NOVEL TREATMENT OF OSTEOARTHRITIS

THERMALLY ASSISTED ELECTRICAL STIMULATION REDUCES INFLAMMATION AND RESTORES CARTILAGE

BioMagnetic Sciences, LLC
NovoPulse®
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novoPULSE® JOINT WELLNESS SYSTEM™

SUMMARY

NovoPulse® Thermally-Assisted Electrical Stimulation provides fast and lasting pain relief and enhances cartilage rejuvenation.

Osteoarthritis (OA) is a degenerative joint disease that affects the quality of life for millions of patients. The underlying causes of OA are inflammation and excessive apoptosis (programmed death) of chondrocytes. Chondrocytes are cells that primarily function to maintain and promote healthy cartilage.

Two recent major scientific discoveries have revolutionized our understanding of pain management and OA treatment: Electric Field Stimulation (EFS) and Thermal Stimulation (TS). EFS activates the anti-inflammatory "adenosine – A2aR signaling pathway", which downregulates joint inflammation and promotes restoration of the cartilage. TS significantly inhibits chondrocytes apoptosis and promotes anabolic (restorative) activities of the cartilage.

The newly developed NovoPulse® technology leverages the latest medical discoveries, synergistically combining EFS and TS for pain management and treatment of OA. With NovoPulse®, EFS is carried into the treatment zone (cartilage) by a pulsed magnetic field (MF) produced by electromagnetic coils. Inside the cartilage, the pulsed MF is converted into Electric Field pulses that interact with chondrocytes and activate the adenosine – A2aR pathway.

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Osteoarthritis is a degenerative joint disease associated with damage to the articular cartilage and surrounding tissues and characterized by pain, stiffness, and loss of function. Articular cartilage is smooth white tissue that covers the surface of all synovial joints in the human body. Its main function is to facilitate the movement of one bone against another. Cartilage contains specialized cells called chondrocytes that produce an extracellular matrix composed of collagen and proteoglycans.

Cartilage is one of the few tissues in the body that does not have its own nerves or blood supply. Nutrition and waste products release depends upon a diffusion process aided by the pumping action generated by the compression of the cartilage.

In addition to proteins and proteoglycans that constitute the extracellular matrix, the chondrocytes produce enzymes causing degradation of the matrix. Through this process, the chondrocytes maintain a permanent turnover and rejuvenation of the cartilage.

In absence of nerves, communication of cartilage tissue with chondrocytes is provided via an electric field. The cartilage is piezoelectric and, if compressed, generates an electric field. On the other hand, chondrocytes have electrically sensitive receptors (**A2aRs**) that receive the electrical signal and react to it by activating the ***adenosine – A2aR signaling pathway***. This signaling pathway performs anti-inflammatory and restorative functions to ensure the appropriate maintenance and timely repair of cartilage and chondrocytes.

OSTEOARTHRITIS: INFLAMMATION AND EXCESSIVE APOPTOSIS – ROOT CAUSES OF DISEASE.

The chondrocytes and cartilage matrix change with injury and/or advancing age. It is generally accepted that the osteoarthritis process includes alterations in the normal balance between synthesis and degradation of articular cartilage. In young individuals, the chondrocytes keep cartilage tissue healthy and functional. But with advancing age, the chondrocytes become incapable of providing adequate cartilage repair and the process is tipped towards degeneration. In the event of trauma, massive necrosis of chondrocytes and strong acute inflammation can become chronic if not fully resolved in a timely manner.

CHRONIC INFLAMMATION AND EXCESSIVE APOPTOSIS ARE TWO UNDERLYING MUTUALLY SUPPORTIVE CAUSES OF OA. FOR A SUCCESSFUL TREATMENT OF OA BOTH OF THEM MUST BE TARGETED.

