Early warning system inflammation

background

An inflammation is basically essential for healing processes, as it tries in the sense of an "early warning system" to eliminate harmful stimuli such as bacteria or foreign substances or to create the conditions for repair operations. For example, it is the natural concomitant of injuries to remove clotted blood and injured or dead tissue by scavenger cells of the immune system. It is caused by so-called inflammatory mediators such as prostaglandin, histamine, bradykinin, etc., which lead to increased permeability of the local blood vessels and thus facilitate the escape of blood plasma and the migration of leukocytes. The result is a swelling of the tissue or an edema. Cytokines such as IL-6 IL-1ß and TNF-alpha are also involved in the inflammatory, since they eg

As important as inflammation and edema are for the healing process, they can be so painful or even harmful to the person affected. The messenger substances prostaglandin, histamine, bradykinin and serotonin also reduce the stimulus threshold at the end branching of sensory nerve fibers (C fibers), ie the sensation of pain increases significantly. As a result of edema, subsequent compression of the blood vessels may occur, which hampers the subsequent healing process. Edema should therefore be kept as low as possible.

frequency

Typical inflammatory examples are injuries or active procedures such as surgery. But also mechanical joint irritation or rheumatism react with an inflammatory event. Thus, over 16.7 million operations per year are performed in German hospitals [1] . In addition, there are 1.9 million outpatient procedures annually [2] . The number of annual sports accidents that require medical care in Germany is 1.5 million [3] - which

corresponds to only 20% of all accidents, so that one can expect 7.5 million injuries per year.

Inflammation musculoskeletal system

Inflammation and associated pain not only occur in injuries but are symptomatic for (rheumatoid) arthritis, for example. Behind this is a malfunction of the immune system, in that T cells are directed against their own tissue, in this case against the inner lining of the joint - with the consequence of destruction of the joint. Involved here are macrophages formed by proinflammatory cytokines (TNF-alpha, IL-1) and of course IgM and IgG antibodies that target collagen and proteoglycans of connective tissue [4] . The prevalence (frequency) of a rheumatoid arthritis (eg chronic polyarthritis of the hands) is about 1%, which means that in Germany about 800 000 people are affected [5] .

The conditions for osteoarthritis are completely different. This is about a joint wear, which can be caused for example by an axial

misalignment. Knots on the wrist joints (Heberden's arthrosis), the finger joints (Bouchard's arthrosis) or pain in the base of the thumb / saddle (Rhizarthrosis), usually have a genetic cause and have no other pain-related movement restriction, no further disease relevance.

It should be noted, however, that for about 85% of all pain in the musculoskeletal system (large joints, tendonitis, intervertebral discs), there is no underlying joint wear and tear, but usually a contraction of muscles and ligaments of the joints. The consequent bruising of sensitive nerves results in a painful restriction of movement. The result is a nutritional disturbance of the articular cartilage, since only sufficient movement in the joint sufficient oxygen and nutrients in the form of a "synovial fluid" can be supplied.

"Osteoarthritis" is one of the most common diseases worldwide. The frequency (prevalence), however, there are different data. They vary between 33% (radiologically diagnosed) in adults [6] and 8.9% of clinically relevant knee,

hand and hip arthrosis [7] . Misunderstandings are also preprogrammed because arthrosis in English is called "osteoarthritis" and thus falsely suggests that it is a basically inflammatory disease. However, this is usually not the cause of the disease, but the possible consequence of a degraded cartilage ("mechanical bone friction").

Conventional therapies

While rheumatoid arthritis is treated with cortisone, chemotherapeutic agents ("methotrexate") or biologics ("inhibition of pro-inflammatory cytokines"), arthritis of the large joints is the standard recommendation for artificial joint replacement. Thus, 200,000 artificial hip joints, 150,000 artificial knee joints and 12,000 artificial shoulder joints are implanted annually in Germany [8] . Accordingly, Germany is in second place in the frequency of hip replacement in the OECD countries after Switzerland [9] .

