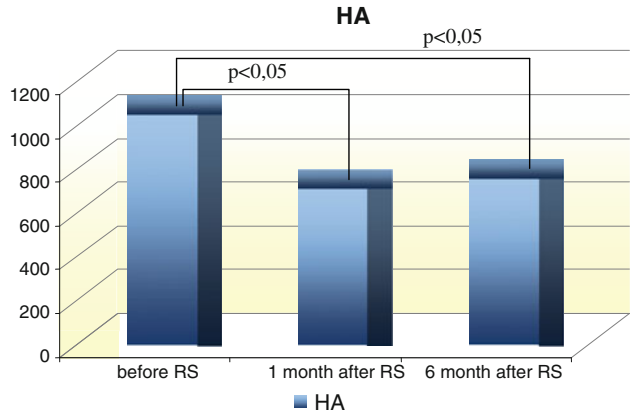

Fig. 1 Hialuronic acid level (HA in ng/ml) in patients with RA

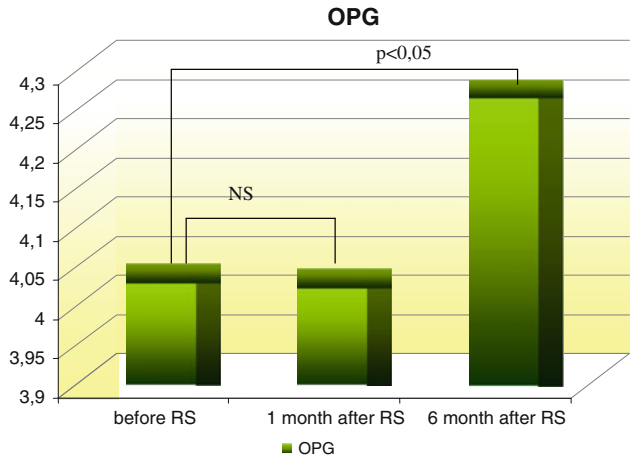

Fig. 2 Osteoprotegerin level (OPG in pmol/l) in patients with RA

We obtained very good results in 12 SPA patients (63.2%)—lack of effusion, in 5 patients good result—mild effusion (26.3%), lack of improvement in 2 patients (10.5%). Very good and good results all together satisfied 17 patients (89.5%).

We did not observe signs of deterioration and no side effects connected with the procedure.

Changes in serum HA, OPG, and SAA levels after RS are presented in Figs. 1, 2, 3, 4, 5, and 6.

Discussion

The primary inflammatory process primarily involving synovial membrane is an essential phenomenon in systemic arthritis; it leads to secondary changes in composition and physico-chemical specificity of synovial fluid. Breakout of synovio-vessel barrier by activated macrophages and lymphocytes, infiltration, and interaction of these cells with synoviocytes, dendritic, and endothelial cells results in fibroblastes expansion, neovascularization, increasing

