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Clinical Study Report
Study of the Efficacy of Karipain Preparations in Patients of Vertebronrological Profile

A range of medicinal products containing Karipain is represented by three products:

- Karipain, lyophilized powder, 1 g, 10 mL bottle, No. 10
- Karipain Plus, lyophilized powder, 1 g, 10 mL bottle
- Karipain, cream, tube 50 g

The main active substance of Karipain preparations is a proteolytic enzyme monothiolic cysteine endoprotease obtained from the milky juice of papaya (melon tree) fruits which selectively affects the tissues of joints and intervertebral discs, promotes lysis of necrotic and degeneratively altered structures, reparative changes in the tissues of the musculoskeletal system.

The essence and mechanisms of therapeutic influence of papain are inextricably linked with pathogenesis and sanogenesis of degenerative-dystrophic changes in the spine and, first of all, in the intervertebral disc.

The intervertebral disc, located between the bodies of the two vertebrae, performs important biomechanical functions, primarily motor and shock absorbing. The structure of the intervertebral disc is represented by an external fibrous ring consisting of parallel collagen fibers and an internal nucleus pulposus – a proteinglycanpolysaccharide complex with significant hydrophility. The intervertebral disc is connected with adjacent vertebrae bodies with hyaline plates which play a crucial role in nutrition and metabolic processes in the disc. Biochemical substrate of the disc is mainly sulfated glycosaminoglycans, hyaluronic acid, hexosamines.

In the process of dystrophic destruction development, due to various causes and, first of all, excessive mechanical loads, the normal structure of hyaline plates is disturbed, which provide the delivery of nutrients to the intervertebral disc, and there is an uncharacteristic pathological mobility of the vertebral motor segment (VMS) in the horizontal plane leading to the detachment of hyaline cartilage and the difficulty of the diffusion of nutrients from the body of the vertebrae to the disc and vice versa. This in turn leads to disequilibrium of synthesis processes: depolymerization of proteinglycanpolysaccharide complexes, reduction of polysaccharides content and increase of collagen fibrils, activation of proteolytic enzymes, change of hydrostatic properties of the disc with the development of its hyperhydration, and further dehydration. Under favorable biomechanical conditions, the hyperhydration of the disc decreases, the pathological elements in the center of destruction are absorbed by macrophages, the focus is replaced by a vascularized granulation tissue, disk trophicity improves, active fibrotization occurs. The damping function of the disk is preserved, although it is reduced. Under adverse conditions, destruction increases, structural and functional components of the disc are destroyed, pathological process progresses.

The natural result of biochemical changes in the nucleus pulposus is a change in its micro- and macrostructure – the nucleus pulposus loses turgor, disintegrates into separate fragments, and the fibrous ring loses elasticity and thins; in its internal and outer layers there are pockets of destruction, forming cracks and radial ruptures. Through the resulting ruptures, the internal fragments of the disc move outside the fibrous ring. The result of the process described above is development of protrusions characterized by protrusions, stretching the rear pole of the disc while maintaining the integrity of the outer layers of the fibrosis ring; hernia characterized by significant local protrusions of the disc and partial or complete rupture of the fibrosis ring with the release of fragments of the disc through it; Schmorl's nodule characterized by a rupture of the hyaline plate with the release of disc fragments through it into the body of the adjacent vertebrae.

Disc ruptures are the starting factor of autoimmune inflammation, as destructive disk structures, especially the nucleus pulposus, are antigens for the tissues of the spinal canal. The autoimmune inflammatory process leads to edema and scar and adhesion changes in the soft tissues of the vertebral canal, in many cases determining the severity of clinical manifestations.

Due to the fact that the VMS functions as a whole, other components of the vertebral segment are involved in the pathological process following the primary destructive lesion of the intervertebral disc with development of spondyloarthrosis, hypertrophy of ligaments and joint capsules, degenerative stenosis of the spinal canal, segmental instability, muscle atrophies, vascular disorders.