PEMF Anti-Inflammation Invitro

The anti-inflammatory effect of PEMF has been known for a long time. For example, in a recent cell culture study it was confirmed that PEMF (4 mT, 5 Hz) leads to a down-regulation of the tumor necrosis factor (TNF-alpha) [10] . This is of great importance because TNF-alpha and IL-1 activate the transcription factor kappa B, which in turn regulates the activation of pro-inflammatory genes. Also, the finding that the various adenosine receptors (A_1 , A_{2A} , A_{2B} , A_3), all of which either reduce the production of cAMP (A_1 and A_3) or increase it ($A_{2A}$and A_{2B}) [11]and down-regulate the pro-inflammatory cytokines TNF-alpha as well as IL-ß via the adenosine receptors A_{2A} and A_3 after PEMF application [12] , [13] , [14] reveals a complex but relatively unambiguous explanatory model.

Besonders eindrücklich kann man das z.B. bei bovinen Zellkulturen sehen, die eine 5-fach höhere Proliferationspotenz besitzen als humane Zellen. PEMF senkten hier die IL-1alpha Aktivität um 10 – 70 % bzw. bei humanen Zellen um 10 – 80 % [15]. Werden z.B. mononukleare Blutzellen von Morbus-

Crohn-Patienten („entzündliche Darmerkrankung“) einem PEMF (45 mT, 50 Hz) ausgesetzt, nimmt das pro-entzündliche IFN-gamma ab und erhöhte sich das anti-inflammatorische IL-10 [16].

In another study with human tendon cells (taken from the semitendinosus and gracilis muscle), PEMF stimulated tendon cell proliferation. At the same time, the anti-inflammatory cytokines decreased significantly after 4 and 12 hours compared to the non-treated cells, without affecting the pro-inflammatory cytokines [17] .

PEMF in rheumatoid arthritis

In animal experiments, for example, the injection of heat-treated tubercle bacteria into the posterior leg of rats produced artificial arthritis (increase in the inflammatory mediator prostate glandin / joint edema). A 90-minute PEMF application (4 µT, 5 Hz, daily) resulted in remission of the symptoms [18] .

In another animal experiment, carrageenan caused artificial inflammation and edema. After a three-hour magnetic field treatment, the symptoms weakened considerably [19] .

A similar result is obtained by a daily (10 mT, 5 Hz) PEMF treatment in rats (artificially caused rheumatoid arthritis). The study bases its analysis on changes in acute phase proteins and macroglobulin and their influence on chronic inflammation [20] .

In another animal study in rats, in which rheumatoid arthritis was provoked by heat-treated tubercle bacteria, PEMF (4 µT, 5 Hz, 90 min, days 14-42 after artificial production of rheumatoid arthritis) resulted in a decrease in edema volume as well as lysosomal Enzyme both in blood serum and in the liver. Likewise, the MPO concentration in the bone decreased [21] . Since this has already been observed in a similar study [22] , the author concludes that the anti-inflammatory potential of PEMF is related to both enzymes.

Explanation:

In joint erosion (erosive synovitis), which is based on rheumatoid arthritis (RA), apparently lysosomal enzymes play a major role [23] . Myeloperoxidase (MPO) is also an important indicator of activity for RA and its associated chronic inflammation [24] .

In a human study (randomized, double-blind) [25] , 31 women were divided into two groups for PEMF intensity (200 μT and 400 μT). The test criterion was the change in pain intensity on the basis of the test forms MPQ and VAS. Although there was no significant but significant pain reduction in both groups compared to placebo.

A similar result was found in a study of 50 rheumatoid patients. Although pain in PEMF decreased in 82% of patients, the pain was only moderate [26] . It is noteworthy, however, that the swelling reduced and also the morning stiffness of the fingers.

In a comparative study (laser versus PEMF), treatment effects on the function of hand mobility (basal joints) and the subjective quality of life were investigated [27] . The setting parameters of 3 mT / 5 Hz were gradually increased to 7.5 mT / 23 Hz. As a result, the laser was superior to the PEMF in pain. With regard to decrease in swelling and quality of life, laser and PEMF were equally effective.