The cartilage degeneration in OA is caused by inflammation driven by residential macrophages and infiltrated immune cells that produce pro-inflammatory cytokines IL-1 and TNF-α, creating a persistent state of inflammation. Chronic inflammation modifies the operation of chondrocytes in several significant ways: it blocks mitosis (cell division) of chondrocytes, inhibits production of new cartilage, increases destruction of existing cartilage, and causes 4 to 5-fold increase in chondrocyte **apoptosis** (programmed cell death). Also, inflamed cartilage chondrocytes produce prostaglandin E2, a pain mediator that induces pain in the arthritic joints.

OSTEOARTHRITIS: INFLAMMATION AND EXCESSIVE APOPTOSIS – ROOT CAUSES OF DISEASE.

In healthy cartilage mitosis and apoptosis are balanced and an adequate number of chondrocytes is maintained; the apoptosis is low and apoptotic cells are quickly cleared by macrophages without causing inflammation.

With OA, a **several fold increase of chondrocyte apoptosis** overwhelms the ability of macrophages to clear apoptotic cells and allows the un-cleared cells to go through ***secondary necrosis – a highly pro-inflammatory process that fuels inflammation in OA and perpetuates its chronic character.***

Significantly influenced by inflammation, the natural history of osteoarthritis is manifested by a steady ***decline of cartilage cellularity, degradation of cartilage matrix and surrounding tissues, and chronic pain.***

CURRENT TREATMENTS

Currently available treatment options for osteoarthritis focus on symptom relief, and disease-modifying agents are lacking. The current standard of care includes common analgesics, non-steroidal anti-inflammatory drugs (NSAID), physical therapy and eventually, joint replacement surgery. Conventionally, OA patients are treated by the administration of a NSAID. NSAIDs have demonstrated ability to relieve pain, improve activity level, and in some cases improve function of the arthritic joints. None of them, however, have been proven to reverse the long-term natural history of osteoarthritis. Moreover, they have been associated with deleterious effects on cartilage when used over prolonged periods of time. Cardiovascular and other side effects from NSAIDs cause over 20,000 deaths annually in the United States.

NSAIDS HAVE DEMONSTRATED ABILITY TO RELIEVE PAIN, IMPROVE ACTIVITY LEVEL, AND IN SOME CASES IMPROVE FUNCTION OF THE ARTHRITIC JOINTS. NONE OF THEM, HOWEVER, HAVE BEEN PROVEN TO REVERSE THE LONG-TERM NATURAL HISTORY OF OSTEOARTHRITIS.

The main drawback of NSAIDs treatment is that they only partially disrupt inflammation, do not downregulate all its components, and do not produce the restorative actions as it naturally happens in the body. Also, NSAIDs do not address excessive apoptosis of chondrocytes - the prime cause of inflammation.

A search for new methods of treatments of OA which address both problems – inflammation and excessive apoptosis of chondrocytes was warranted.

NEWLY DISCOVERED NATURAL REGULATOR OF INFLAMMATION: ADENOSINE - A2aR PATHWAY.

Adenosine is a purine nucleoside generated by metabolically stressed or inflamed tissues that is recognized as a major endogenous anti-inflammatory regulator. Under normal conditions, adenosine is continuously released from cells as a product of ATP degradation. Adenosine concentration in extracellular space is controlled by an enzyme called adenosine deaminase (ADA) which breaks it down and keeps the concentration level in high-nanomolar to low-micromolar range. However, during conditions of stress, such as inflammation, levels of extracellular adenosine rise dramatically (up to 200-fold). Adenosine regulates the function of both the innate and adaptive immune systems through targeting virtually every cell type that is involved in orchestrating the immune/inflammatory response. This broad action of **anti-inflammatory adenosine – A2aR signaling pathway** is a result of the predominant expression of A2aRs on all immune and parenchymal cells including chondrocytes. **Adenosine - A2aR pathway** activation inhibits early and late events occurring during an immune response, which include immune cell trafficking and proliferation, pro-inflammatory cytokine production, and cytotoxicity.

In the late stage, additional to limiting inflammation, adenosine - A2aR pathway participates in tissue remodeling and restoration. Developing a means for activation of adenosine - A2aR pathway in chondrocytes would be highly beneficial for treatment of OA.