The clinical manifestations of the above degenerative-dystrophic process in the spine are extremely variable – from the virtually absence of symptoms in the early stages of the process and in the period of compensation to expressed persistent pain manifestations and motor disorders in the structure of reflex, radicular and radicular-vascular syndromes.

Conservative therapies currently in use, including medications and non-drug therapy, are in most cases targeted at eliminating clinical manifestations of degenerative-dystrophic process, but not sufficient to affect its pathogenesis and developed structural changes (hernia, stenosis, arthrosis). Surgical interventions in many cases have a rapid clinical effect, but are traumatic and fraught with complications. When analyzing the results of surgical treatment, most authors give a restrained assessment of the remote results: depending on the type of operation, 7 to 45 % of patients have poor treatment results and remain permanently invalidated.

The search for new methods of treatment of degenerative-dystrophic pathology of the spine has been conducted for a long time. One of the methods of treatment is the use of polyenzymatic drugs. The use of polyenzymatic drugs (papain, lekozym) for the treatment of degenerative diseases of the spine began in the 70s of the last century. Various methods of administration of the drug were developed and applied in the area of the affected intervertebral disc – acupuncture intradisc, intramuscular or subcutaneous administration with subsequent galvanization or ultrasound treatment, percutaneous electrophoretic.

Papain, penetrating into tissues, and creating a depot in the area of the affected intervertebral discs, causes an increase in the synthesis of collagen proteins, which leads to moderate scarring of the loose fiber part of the disc, promotes biosynthesis of chondroitine sulfates and restores disc turgor. The disc increases in volume due to the hydration of the connective tissue, becomes more elastic while maintaining its mechanical strength. By acting on hernia protrusion, papain causes its lysis with a decrease in the size of protrusion and a decrease in its pressure on the nerve spine. Physiotherapeutic method of administration of papain drugs has certain advantages over injection method: it is highly effective, has no typical injectable complications (toxic allergic due to a large dose of the drug injected at a time and accumulation of products lysis disk core), painless, is not invasive, does not require highly qualified personnel and complex equipment, as well as hospitalization of the patient (the majority of patients receive outpatient treatment).

In connection with the development of new modern papain drugs, we conducted a study of the preparations Karipain Plus and Karipain cream produced by NPC AS-COM LLC (Moscow, Russia).

The composition of Karipain Plus includes enzymes – papain, lysozyme, bromelain, collagenase, proteinase and a group of excipients. The fundamental difference between Karipain Plus and drugs of the previous generation is the presence in its composition of two enzymes in a certain concentration – collagenase and bromelain.

Bromelain is a group of sulfohydryl proteolytic enzymes obtained from Ananas comosus (pineapple). The main component of bromeline is sulfohydryl proteolytic fraction. Bromelain also contains peroxidase, acid phosphatase, several varieties of protease inhibitors, and organically bound calcium. Bromelain has pronounced decongestant, anti-inflammatory and antibacterial properties, prevents atherosclerosis, accelerates wound healing, and has a beneficial effect on cartilage tissue.

Collagenase is an enzyme obtained from the Kamchatka crab pancreas. Collagenase selectively effects the main components of connective tissue. Viable muscles, granulation tissue and epithelium are not affected by the enzyme. Collagenase is used for the treatment of keloid scars, contractures, scars. It is inserted from a positive pole by electrophoresis.

Current statistics suggest that Karipain Plus is a new highly effective enzymatic agent for the treatment of osteochondrosis and intervertebral hernia, joint hernia contractures, keloid scars of different origin, adhesion processes, arthroso-arthritis of large joints.

The composition of Karipain cream includes papain, glucosamine hydrochloride, hyaluronic acid, a group of excipients.

Glucosamine is an aminosaccharide obtained from the shell of crustaceans. Glucosamine is the most important metabolite of articular cartilage, capable of having chondroprotective and regenerating effect.

Hyaluronic acid is polysaccharide, the most important component of articular fluid. It suppresses the degeneration of articular cartilage, normalizes the properties of articular fluid, reduces the perception of pain.