PEMF for knee and hip osteoarthritis

In a randomized, double-blind pilot study, 27 osteoarthritis patients (mainly knee arthrosis) received a total of 18 half-hour PEMF treatments (1 - 2 mT, <30 KHz, square pulse) within one month. A total of 6 symptom parameters were examined. Result: Compared with the placebo treatment, which showed a 2 - 18% improvement in symptom parameters (including pain reduction and improvement of functionality), it was 23 - 61% under PEMF [28] .

Definitions:

The VAS Pain Scale ("Visual Analog Scale") measures the patient's subjective pain severity. This crosses the perceived intensity of pain on a numerical scale of 1 - 10 or on a visual scale of 1 - 100 mm. The error rate when filling out is very low at 4 - 11%. Since it is higher in elderly or desoritized patients, a verbal rating scale is usually preferred [29] .

The WOMAC Index (Western Ontario and McMaster Universities Osteoarthritis Index) [30] aims to assess the effects of osteoarthritis on affected patients. For this a total of 24 questions on pain (5 questions), stiffness (2 questions) as well as joint functions (17 questions) are asked. The WOMAC Score is the most widely used Patient Reported Out (PRO) instrument in clinical trials and is available in over 65 languages

A randomized, double-blind study with 34 knee osteoarthritis patients: The assessment according to the pain scale VAS had to be at least ≥ 4 in the entrance examination. The patients also had to have at least 2 hours of mobility / daily and were also not allowed to have knee surgery or cortisone therapy

before. Compared to placebo, the pain score after VAS decreased by 50 +/- 11% after one day and continued after 42 days until the end of treatment. Overall, the pain reduction with PEMF was three times as high as with placebo [31] .

In a study of 28 elderly patients aged 60-83 years suffering from bilateral knee arthrosis, only the right knee was treated for a period of 6 weeks (3 x weekly 30 minutes), ie, the left knee served as a control. Result: In the VAS, the pain in PEMF decreased by 49.8 +/- 2.03 versus 11 +/- in the other leg. The WOMAC test, which also examined stiffness and joint function, also showed a significant improvement [32] .

In a Cochrane review, a systematic review that is internationally recognized as the ultimate quality standard in evidence-based medicine, 9 studies involving a total of 636 osteoarthritis patients were included. Here, the PEMF treatment achieved a pain reduction of 15.1 points on a pain scale of 100 compared to placebo. However, no significant effects on joint function were observed [33] .

In a randomized, double-blind, 66-patient study (radiologically confirmed knee osteoarthritis), there was a significant reduction in pain (VAS and WOMAC scales) compared to placebo under 1-monotherapy PEMF treatment. Also, the pain tolerance improved with regard to PPT, ie tenderness. It is also astonishing that 26% of the PEMF group stopped taking NSAID analgesics [34] .

In another review [35] that analyzed and evaluated 36 randomized, double-blind studies involving a total of 2,443 osteoarthritis patients, 33 studies achieved three or more of the five required methodological criteria. The patients had an average age of 65.1 years and the mean baseline VAS analog scale was 62.9 mm. Result: After 4 weeks, additional short-term pain reduction could not be recorded by additional methods such as manual acupuncture, static magnetic fields and ultrasound. In contrast, a slight pain reduction of 6.9 mm was achieved with PEMF (different intensities / frequencies 10-200 Hz).

A review from 2009 analyzed the study situation on cell cultures, animal and human studies. Overall, the authors conclude that PEMF can treat pain, inflammation and joint dysfunction in both osteoarthritis and rheumatoid arthritis. Arthrosis not only relieves pain and reduces inflammation, but also protects the cartilage and bone [36] .