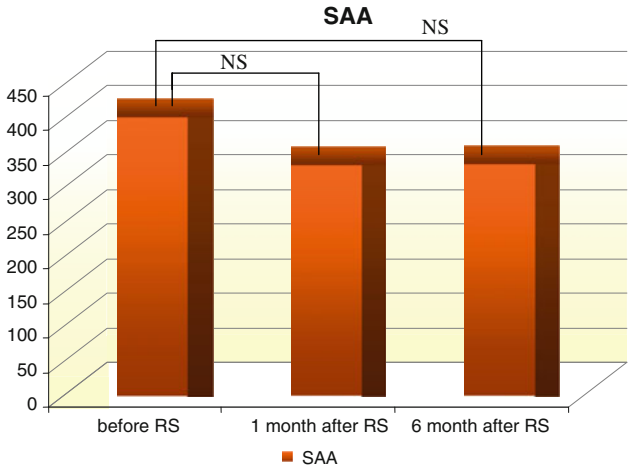

Fig. 3 Serum amyloid A level (SAA in ng/ml) in patients with RA

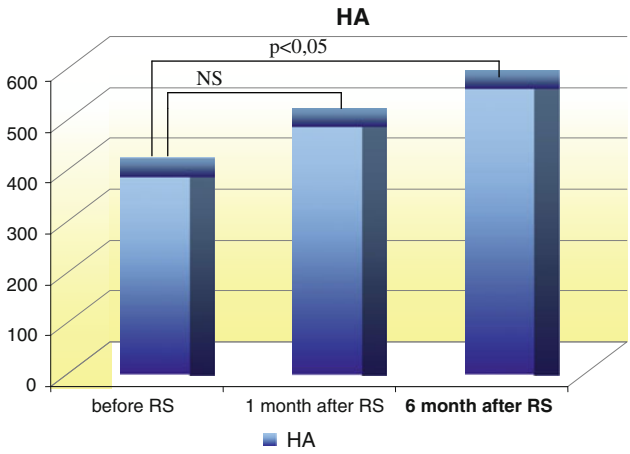

Fig. 4 Hialuronic acid level (HA in ng/ml) in SPA patients

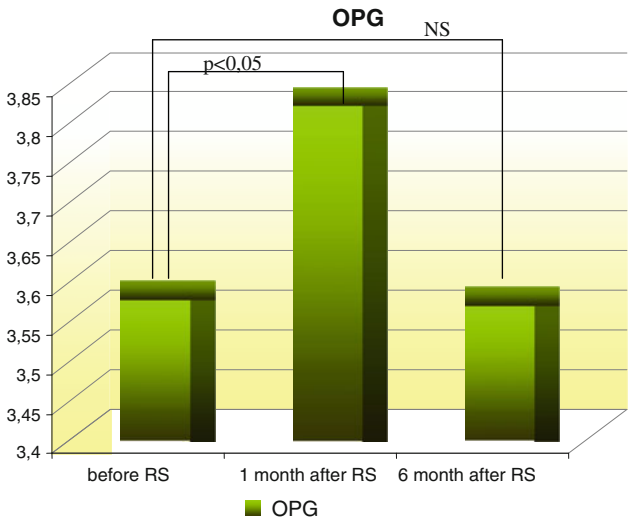

Fig. 5 Osteoprotegerin level (OPG in pmol/l) in SPA patients

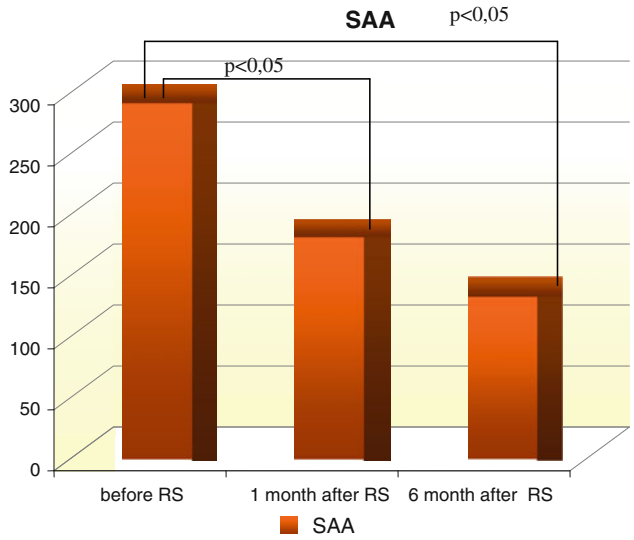

Fig. 6 Serum amyloid A level (SAA in ng/ml) in SPA patients

expression of proinflammatory cytokines, chemokines, and metaloproteinases [5, 6]. The newly synthesised pathological tissue named pannus is responsible for destruction of all joint structures. The purpose of RS is obliteration of hypertrophic and infiltrated synovial membrane and joint protection before damage [7].