Having this composition, Karipain cream can be successfully applied not only in discopatheis, but also in degenerative-dystrophic changes in the articular apparatus.

The aim of the study is to study the therapeutic possibilities, efficacy and safety of Karipain series for subsequent introduction into treatment and rehabilitation schemes in patients vertebroneurological profile.

Materials and Methods of Study

The study was conducted in a group of patients (22 patients) with verified degenerative-dystrophic changes in the spine. Of the patients included in the study, 15 (68.18 %) were female, 7 (31.82 %) were male. The average age of patients in the group was 44.3 years.

Criteria for selection of patients in the study group:

– Presence of discopathies (protrusions, hernia) according to MRI study

– Presence of other pronounced degenerative-dystrophic changes in the spine (deformative changes, spondyloarthrosis, spondylosis, degenerative stenosis of the spinal canal, scar and adhesion changes) according to MRI and X-ray studies

– Presence of clinical neurological symptoms represented by pain, myodystonic, motor, sensory and other disorders.

Clinical syndromology in the group of patients was presented:

- Lumbalgia, lumboishialgia: in 7 patients
- Cervicalgia, cervicobrachyalgia: in 2 patients
- Combination of cervicobrachyalgia and lumboshyalgia: in 2 patients
- Root compression L_5: in 2 patients
- Root syndrome S_1: in 3 patients
- Combined root syndrome L_5 and S_1: in 2 patients
- Myelopathy, myeloischemia: in 4 patients.

Structural degenerative-dystrophic changes in the spine were presented: protrusions of intervertebral discs at the lumbar level in 2 VMS in 2 patients, lumbar protrusions in 3 patients, cervical potrusions in 2 patients, disc hernia on lumbar level in 1 VM in 7 patients, lumbar disc herniation in 2 VMS in 4 patients, disc herniation at cervical level in 1 patient, combination of protrusions and herniation at lumbar level in 3 patients.

5 patients had hypertrophy of yellow ligaments with stenosis of the spinal canal, 8 patients – deforming spondylosis. In 4 patients, MRI data indicated possible scars and adhesions in the area of hernia propulsion.

Karipain Plus was introduced by the method of electrophoresis, Karipain cream – by the method of phonophoresis.

Electrophoresis Technique

Karipain Plus, 1 bottle, was diluted with 10 ml of saline just before the procedure. It was applied to the filter paper placed on the electrode of the positive pole which was applied to the skin in the projection of protrusion (hernia) of the intervertebral disc. A 1 % solution of nicotinic acid was applied to the electrode of the negative pole and placed it in the projection zone of pain on the limb. Current up to 10 mA, exposure time 15–20 min.

Phonophoresis Method

5 g of Karipain cream were applied to the projection area of the disc protrusion (hernia) immediately after the procedure of electrophoresis with Karipain Plus. The zone was treated with ultrasound at frequency of 880 kHz in a continuous mode, with a power of 0.6 W/cm^2, exposure time of 5 minutes per zone.

To neutralize the masking of the analgesic activity of Karipain during the course of therapy indication of analgesics, corticosteroids, NSAIDs were avoided. Other types of medical therapy, as well as massage, manual techniques were carried out in the necessary scope.

The efficacy of Karipain therapy was assessed according to the following criteria:

- Subjective feelings of the patient after the course of treatment with graduation “significant improvement”, “moderate improvement”, “slight improvement”, “lack of dynamics”, “deterioration”
- Dynamics of visual analogue scale (VAS) of pain

– Objective data of clinical study: evaluation of muscle strength, dynamics of neurological status indicators, estimation of spine mobility (Otto's, Tomayer's, Schober's tests)
– Dynamics of MRI data: research.

