International Journal of Clinical Medicine, 2015, 6, 500-505
Published Online July 2015 in SciRes. http://www.scirp.org/journal/ijcm
http://dx.doi.org/10.4236/ijcm.2015.67067

Target Transfusion Intra-Articular Therapy for Osteoarthritic Joints

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Received 26 September 2013; accepted 17 July 2015; published 20 July 2015

Abstract

The comparison of biochemical composition and biophysical properties of synovial fluid and blood serum leads to a conclusion about the pathogenetic expediency of using serum as a corrector of synovial medium of osteoarthritic joints. Serum modification was realized by preliminary prescription of a single-dose drug to the patient. Then, the patient's blood was sampled in the period of its maximal saturation with the drug. Autoserum from such blood samples was injected thrice into the knee joints affected by osteoarthritis of the 2nd or 3rd stages. The value of treatment results after 4 - 6 months of described therapeutics shows a significantly better therapeutic effect in the experimental of patient's group as compared with the control group. The effect is connected with pain diminishing, normalization of the tissue joint nutrition, suppression of the local inflammation, and improvement of cartilage lubrication.

Keywords

Osteoarthritis, Chondroprotection, Blood Serum, Intra-Articular Therapy

1. Introduction

Pathogenesis of degenerative-inflammatory changes of joint synovial medium at osteoarthritis (OA) has been associated with disturbing homeostasis of joint cartilage and synovial liquid (synovia). OA is developing when the balance of degradation and rehabilitation of joint tissue has been violated. OA brings cartilage to failure by initialing deterioration of the joint function. Early changes induce chondrocytes mitosis growth of proteoglycans and collagen synthesis in order to restore the initial cartilage state. The composition and size of collagen fibers stop changing, and proteoglycans begin to destroy faster than synthesis. In response to intensified activity chondrocytes, the matrix metalloproteinase activity is increasing. The latest is responsible above all for the cartilage degradation of a sick patient. Fermentative disintegration of collagen fibers causes erosion, mikrocracking and

fibration of the cartilage [1].

The misbalance of the destructive and synthetic chondral processes is intensified by structural changes in synovia. Decrease of the quantity, lowered viscosity of synovia, and reduction of concentration and molecular weight of hyaluronic acid lead to deterioration of synovial lubricity and shock-absorbing ability of the joint. Synovia tents to worsen its inherent tribological, metabolic, trophic and barrier functions [2]. The occurrence of infectious agents in a joint creates immunologic complications because pathologic antibodies are accumulated in synovia. They forms bond with cartilage proteins and synovium so that the immune system shows pathological hostility relative to tissues of its own joint.

A variety of not clearly understood mechanisms of OA etiopathogenesis is the reason why the effective therapeutic strategies are absent for the immediate prevention of disease propagation and fast recovering of joint functions in the patients suffering OA. The situation is aggravated by the following. The drugs traditionally used in orthopedics—non-steroid anti-inflammatory, glucocorticosteroids, immunomodulators, etc.—should pass a metabolic route and deposit in tissues prior to reach the articulate cavity. Penetration of drugs into the joints is hampered in the case of OA by inflammatory, commissural and degenerative changes in the tissues of the joint capsule and synovial membrane. This path weakens considerably the effect of pharmacotherapy of joints and favors side effect initiation.

Modern tendency of orthopedics lies in chondroprotection, namely protection of joint against destruction and wear trough medical correction of cartilage regeneration and therapeutic normalization of interactions between the components of the joint synovial medium. The development of polyfunctional medicines compatible with human organism, *i.e.* lubricating liquids, has become true. Injection thereof into the joint can solve a complex of the following problems: restoration of normal lubrication of movably conjugated cartilages, suppression of inflammatory processes, revival of synovial membrane, regeneration of damaged areas of cartilage tribosurface [3]. The analysis of the problem of chondroprotection and experimental search for biocompatible synovial substitutes has brought us to a conclusion on reasonability of using blood serum as a lubricating fluid for joints [3] [4].