In our research, we took into consideration, beyond clinical examination, results of laboratory tests, scintigraphic investigations, and generally used in daily practice scales and questionnaires for general disease activity evaluation. According to collected data, we observed that mentioned parameters undergo dynamic changes influenced by local therapy used. Results interchangeably indicate not only local efficiency of RS but also favorable influence of procedure on systemic inflammatory process as well.

The presence of knee effusion during physical examination in the sixth month of observation was the most important feature of treatment efficiency.

Treatment of knee effusion with the use of RS was safe and efficient—we did not observe any procedure-related adverse events.

We found only a few articles in professional literature available evaluating influence of RS on unspecific, systemic inflammatory process, and the reports are contradictory [8, 9]. Spooren and co-workers did not find any influence of ^{90}Y RS on red blood cells count, ESR, and rheumatoid factor level in osteoarthritis and in patients with RA [9]. Schutte and Rau came to the different conclusions. In patient's group with improvement after RS, they observed simultaneously increased level of hemoglobin and decreased level of ESR [8].

We found in our research statistically essential decrease in CRP concentration and ESR in the first and sixth month after RS in patients with RA. We observed decrease in DAS (disease activity score), RADAI (rheumatoid arthritis disease activity index), HAQ (health assessment questionnaire), VAS (visual analog scale)—physician evaluation of disease activity, VAS—patient's pain and disease activity assessment scales, and swollen and tender joint counts in the first and sixth month after RS.

The obtained results indicate the favorable influence of local RS therapy on unspecific, systemic inflammatory process and general disease activity.

In RA and SPA patients with good and very good treatment results, local and general improvement was obtained within the first month and had a permanent character, lasted for the whole 6-month observation period.

It is known that RS has influence on different synovial cells metabolism, refractory to this phenomenon, secretion of some markers activity have been changing, among others HA, which is synthesized by fibroblastes (synoviocytes B in synovium) penetrates blood via lymph vessels and it is eliminated by liver. Research conducted on animals and humans in vivo confirmed its protective role for articular cartilage provides chondrocytes viability and decreases proliferation of synovial cells. HA has anti-inflammatory properties and binds free ties. It plays important role in correct joints' motion, reduces friction, and creates kind of "lubrication" covering articular surfaces [10–13].

The highest concentration of HA is observed in patients with RA, a little bit lower in AS and PsA patients; in osteoarthritis patients, HA level is comparable to population of healthy persons [14, 15]. It is known that HA concentration correlates with objective markers of inflammatory process in RA and AS such as CRP level and ESR value and additionally in AS with a scope of spine motion. The higher level of HA is presented in AS patients with peripheral joints involvement [15]. High level of HA in patients with systemic inflammatory arthritis results from overproduction of polysaccharide within synovial membrane, while it is not related to poor liver elimination, it reflects the degree of cartilage degradation [16, 17]. Some authors include HA to one of the most important markers of RA and juvenile arthritis activity [18].

We found in our research highly significant statistically decrease in serum HA level in patients with RA in the first and sixth month after RS which suggests important influence on this treatment on reducing of local inflammatory process through interaction on synovial membrane of the treated knee joint. However, increase in the HA level was observed in SPA patients in the sixth month after RS.

Another group of proteins used in monitoring of inflammatory activity and taking part in maintaining bone tissue homeostasis is a system of receptors and ligands of cancer necrosis factors. OPG is a protein belonging to a family of receptors of cancer necrosis factors, universally it is found in a body, produced within the heart, lungs,

kidneys, intestines, bones, and by hematopoetic cells. OPG is produced in large quantities by synovial membrane fibroblasts. RANKL (receptor activator NF-κB ligand) belongs to a family of proteins of cancer necrosis factors, produced by mature osteoblats and their precursors, macrophages, and activated lymphocytes T [19, 20]. RANKL regulates differentiation of osteoclasts and dendritic cells, acts through a receptor RANK (receptor activator NF-κB) situated on a surface of target cells [19]. OPG has ability of binding RANKL, it constitutes its soluble receptor, binding block of RANK from RANKL stops osteoclasts maturation just at its initial stages. Differentiation, maturation, and activity of osteoclasts, and so intensity of the bone resorption depend on relative balance between the concentration of RANKL and OPG. The RANKL advantage over OPG is increasing pathologically the process of the bone resorption, a phenomenon responsible for the generalized and periarticular osteoporosis development, and for bone erosions in systemic arthritides [19–21].