Study Results

12 patients received Karipain Plus with electrophoresis method. Of these, 8 patients took a course of therapy in the form of 20 procedures, 3 patients took 2 courses of therapy in the form of 30 and 20 procedures with an interval between treatment courses during a month. One patient withdrew from the study after 6th procedure due to the developed allergic reaction to the form of urticaria and did not complete the course of treatment. Electrophoresis of the drug Karipain Plus was mainly carried out in young and middle-aged patients with a predominance of degenerative-dystrophic changes in intervertebral discs (protrusion, hernia) and less pronounced changes (according to radiography and MRI - studies) in other VMS structures.

In 10 patients of predominantly older age group, in whom discopathy was combined with pronounced degenerative-dystrophic and deformative changes in VMS (spondyloarthrosis, deforming spondylosis, degenerative stenosis of the spinal canal) electrophoresis with Karipain Plus was combined with phonophoresis with Karipain cream. All 10 patients took a course of 20 electrophoresis and phonophoresis sessions.

After the course of therapy with Karipain drugs, patients evaluated the results of treatment as: "significant improvement" – 3 patients, "moderate improvement" – 11, "slight improvement" – 4, "lack of dynamics" – 4 patients, "deterioration" – no.

According to VAS data, the average value in the group of examined persons before the beginning of treatment was 6.7 points (out of possible 10). After the treatment in patients receiving electrophoresis with Karipain Plus the average value was 4.5 points, and in patients receiving electrophoresis with Karipain Plus in combination with phonophoresis with Karipain cream 4.8 points. It should be noted that the overall dynamics of pain reduction under the influence of therapy is very noticeable, and the slightly worse indicators of VAS in patients receiving Karipain Plus and Karipain cream are explained by significantly more pronounced degenerative-dystrophic changes in VMS with intense and more persistent pain manifestations.

According to the results of vertebroneurological examination (assessment of neurological status, state of muscle tonicity, motor activity, mobility in the spine in diagnostic tests) the improvement of state was observed in 17 (77.27 %) patients and consisted in the reduction of myodystonic manifestations, reflex asymmetries, pareticity of muscles in the zone of innervation of the compromised roots, posture disturbances, increase in the volume of movements, normalization (or trend towards normalization) of the biomechanics of the spine. It should be noted that the rate of compensation development and the depth of compensatory changes were slightly higher in patients receiving electrophoresis with Karipain Plus in combination with phonophoresis Karipain cream in compared to patients receiving only electrophoresis with Karipain Plus.

Control MRI tests were performed in 9 patients in 2 to 5 months from the beginning of treatment. In 2 cases, a significant decrease (lysis) of hernia was revealed. In 2 more cases, there was a decrease in the foci of bone reconstruction in the subchondral areas of the vertebrae bodies and a tendency to normalize the structure of the bone modified before the beginning of treatment.

Assessing the nature and frequency of adverse reactions (complications) of therapy with Karipain, a fairly favorable profile of drug safety should be noted. Only in one case an allergic reaction developed in the form of generalized rash, itching of the skin, fever of the body. The therapy was suspended, an anti-allergic scheme of treatment was carried out, after 7 days an attempt was made to resume treatment with Karipain which led to a recurrence of allergic manifestations. The patient finally withdrew from the study. Local reactions (in 3 cases) were observed more frequently in the form of rash in the electrode setting which, however, did not lead to a change in the treatment regimen. There were no other complications (side effects) of therapy.

Conclusions

1. Karipain is a highly effective treatment and rehabilitation agent that promotes reparative recovery processes in the vertebral motor segment in discopathy (hernia, protrusions) and other variants of degenerative-dystrophic pathology.
2. The efficacy of Karipain preparations was confirmed by the results of clinical examination and data of magnetic resonance tomography in 17 out of 22 patients with disocopathies, degenerative-dystrophic changes in VMS and vertebroneurological symptoms, accounting for 77.27 % of the study group.

3. On the basis of theoretical substantiation and clinical experience, an optimal therapeutic scheme has been developed, including combined application of electrophoresis with Karipain Plus and phonophoresis Karipain cream.
4. The products of Karipain preparations can be recommended for use in treatment and rehabilitation schemes in patients with vertebroneurological profile with degenerative-dystrophic changes in the spine, discopathies.

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