Transfusal chondroprotection, intra-articular therapy of joints by blood (own or donor's of identical group) serum, has formed a new direction of transfusal-infusal therapy. The practice of OA treatment by this method has proved that it is expedient to modify blood serum by drugs of the target action. This modification can be done most safely in patient's organism. A necessary drug is selected on the base of OA etiopathogenesis, anamnesis and analysis of a list of drugs most effective for the patient. This drug is introduced in the organism by peroral, intramuscular or intravenous methods depending on the dosage form. Biosynthesis of a new transport medicinal complex is performed in the period when the maximal saturation of blood by the active components of the drug occurs. The composition of the complex is individual, since blood serum has been originally only inherent to a patient quantity of protein molecules that binds the active substance of the drug [5]. Patient's organism finds the concentration of the drug forming medicinal complex with serum in a natural way.

2. Materials and Methods

The comparative evaluation of biochemical and protein composition of synovia and blood serum was fulfilled with the help of a standard laboratory biochemical analysis and electrophoresis following Laemmli's method (sodium dodecyl sulfate polyacrylamide gel electrophoresis) [6]. Structural changes in the liquids under study were registered by the method of electret-thermal analysis (is used in physics of dielectrics) using the procedure from [7]. Lubricity was estimated by on the original pendulum tribometer. The static magnetic field (intensity ~1 kA/m) was generated in the bearing of the pendulum so as to simulate the biophysical field of a synovial joint [8].

Clinical tests with participation of volunteers were conducted by observing ethical norms and regulations specified at the 18th World Medical Assembly, Helsinki (1964) and adjusted to the modern problems of medical experiments at 41th World Medical Assembly, Hong Kong (1989).

Criteria of the patient choice were the following:

1) patients aged from 40 till 65 years,
2) 2nd or 3rd OA stage according to I. Kellgren,
3) intra-articular usage of chondroprotectors is excluded for 6 months before test,
4) intra-articular injections of glucocorticosteroids is excluded for 2 months before test,

5) informed patient's consent.

Criteria of exclusion:

1) uncontrolled somatic diseases,

2) contra-indications for joint punctures,

3) psychic diseases in anamnesis.

The groups of patients with knee joints affected by OA (experimental (16 persons, 18 joints) and control (14 persons) ones) were formed after addressing the doctor with a persistent request of above-described therapeutics of joints. Etiopathogenetic OA relationship with the reason that caused or aggravated the disease was determined based on the history, results of synovial and blood analysis.

Most of the patients of the experimental group were informed on inevitability of endoprosthetics of the affected joints, and they have given their consent. The treatment was carried out as follows. A peroral or intramuscular drug of a special purpose was prescribed to the patients. When maximum concentration of the drug was reached in the bloodstream, a blood specimen of 30 ml was taken from the elbow vein. The syringe was incubated at temperature 18˚C - 19˚C in aseptic conditions for 5 - 6 hours in vertical position. The serum (5 - 7 ml) containing a complex drug with proteins, a clot of fibrin and blood cell precipitation was formed as a result of fractionation. The serum was taken out by second sterile syringe. Its needle was changed for new sterile needle before injection to the joint. The injections of the modified serum to the knee joints were carried out thrice with intervals 5 - 7 days. The volume of the first injection is 4 - 5 ml, second and third 5 - 7 ml. The patients of the experimental group had no any other treatment of the joints.

The international rating system HSS for knee joints [9] was used for evaluation of specific symptoms and limitation degree of joint functions. The functioning of a healthy joint corresponds to 100 points according to this scale. The functions of knee joints were evaluated prior to and after every three injections, and 4 - 6 months after termination of the treatment. The significance of therapeutic effect was controlled by a meta-analysis described in Cochrane's systematic survey [10] devoted to examination of the proofs on the effectiveness of viscosupplemental therapy of knee joint OA.

Therapeutic safety of new drugs was estimated clinically, and by dynamics of laboratory results.

3. Results and Discussion

The comparison of biochemical and protein compositions of synovial and blood serum has confirmed the identity of molecular and weight distribution their protein fractions over a range 20 - 200 kDa as well the absence of hyaluronic acid in serum and fibrin in e healthy synovial. The structural similarity of supermolecular protein-polysaccharide formations of synovia and serum was determined by the electret-thermal analysis. The liquid samples were heated at a fixed rate and a current was registered (nA) induced by thermal breaking of inter- and intramolecular bonds in protein formations [11]. It was discovered with the help of a pendulum tribometer that serum and synovia demonstrate practically identical lubricity and record-low friction coefficient of the order of 0.01 that exponentially lowers during 30 - 40 min under the effect of a constant magnetic field [12].