ELECTRIC FIELD STIMULATION REDUCES INFLAMMATION IN OA.

It is well established that natural wound healing involves generation of endogenous electric field stimulation (EFS). Recently it has been discovered that the endogenous electric field controls the processes of healing and remodeling of bones and cartilages.

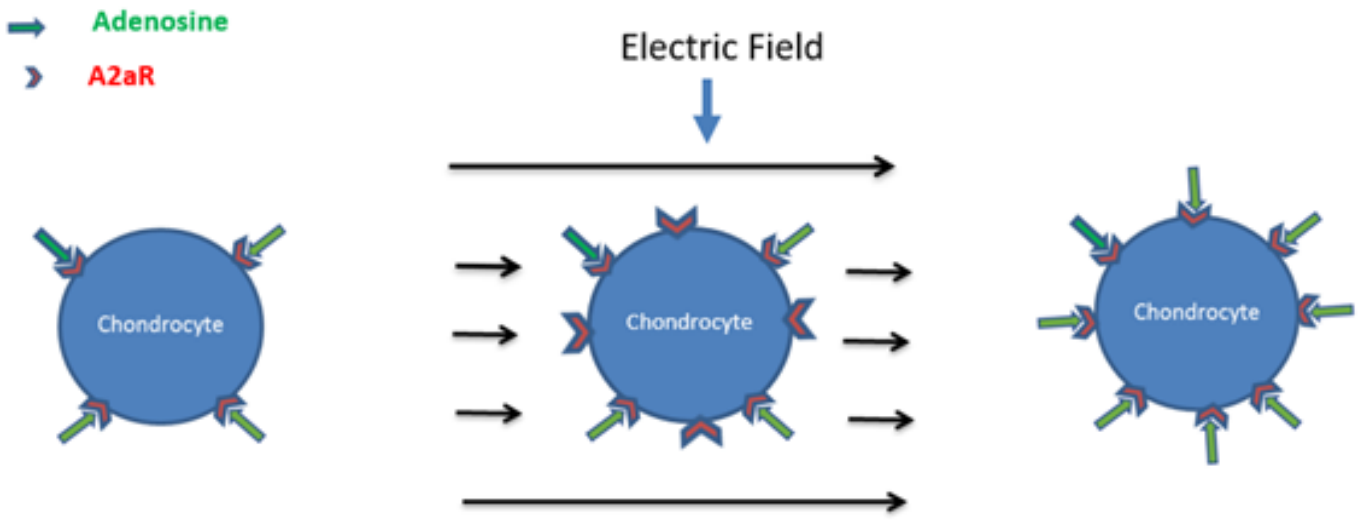
Exogenous EFS has been suggested for treatment of OA. In this case the therapeutic electric field is carried into the treatment zone (cartilage) by a pulsed magnetic field (MF) produced by a set of electromagnetic coils located outside the body. In the treatment zone the pulsed MF converts into EFS pulses. For the EFS to interact with the cell, the individual pulse duration must be greater than the relaxation time of the cell (1μs). After a transient process in the 1st μs, the electric field is pushed out of electrically conductive cytosol (Faraday cage effect) increases about 1000 times to the level of several V/cm and concentrates in the dielectric lipid membrane, where it stays until the end of the pulse. This relatively strong electric field interacts with A2aR imbedded in the membrane causing their translocation to the surface of the membrane, whereby they become available for binding with adenosine and transduction of the **adenosine – A2aR pathway signal** into the cell.

DURING A TREATMENT SESSION, THE ELECTRIC FIELD STIMULATION MORE THAN DOUBLES THE CONCENTRATION OF A2A RECEPTORS ON THE CELL SURFACE AND POTENTIATES THE DOWNSTREAM SIGNAL FOUR-TIMES ABOVE THE BASE LEVEL.

During a treatment session, the electric field stimulation more than

ELECTRIC FIELD STIMULATION REDUCES INFLAMMATION IN OA.

doubles the concentration of A2a Receptors on the cell surface and potentiates the downstream signal four-times above the base level.