PEMF in tendopathy and tendinitis

Unlike tendinopathy, which is a degenerative change of the tendons, the name "tendinitis" suggests a primary inflammatory disease. Since inflammatory parameters obviously do not play a major role, it is hardly surprising that the causes of the causes are still largely obscure. Operational inspections even seem to refute an inflammatory process [37] . It therefore makes sense to treat the pain syndromes tennis elbow, golfer's arm, shoulder-arm syndrome and fibromyalgia (generalized tendomyopathy) in a separate document.

Excursus wound healing:

Wound healing can be divided into the four phases of inflammation, proliferation, re-epithelialization and tissue remodeling. In almost all phases so-called proteases play a key role. In the inflammatory phase, these enzymes (eg metalloproteinases MMPs, serine proteases such as elastin) cleave the proteins of the damaged extracellular matrix (ie collagen, elastin, proteoglycans, etc.) to allow new tissue to form. In the proliferative phase they improve the capillarization and in the remodeling they help to a good epidermal scarring.

It becomes dangerous if too much protease is formed. Because then there is an undesirable degradation of newly formed tissue and other proteins (eg growth factors). This prolongs the inflammatory process and destroys normal tissue [38] . Of course, certain pro-inflammatory cytokines (TNF-alpha) are also suitable as an indicator of poor wound healing. In any case, it has been shown in animal experiments as well as in clinical studies that there is increased protease activity in wounds without healing progress [39] , [40] . Otherwise, of course, proteases belong to the essential wound healing process.

The keratinocytes often mentioned in studies are cells of the epidermis (epidermis), which consists of 90% keratinocytes.

PEMF wound healing studies

From previous studies it is known that PEMF promote the proliferation, ie the rapid growth of keratinocytes [41] . In a cell culture study, it was possible to demonstrate that, compared to a control culture, the cell-free area under PEMF decreased in a time-dependent manner. Likewise, a modulation of metalloproteinases, cytokines and keratinocytes was shown [42] .

Too long or overshooting an inflammatory phase leads to hypertrophic scars, keloids or to chronic wounds and ulcers. In a review, the important anti-inflammatory effects of PEMF in wound healing or in poorly healing wounds are worked out [43] .

Another review refers to the increasing prevalence, ie the incidence of chronic ulcers, which is about 0.3% of the population. As a result, three mechanisms of action of PEMF are emphasized: 1. An anti-inflammatory (anti-inflammatory) effect in that the healing process by the modulation of cytokines is a successful change from a pro-inflammatory to an anti-inflammatory state. 2. A vascular reconstruction process that results from endothelial cell proliferation and the production of FGF-2 growth factor (fibroblast growth factor). 3. A re-epithalation effect by stimulating collagen formation [44] .

PEMF studies wound healing post-op

Es ist bekannt, dass ein Jahr nach einer Totalendoprothese des Knies (TEP) ein erheblicher Prozentsatz der Patienten sich nicht vollständig erholt und weiterhin Schmerzen hat. In einer Studie mit 33 Patienten wurden diese randomisiert und einer Kontroll- und PEMF-Gruppe zugeteilt (also keine Placebostudie). PEMF (1,5 mT / 75 Hz) wurde dabei postoperativ 4 Stunden täglich über 60 Tage eingesetzt (tragbares, batteriebetriebenes Gerät).

Result: As early as 4 weeks after the TEP, pain, knee swelling and functional score were significantly below the control group. Even after a 6-month follow-up, the pain was still significantly lower. Three years after surgery, severe pain and isolated mobility problems were reported by a significantly smaller group of PEMF patients. The authors suggest that early inflammation reduction was crucial for the favorable outcome at follow-up [45] .

In one study, the question was raised to what extent PEMF treatment in the case of an implantable implant can improve the treatment outcome. For this purpose, 11 patients received four tipped implants in the upper and lower jaw and underwent immediate stress rehabilitation. Each patient received two special PEMF systems, one for each cheek. In the sense of a randomization, the systems, one of which was a placebo device, were then changed. Result: In most patients there was no difference between PEMF and placebo 48 hours after surgery for swelling and pain. Although the study has some design deficits,

it should be noted that it was not possible to influence the surgical consequences [46] .