Clinical observations of the patients in both groups before treatment have shown the following results.

Joint fractures, meniscectomy and (or) cruciform ligaments plastics were observed in the patients suffering from posttraumatic OA. The cells and biochemical synovial composition within the normal range. Single polynuclear cells were found by a microscopic examination of synovial smears. The results of integrated blood analysis were within the normal range or discovered weakly positive C-reactive protein.

The duration of disease of the patients with rheumatoid OA exceeded 7 years. Glucocorticosteroid therapy has given a positive effect. The concentration of neutrophilic leucocytes in synovial smears varied within 55% - 87% with the presence ragocytes. The total concentration of protein increased by 53 g/l, mainly at the expense of γ-globulines, fibrin and C-reactive protein. The results of blood analysis show the increasing concentration of leucocytes, lymphocytes, rise of the rate of erythrocyte sedimentation (RES). Positive C-reactive protein and rheumatoid factor, disproteinaemia in the form of increasing fractions of α_2- and γ-globulins in the biochemical analysis, also the detection of histocompatibility antigens HLA DR4, Dw4 and DQ7 have supported the diagnosis.

Three of the patients have suffered from bacterial arthritis more than 5 years ago at the background of initial knee joint OA as a complication of the kenalog intraarticular injections. Later on these patients have felt acute pain syndrome with synovitis 3 - 4 times a year. In condition of acute pain the volume of synovia in joints

reached 80 ml, its viscosity fell appreciably, cytosis exceeded 5×10^{10} l^{-1} due to neutrophiles. *St. epidermidis* was separated from a joint of one of the patients in the process of the last acute condition. The inflammatory changes in synovia appeared with viscosity reduction, turbidity, presence of fibrin filaments, increase of neutrophilic leucocytes till 71%, lowering of glucose concentration, rise of lactic acid. Blood analysis under the acute conditions has displayed the increase of neutrophilic leucocytes concentration, RES acceleration, sharply positive C-reactive protein. Nonspecific moderate expressed inflammatory changes were revealed in synovia from diseased joints 1 week after disappearance of skin display of herpetic infection and 2 weeks after recovery from respiratory infections.

For a target modification of serum single doses of drugs traditionally used for treatment of above-cited illnesses were applied. In peroral or intramuscular forms were prescribed doxycyclin, arbidol, cycloferon, polcortolon, diclofenac. The time of maximum concentration of the drugs in the bloodstream was defined using instructions for the drugs. So, the peroral 200 mg dose of doxycyclin binds till 93% with blood proteins after 2 hours and its maximum concentration 2.6 mg/l is established in plasma. Doxycyclin is produced not only as antibacterial but also for chondroprotective use owing to suppression of matrix metalloproteinases and synthase of nitrogen oxide.

Maximum concentration of arbidol settles in blood plasma 1.5 hours after giving 100 mg of the drug. Arbidol forms complex compounds with serum albumin hindering thus virus penetration in the joint tissue cells, suppressing fusion of the virus shell with cell membranes.

Cycloferon is a low-molecular interferon inductor having a wide span of biological activity (immunomodulating, antivirus, anti-inflammatory). The blood enriched by cycloferon was sampled 1 - 2 hours after the intramuscular or intravenous 0.25 g drug introduction.

After receiving a minimal single dose of polcortolon (4 mg) its active substance triamcinolone is soaked from the intestinal tract (bioaccessibility 20% - 30%). After 1 - 2 hours, its maximum concentration is formed in the patient's blood. The bonding of triamcinolone with serum proteins (mainly with globulins) averages to 40%.

Diclofenac taken peroraley soaks from the intestine fully. During "first passing" it is metabolizing in the liver. Then, about half of the taken drug merges in the bloodstream. The bonding of diclofenac with serum proteins is 99%. After 2 - 4 hours its maximum concentration in blood is registered.

The serum saturated with doxycyclin was injected in the knee joints of the experimental group with posttraumatic OA and one of the patients having bacterial inflammation (on the base of sensitivity of earlier excreted *St. epidermidis* to doxycyclin). The composition of autoserum and polcortolon was introduced intraarticularly to the patients with rheumatoid OA. Serum of the patients suffered from influenza was modified by arbidol, and acute condition of herpetic infection by cycloferon. Diclofenac was bonded with serum to stop the articular syndrome at acute condition of posttraumatic OA in four patients, and in two patients suffered earlier from bacterial arthritis.

