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EFFICACY AND SAFETY OF COMBINED TREATMENT WITH GUNA MD – LUMBAR AND GUNA – MD ISCHIAL COLLAGEN INJECTIONS IN PATIENTS WITH LUMBAR DISC HERNATION

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ABSTRACT
Collagen is the most abundant protein in the human body. The collagen reticulum (matrix) is widely spread in the intervertebral discs, ligaments, muscles and tendons, these structures are responsible for the mobility and stability of the spinal column. Structural impairments of the extracellular matrix facilitate lumbar disc herniation and collagen injections are a new physiological therapeutic approach.
GUNA MD Lumbar and GUNA MD Ischial are used as paravertebral intramuscular injections in 25 patients with lumbar disc herniation. The treatment is performed as outpatient by special protocol including 10 procedures.
64% of patients have chronic low back pain (more than 6 months duration). According to VAS, intensity of low back pain is 6.6 scores in the treatment's beginning and 1.6 scores ($p < 0.001$) at the end of observation (52% have 0 points).
79% of patients estimate efficacy s very good or good and no side effects are observed.

KEY WORDS: collagen, disc herniation, GUNA.

Low back pain is one of the most frequent complaints in routine neurological practice. It is usually a symptom of structural and degenerative alterations of the tissues surrounding and between the vertebrae and intervertebral discs, intervertebral joints, the ligaments around the vertebral column and the muscles and their tendons. Lumbar disc herniation is the cause of acute pain at waist level in around 8% to 10% of patients with lumbalgia. This percentage, however, increases to up to 40% for chronic pain in the same area (1). The intervertebral discs are cartilaginous structures that guarantee the flexibility of the vertebral column and take the pressure off the spine when walking, jumping, bending over and lifting objects of varying weights. The loadbearing component (matrix) of these cartilaginous structures is made up of collagen. The collagen reticulum forms the basis of the ligaments, muscles and tendons, whilst sheathing and delivering stability to the vertebral column. A collagen network is also found in nerve sheaths and in the soft tissues surrounding the spinal structures (intercellular space, connective tissue). Ageing and other factors cause the collagen network to become loose and break up, consequently weakening the structures it constitutes (2). This decreases the time to the onset of the first pain symptoms at waist level and of the first radiculopathy symptoms secondary to disc herniation. Pain and limited waist movement are the main symptoms of disc herniation. The phospholipase A2 enzyme releases arachidonic

acid from the cell membranes and is the main mediator of neurogenic inflammation and nerve root oedema. The pain is caused by the cytokines in the intervertebral discs (1,5).

Treatment of the acute waist pain (nociceptive or neuropathic) usually includes muscle relaxants, non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, including opiate analgesics, corticosteroids and physiotherapy. Chronic lumbalgia often has a mixed pathogenesis (nociceptive and neuropathic) and treatment therefore requires the addition of anticonvulsants to the background treatment (Gabapentin, Pregabalin) and antidepressant therapy (tricyclic and SNRI).

Therapy with ampoules containing collagen and excipients of natural origin is a new physiological approach intended to improve the quality of life of these patients (4). Unlike all the standard treatment options mentioned above, collagen for injection strengthens and reinforces the cartilaginous structures and, in turn, the intervertebral discs, as well as all structures surrounding the vertebrae – ligaments, tendons and the intercellular space of the connective tissue. Nerve sheaths are also strengthened, which facilitates recovery under compression (3).

The collagen ampoules are administered by injection, in the form of a local subcutaneous or intramuscular or intra-articular or peri-articular injection. The product's excipients carry the collagen to the desired target location. Moreover, the collagen ampoules can also be used in combination with physiotherapy equipment, such as Gunaphoresis, which utilises magnetophoresis and ferromagnetic resonance to permit deeper penetration into the tissues and joints and a high product-absorption rate (4).

The aim of this open-label post-marketing study was to establish the efficacy and tolerability of the local paravertebral or intramuscular administration of collagen ampoules (GUNA MD – Lumbar and GUNA MD – Ischial) in patients with lumbar disc herniation.

Methods and materials

25 patients were included in the study – 9 women and 16 men, aged 27 to 83 years (mean age 51.36 years) with disc herniations in the lumbar spine, as established through medical neuroimaging methods (computed tomography or MRI). In 6 cases, the disc herniation was at L4-L5, in 5 cases it was at L5-S1 and in 14 cases disc herniation was observed in two or more points (from L2-3 to L5-S1). The duration of the treatment was as follows: up to 1 month in 4 patients (16%); up to 6 months in 5 patients (20%) and over 6 months in 16 patients (64%). Some patients had had chronic relapsing pain for more than 10 years. The study was conducted according to a dedicated protocol, once subjects had signed an informed consent form. Duration of the disease, administration of previous medicinal and/or physical therapy (discontinued at least 72 hours before the treatment with collagen ampoules), pain intensity (using a ten-point visual analogue scale [VAS]), presence of growth phenomena, vertebral syndrome, and finger to floor distance were recorded.

The collagen ampoules were administered as monotherapy, locally, paravertebrally in the lumbar region at the point of maximum pain on palpation, under measured pressure. The administration regimen included a total of 10 single applications, initially on three consequent days, followed by twice-weekly injections for two weeks and one weekly administration for the subsequent three weeks. In all study subjects, therapy was preceded by NSAID treatment of varying duration, combined with a muscle relaxant and/or physiotherapy intervention, without a significant impact on the subjects' main complaints.