In a randomized, placebo-controlled, double-blind study, 24 patients underwent PEMF treatment following surgical breast reduction due to macromastia (above-normal breast enlargement). Results: Only one hour after PEMF, the average pain scores (measured with VAS) dropped by 57% compared to placebo and 300% after 5 hours - which continued for 48 hours. In addition, the need for painkillers (opiates) in the verum group decreased 2.2-fold. In the PEMF group, the average IL-1-beta concentration in wound fluid was 275% lower. There were no changes with respect to TNF-alpha, VEGF and FGF-2 [47] .

Study on Breast Reconstruction after Mamma-Ca (Procedure: Pedicled TRAM flap plastic / here abdominal intrinsic tissue is used for breast augmentation and also muscle tissue is used without interruption of the blood supply). This surgery is known to be very complex and painful. 32 patients in a randomized, placebo-controlled study: The result: 5 hours after surgery, the

pain score (VAS) was 2-fold higher in the placebo group and 4-times higher in the 72-hour group than in the PEMF group, which also reduces painkillers in the placebo group doubled and the mean interleukin-1β concentration in wound exudate was even 5-fold higher. The authors conclude that PEMF improves the speed and quality of wound healing after surgery [48] .

Also of interest is a randomized double-blind study on wound treatment after surgical esthetic breast augmentation. 42 healthy women were included in the three groups a) bilateral PEMF treatment, b) bilateral placebo treatment, and c) one breast with PEMF and one breast with placebo treatment. Result: On the basis of a VAS scoring, the pain in the PEMF group decreased by almost the factor 3 compared to placebo after the 3rd postoperative day and remained at this level until the 7th day. Correspondingly, the use of painkillers decreased threefold [49] .

A special type of wound healing requires chilblains / frostbite, which originate at high altitudes (Plateau Frostbites PF). Thus,

the combination of cold and hypoxia (oxygen depletion) seems to cause greater tissue damage than cold alone, which is apparently related to differences in microcirculation and histopathological changes in the various tissue layers [50] .

In a PEMF study, 69 rats in a randomized study design were divided into three groups: healthy animals, animals with partial frostbite (PTPF) on the back and those whose PTPF were treated with PEMF daily. Result: In the PTPF-PEMF group, microcirculation recovered and wound healing improved 25% faster than in the PTPF rats. Histopathological examinations revealed an accelerated growth of various deeper tissue layers, which is related to the depth effect of magnetic fields [51] .

In einer weiteren randomisierten, doppelblinden und placebokontrollierten PEMF-Studie mit 72 Frauen, wurde die mögliche Schmerzreduzierung, der Analgetika-Verbrauch sowie die Wundheilung nach einer Sektio (Kaiserschnitt) untersucht. Die Patientinnen wurden hierfür in zwei Gruppen (Placebo- und Verum) zu jeweils 36 Personen geteilt. Die Befragung erfolgte

anhand der VAS-Skala 2, 4, 6, 12 und 24 Stunden sowie 2, 4 und 7 Tage nach dem Eingriff. Ergebnis: In der aktiven PEMF-Gruppe war der postoperative Schmerz zu allen gemessenen Zeiten signifikant schwächer als bei Placebo.

Significantly fewer women (36% vs. 72%) reported severe pain within 24 hours of the section. This was also reflected in the analgesic consumption, which was 2.1 times lower in the PEMF group. After seven days, the wound healing process in the PEMF-treated patients had progressed significantly better, ie no exudates (inflammatory wound drains), erythema (increased local perfusion of the skin tissue, eg due to inflammation) or edema were detected. Also, high patient satisfaction was reported [52] .

Conclusion

By inhibiting inflammation, removing edema and improving microcirculation, PEMF significantly reduces pain in advanced arthrosis and postoperative healing, whether after endoprosthetic

implantation, esthetic breast surgery or general postoperative wound treatment. Rheumatoid arthritis is also alleviated by PEMF (pain, swelling, stiffness), although here the results in terms of pain symptoms are rather modest.

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