The results of treatment are listed in the **Table 1**.

Table 1. Results of treatment knee joints.

Etiology of OA/number of joints	Average age of patients	Rating of joint function (average point)		
		Before treatment	After 1, 2 and 3 injections	After treatment (months)
		Experimental group		
Traumatic/7	57	55	77/78/89	88 (5)
Rheumatoid/5	63	45	65/74/77	77 (4)
Bacterial/3	52	57	63/83/88	87 (6)
Viral/3	43	55	60/71/77	77 (5)
		Control group		
Traumatic/7	55	58	61/66/78	77 (6)
Rheumatoid/7	61	45	49/57/68	67 (5)

Above presented results correspond to the category of randomized controlled trials: test time exceeded 2 months, there were no patients that discontinued test (not more than 50% are admitted) [10]. Meta-analysis has shown that 95% confidence intervals of difference of the mean therapeutic effect values in the experimental and control groups did not cross zero. This testifies about better effectiveness of the treatment in the experimental group. Heterogeneity of the results was statistically significant. The value of therapeutic effect of the new OA treatment method represented as a weighed difference of the mean values with the confidence interval 95% is 5.01. This is a proof to superiority of the new method over the traditional one.

All patients of the experimental group have felt lowering of pain in joints under loading and its significant alleviation or disappearance during rest, reduction of crunch, joint stiffness, possibility longer painless stay of the leg in a forced position. Any complications or allergic reactions of the patients were not registered during treatment. The dynamics of laboratory analysis results has disclosed a stable tendency towards lowering of pathologic deviations and normalizing of the organism functions. 4 - 6 months after the last injection, function of the joint of all patients in the experimental group remained at the reached level, the dose of inflammatory and analgesic drugs was diminished and prescription of endoprosthetics was rejected. The therapeutic effect in the control group of patients has remained after 5 - 6 months of treatment at the background of previous doses of supporting drugs.

No doubt, the clinical effect of treatment in the experimental group of patients was reached because the drug bonded with serum proteins occurs directly in the diseased joint escaping the metabolically active organs and altered by fibrosis joint capsule. The drug dissociates in the latter from protein and creates a medical effect in synovial joint medium. This allows minimizing the dose of the drug and lowering the risk of unwanted reactions. The preparation rich with proteins, *i.e.*, carriers of biologically active substances, enters with injection the joint cavity instead of pathologically changed synovia containing products of tissue degradation, proinflammatory cytokines, matrix metalloproteinases, etc. Because of tissue trophics, protein, water, and salt exchange in the joint are normalizing. Lubricity of this preparation is considerably higher than of the pathologically changed synovial of diseased joint [13]. This relieves pain syndrome due to improvement of sliding of degenerative changed cartilage. Of course, the mechanisms by which the modified serum exerts positive influence upon OA joints require further research. There is an actual question: whether the *max* concentration of the drug naturally bonded with autoserum proteins is suffice for treating patient's joint? Nevertheless, the expressed positive effect of the new preparations for treatment of OA knee joints can be admitted as determined. A course therapy using preparations on the base of serum should include in recommendations for treatment of OA when the prolonged peroral receiving of analgesics and anti-inflammatory drugs is not effective or contra-indicated.

4. Conclusion

The method of OA treatment by blood serum can be realized in hospitals and clinics in accordance with standard principles of intraarticular injections. Preliminary saturation of serum by a target drug made in patient's organism in a sealed volume and sterile conditions allows minimizing the probability of septic complications, to lower time and material quantity spent on treatment. The initial results of laboratory and clinical research show the expediency of further studying metabolic effects of medicine composition based on blood serum. The necessity of transfusal chondroprotection development with the help of specialists in the field of immunology, virology and microbiology is quite evident. Elaboration of immunomodulating drugs for treating OA, suppressing catabolic processes in joints by means of regulating intercellular and intermolecular pro- and anti-inflammatory interactions is an urgent problem today, whose solution allows improving life quality of patients, to expand its functional possibilities, and to weaken the sharpness of the global problem of joint pathology.

Acknowledgements

Author (Yu. M. Cherniakova) thanks and remembers Dr. Sci., Professor L.S. Pinchuk, which was her scientific mentor and which was died in August 2013.

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