Subjective pain symptoms and change in neurological status were assessed at three timepoints: before the first administration and at the seventh and tenth administrations. At the end of the course of treatment, overall efficacy was assessed using a ranking scale with 5 possible outcomes: very good, good, satisfactory, poor and lack of efficacy. The tolerability of the collagen ampoules was evaluated as: very good, good, satisfactory or presence of adverse drug reactions.

Results:

Two participants did not complete the study and dropped out of the study at the 5th and 8th administrations due to lack of efficacy. The full treatment regimen was administered as per the protocol in the remaining 23 patients.

The patients' main subjective complaints were low back pain with or without radiation to the lower limbs. Some of the patients reported "stiffness" and limited movements at the waist or tingling and paraesthesia in either of the lower limbs.

The baseline lumbalgia values, assessed using the VAS, varied from 6 points to 10 points (mean value of 6.6 points). At the 7th visit, the values had dropped to 2.6 points ($p<0.001$), and at the 10^{th} visit they had dropped to 1.6 points ($p<0.001$). For 12 patients (52%), the VAS score was 0 at the end of the study. **(fig. 1).** There was no relationship between initial pain intensity (both spontaneous and induced) and its final assessment at the tenth visit. The improvement in pain syndromes most frequently occurred between the third and the fifth administration of GUNA MD – LUMBAR and GUNA MD – ISCHIAL. In addition to the decrease in pain intensity, regressions in growth phenomena (as assessed using Lasegue, Neri and Bonnet tests), decreases vertebral syndrome and decreases in the finger to floor distance (from 50 – 60 cm to 0 – 10 cm) were also observed.

Figure 1. *Changes in pain assessed by VAS*

The results of the final assessment of treatment efficacy, carried out at the tenth visit are presented in **Figure 2.** In 66% (15) of patients completing the full course of treatment, a very good effect was reported, in terms of both subjective complaints and objective neurological symptoms. Three patients (13%) judged treatment efficacy to be "good"; four (17%) judged it to be "satisfactory" and only 1 patient (4%) judged it to be "poor".

Figure 2. *Final assessment of treatment efficacy*

The tolerability of the collagen ampoules in all 23 patients was very good, with a complete absence of side effects and adverse drug reactions (both local and systemic).

Discussion

Collagen is the most abundant protein in the human body, making up 25% to 30% of our entire protein mass (4). It is contained in muscles, ligaments, bones, joint capsules, serous membranes, skin and the extracellular space, where it is present in the extracellular matrix. The impaired structure of the extracellular collagen matrix and its insufficient recovery leads to slowed functioning of the transport systems (3). The extracellular matrix (ECM) is not a static space between the capillaries and the cells, rather a morphological and functional system, defining a continuous interaction between the vascular endothelium, matrix and

membrane receptors. The connection between neuropeptides, cytokines and hormones (neuro-immuno-endocrine homeostasis) takes place in the ECM. Inappropriate waste product elimination is associated with a build-up of toxic substances, impaired oxygen saturation of the tissues, decreased intake of nutritional substances and decreased hydration. Disc degeneration and annulus fibrosus tears in disc herniation lead to the accumulation of a significant amount of degradative enzymes and chemical irritants between the disks (1, 5). From a biochemical standpoint, disc degeneration is related to a progressive loss of glycoproteins and proteoglycans in the intercellular space. Changes occur in the glycosoaminoglycans and there is an increase in keratin sulfate and a build-up of elastin (1, 2). Collagen matrix impairment is associated with a decrease in the capacity to withhold water molecules and the water content of the nucleus pulposus consequently decreases by approximately 30% (2). The dehydrated disc thins and fibrotic alterations develop within. Similar degenerative alterations also occur in the annulus fibrosus. The collagen fibres swell and the distance between them increases. Fissures form in the lamellar structure and elasticity decreases (1, 5).

Treatment with collagen ampoules is a new physiological approach to the treatment of different types of inflammatory and degenerative musculoskeletal disease and their local administration has a strengthening effect on the collagen structures. The small doses act singularly, altering the physiological conditions within the extracellular matrix. This causes protease activation and the stimulation of cell functions. Apoptotic processes are inhibited, and metabolism is boosted, whilst local inflammation decreases and the collagen tissue structures strengthen (3, 4). Nerve sheaths are also strengthened, thereby facilitating their recovery upon compression. The strengthening of the aforesaid structures leads to a decrease in or resolution of pain symptoms, followed by an improvement in the movement of the corresponding vertebral segment. The stimulation of intercellular space drainage exerted by the collagen and its positive effect on the tone of the capillary wall and cell repair process make the collagen ampoules a decisive factor in reducing inflammation in the soft tissues surrounding the vertebral column.

The treatment of discogenic pain in the lumbar region conducted with two types of collagen ampoules – GUNA MD – LUMBAR and GUNA MD – ISCHIAL is technically easy, efficacious and safe. This type of therapy can find broad application in routine neurological practice, particularly in patients with chronic low back pain. The excellent tolerability and lack of adverse drug reactions make the use of these ampoules suitable even in patients with concomitant conditions (ulcerative disease, poorly-controlled hypertension, severe diabetes mellitus, kidney impairment etc.), where the use of NSAIDs and corticosteroids is limited or contraindicated. In such cases, the collagen ampoules can be considered as the treatment of election.

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