In conducted examinations, we stated an essential statistical increase in the OPG concentration after the first month from RS in SPA patients and after the sixth month from RS in patients with RA, which suggests the protective influence of this procedure on joint cartilage and on sub-cartilage bone layer.

In the group of SPA patients after RS, we observed essential statistically decrease in the SAA concentration after the first and sixth month from performing the procedure.

SAA is produced in the liver, after being released to blood, it is bound with HDL (high density lipoproteins) fulfills anti-inflammatory functions; its concentration in serum repeatedly grows during the inflammatory reaction. It is a fundamental marker of acute phase, SAA synthesis is mainly stimulated by Il 1 and Il 6. RA and SPA are included in typical inflammatory chronic arthritides, where SAA high concentrations in the patients' serum are stated. HDL molecules are protecting SAA from the proteolysis. Complexes HDL-SAA are responsible for chemotaxis of monocytes, lymphocytes, mast cells and are activating tissue proteinases: collagenase and stromyelysin. Complexes HDL-SAA are the source of cholesterol for the regeneration of cells damaged by the inflammatory process and simultaneously can act as the carrier of lipids by binding the excess of cholesterol in serum, which is being freed from destroyed tissues. The SAA excess in the chronic inflammable process in relation to the organic protein deposition leads to the reactive amyloidosis. The frequency of amyloidosis appearance in RA fluctuates from 11 to 30%, most often accompanies AS on the SPA course (6%).

In own examinations statistically essential negative correlation was stated between the anatomical stage and the effectiveness of therapy. This observation is matching data in literature [22, 23].

No essential statistical relations were found between the age of patients, sex, duration of illness, number of RS performed earlier, number of modifying drugs used earlier, and the subjective and objective evaluation of the joint treated before the procedure with the therapy effectiveness.

Initial, general activity of arthritis evaluated on the basis of the concentration of acute phase proteins (CRP, fibrinogen, albumin), OPG, HA, SAA in serum, number of painful and swollen joints, questionnaires (HAQ), indices (RADAI), scores (DAS), and local evaluation based on articular liquid examination (pleocytosis with smear) did not correlate with the therapy effectiveness.

The response to treatment in groups of RA and SPA patients after RS was also determined on the basis of changes in the third metabolic phase of the three-phase scintigraphy of knee joints. Statistically significant positive correlation between the effectiveness of therapy evaluated on the basis of the physical examination was stated toward the effusion and the initial value of the J/B rate established before the treatment. Achieved results are matching data from the literature [23–27]. The effectiveness of therapy negatively correlated with the J/B value after 6 months observation. So the initial value of the J/B rate is prognosing the effectiveness of therapy. The J/B rate is not correlating with the subjective evaluation made before and after 6 monthly period of observation.

Conclusions

1. Radiosynoviorthesis with ^{90}Yttrium is safe procedure in persistent knee joints effusions in relation to rheumatoid arthritis and spondyloarthropaty patients.
2. Radiosynoviorthesis with ^{90}Yttrium of knee joints in spite of being local treatment reduces unspecific inflammatory process and systemic disease activity in subjects with rheumatoid arthritis and inflammatory spondyloarthropaties.
3. Radiological stage has negative correlation with treatment efficacy.
4. Favorable changes of serum bone and cartilage turnover markers as the effect of therapy indicate protective impact of radiosynoviorthesis on those articular structures.
5. Therapeutic response after radiosynoviorthesis based on physical examination, biochemical markers of acute phase, specific scales, and questionnaires is gained quickly and lasts for a minimum of 6 months.

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