Electric Field Stimulation increases number of A2aRs on the cellular membrane

Adenosine – A2aR signaling pathway stimulates anti-inflammatory and anabolic (restorative) activities of chondrocytes; it accelerates natural healing of cartilage and subchondral bones and reduces pain by suppressing production of the pain mediator prostaglandin E2.

Multiple studies have demonstrated effectiveness and safety of pulsed EFS therapy in suppressing inflammation in osteoarthritis.

THERMAL STIMULATION BLOCKS APOPTOSIS OF CHONDROCYTES.

Thermal stimulation of the joint increases blood flow around articular cartilage, promotes diffusion of nutrients and removal of the waste products, and partially reduces pain. The most important aspect of using TS for OA is the generation of so called “heat shock proteins” (HSPs). HSPs play numerous roles in cell function, including modulating protein activity, regulating protein degradation, facilitating protein translocation across organelle membranes, etc. The fundamental biological function of HSPs is to preserve cell survival by maintaining the vital functions of proteins and protecting cells against apoptosis. Notably, improved protein function leads to 4-7 fold increase in chondrocyte metabolism and production of the extracellular cartilage matrix that significantly accelerates repair of cartilage.

AFTER A SESSION OF TS, THE CONCENTRATION OF HSPS STAYS ELEVATED FOR 72 HOURS. THIS POINTS TO THE OPTIMAL REGIMENT OF TREATMENT AT LEAST 3 TIMES PER WEEK, WITH THE BEST RESULTS, DELIVERED AT 1-2 TREATMENT SESSIONS EVERY DAY.

Thermal stimulation can be synergistically combined with EFS: EFS prevents HSPs degradation by inhibiting adenosine deaminase activity thus promoting accumulation of HSPs in the cells. In practical terms, HSPs can be induced by local thermal stimulation with temperatures 39-41 degrees C for 15-30 minutes. After a session of TS, the concentration of HSPs stays elevated for 72 hours. This points to the optimal regiment of treatment at least 3 times per week, with the best results, delivered at 1-2 treatment sessions every day.

THERMAL STIMULATION BLOCKS APOPTOSIS OF CHONDROCYTES.

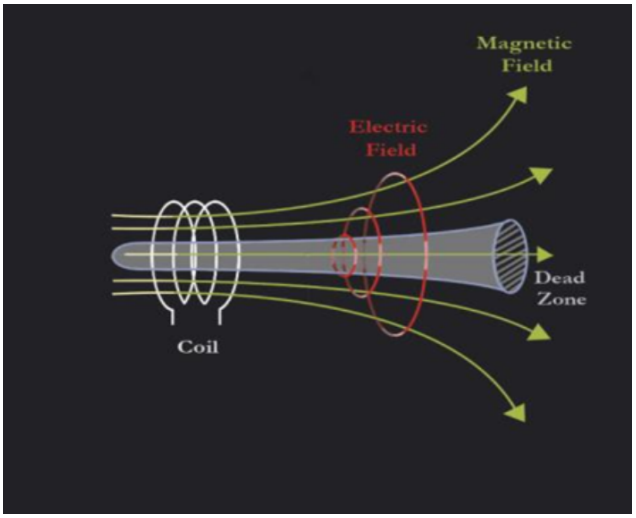
The main therapeutic target of TS is apoptosis. The TS inhibits apoptosis and decreases secondary necrosis – the main pro-inflammatory stimulus that fuels inflammation in OA.

NOVOPULSE® REDUCES INFLAMMATION, BLOCKS APOPTOSIS AND PROMOTES CARTILAGE RESTORATION.

In treatment of OA NovoPulse® technology pursues two targets: inflammation and apoptosis.

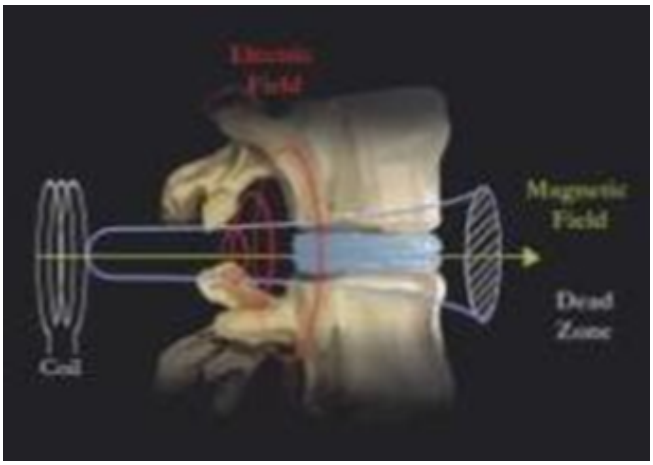
The great majority of Pulsed Electromagnetic Field (PEMF) devices on the market are advertised by manufacturers as having the highest magnetic fields, which misses the point, because ***the active agent that provides biological effects is the electric field, not the magnetic field.***

Also, the distribution of the electric field in and around the coil is significantly different from that of the magnetic field: in the center of the coil where the magnetic field is at maximum, the electric field is zero and has very low values around it, comprising a “dead zone” where no therapy is delivered.

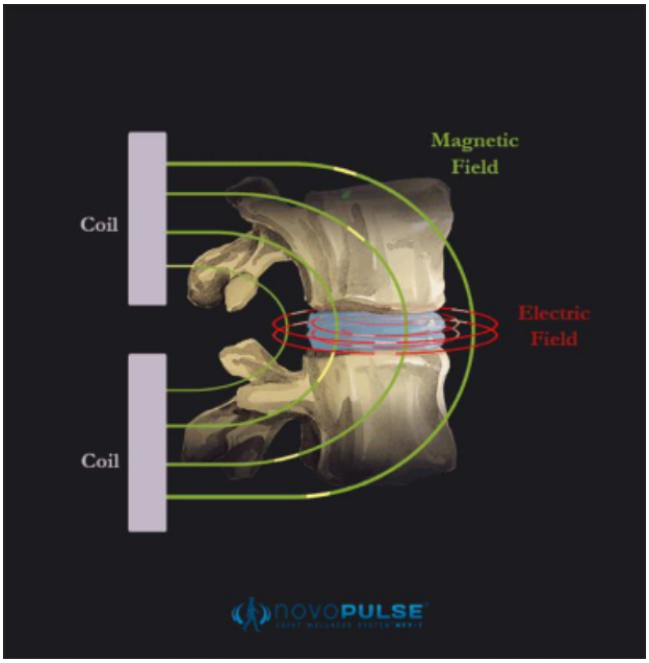


NOVOPULSE® REDUCES INFLAMMATION, BLOCKS APOPTOSIS AND PROMOTES CARTILAGE RESTORATION.

Another problem is that the cartilage in joints is a thin layer of tissue located between two bones. Bones have several times higher electrical resistivity than cartilage. If the EF, applied to the cartilage, crosses the adjacent bones, only a small fraction of EF is delivered into the cartilage, the rest is absorbed by bone.



The NovoPulse® device has a unique four-coil system to overcome this drawback. The system is designed to generate high EF and deliver it into the discs and facet joints parallel to the cartilages, which allows avoiding losses of EF to the dead zones or adjacent bones.



THERMALLY ASSISTED ELECTRICAL STIMULATION

Scientists from the medical school of Kyoto University, following a multiyear study, concluded that the best way to treat OA is to combine EFS and TS in one treatment. NovoPulse® is the only technological implementation of this philosophy.

The NovoPulse® has uniquely designed a computer-controlled thermal stimulation provided by four heating pads, efficiently utilizing the power from the stored magnetic field after the end of each pulse.

The NovoPulse® device is designed for treatment and pain management of OA of low back including deteriorated discs and facet joints. It can be used also for other joints in the body affected by OA.

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