EFFECTIVENESS OF DIFFERENT CRYOTHERAPIES ON PAIN AND DISEASE ACTIVITY IN ACTIVE RHEUMATOID ARTHRITIS. A RANDOMISED SINGLE BLINDED CONTROLLED TRIAL

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OBJECTIVE: Local cryotherapy is used to relieve pain and inflammation in injuries and inflammatory conditions. Whole-body cryotherapy is an extreme method administered at -110 degrees C for 2 to 3 minutes. The aim of the study was to compare the effect of cryotherapies on pain and inflammation in patients with rheumatoid arthritis (RA). METHODS: Sixty patients with active seropositive RA were recruited in a randomised controlled single-blinded study to receive whole-body cryotherapy at -110 degrees C, whole-body cryotherapy at -60 degrees C, application of local cold air at -30 degrees C and the use of cold packs locally. In the final analysis, the last 2 groups were pooled. The patients had 2-3 cryotherapy sessions daily for one week plus conventional physiotherapy. Clinical and laboratory variables and patient's and physician's global assessments were used to assess the outcome. Disease activity was calculated by DAS. RESULTS: Pain decreased in all treatment groups, most markedly in the whole-body cryotherapy (-110 degrees C) group. DAS decreased slightly with no statistically significant differences between the groups. No serious or permanent adverse effects were detected. Six of 40 patients (15%) discontinued the whole-body cryotherapy. CONCLUSION: Pain seemed to decrease more in patients in the whole-body cryotherapy at -110 degrees C than during other cryotherapies, but there were no significant differences in the disease activity between the groups. However, cryotherapy at -110 degrees C is expensive and available only in special centres and may have minor adverse effects. Based on our results, whole-body cryotherapy at -110 degrees C is not superior to local cryotherapy commonly used in RA patients for pain relief and as an adjunct to physiotherapy.

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CRYOTHERAPY

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Cryotherapy is a form of physical therapy that can be applied locally and systemically. Local cryotherapy administered for instance as cold packs, cold air or sprays lowers skin and tissue temperature and subsequently decreases neuronal activity and tissue blood flow. In clinical trials cryotherapy showed analgetic effects and reduced local edema; this treatment is therefore an option in patients with painful and inflammatory rheumatic diseases and after traumatic injuries.Only scant experimental and clinical data are available for cryotherapyat -110 degrees C. The analgetic effects demonstrated so far and the high percentage of adverse events observed with this challenging method currently do not support its routine use in clinical practice.

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Cryotherapy in treatment of rheumatoid arthiritis

Cold therapy is probably one of the oldest treatment modalities. Regular application of cold material on painful or inflamed parts of the body improves symptoms by alleviating pain by decreasing blood flow to the inflamed organ or body part, thereby decreasing sensation. People noted this phenomenon hundreds, if not thousands of years ago. Controlled local application of ice packs is an ordinary treatment in modern rheumatology. Application of coldness on almost the whole body has been used for centuries through a widely present practice of cold water swimming. There are many cold water swimmers in present time. These people, carried by some innate feeling, try to achieve a higher level of health through this practice. The modern version of the application of cold objects on the whole body is whole body cryotherapy. This novel wellness modality has significant potential to improve symptoms in different diseases, but also it improves general health. Cryogenically cooled air which is used in cryotherapy has a temperature of - 100°C and lower (Lubkowska 2012). Cold application in cryotherapy procedure is strictly controlled. Duration of a single session in a suitable chamber, with a patient in minimal clothing, is one to three minutes (Westerlund 2009). The procedure was originally introduced in 1978 by Prof. Toshiro Yamauchi and his team in Japan (Lubkowska 2012). In this pioneering achievement, cryotherapy was used for the treatment of rheumatism. Until today the list of potential indications became significantly longer. Strictly controlled use of cryogenically cooled air has a target to achieve a temporary decrease in body temperature. This transitory drop in body temperature results in certain desirable physiological changes. Some of the favourable physiological responses include an increase in hormones such as beta endorphins and norepinephrine, and

stimulation of blood flow (Lubkowska 2012). Repeated sessions of cryotherapy has a potential to result in therapeutic effects. The scientific popularity of the procedure has skyrocketed in its short history. There are numerous scientific articles about its existing and possible role in the treatment of different diseases. The primary indication for cryotherapy, rheumatism, is also existent today. The procedure has a positive impact on pain, fatigue and walking time in rheumatoid arthritis patients (Gizin ska, Rutkowski et al.2015).

Other rheumatological and orthopedic conditions, such as ankylosing spondylitis and tendinitis, are also indications for the treatment in cryochambers (Lubkowska 2012). Many individuals who repeatedly used the procedure for other reasons noted psychic benefits of it. Their mood improves, same as a sleep. Scientists have examined this phenomenon and proposed a role of cryotherapy as a useful adjunct treatment of depressive and anxiety disorders (Rymaszewska,Ramsey & Chł adzin ska-Kiejna 2008). The procedure has a positive impact on sleep quality (Lubkowska 2012). The use of cryogenically cooled air has found its place as the helpful treatment in the complex disease such as multiple sclerosis. Cryotherapy sessions result in improving functional status and fatigue in multiple sclerosis patients (Miller, Kostka et al. 2016). There are sound theoretical models which support the possible role of cryotherapy in weight loss and immunity. It is important to say that use of the treatment is not limited to pathological states. Cryotherapy is regularly used by many athletes because of its potential to speed recovery (Lubkowska 2012). In fact, the positive impact of cryogenically cooled air is there for everyone. Cryotherapyis our new weapon in achieving wellness and adjunct treatment of numerous diseases.

Contribution of Cryogenically Cooled Air on Wellness

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Localised cryotherapy in anti-aging treatments

Ageing is an inevitable reality that entails changes in an individual's physical appearance and overall health status. In fact, according to the Global Health Observatory (GHO) data reported by the World Health Organization (WHO), the average life expectancy of the global population in the year 2015 was 71.4 years (World Health Organization,2016). Moreover, by the year 2030, it is expected that one out of five of the global population will be over 65 years old. Hence, extensive research studies have focused on methods to defy the ageing process, preserve vigor and prolong an individual's lifespan while maintaining a good quality of life in the advancing years (Low, 2013).

To achieve the goal of delaying the onset of diseases or decline in health status related to the ageing process, the National Institute on Ageing (NIA), which is part of the U.S. Federal Government's National Institutes of Health (NIH), exerted its best efforts to increase awareness on various methods that promote longevity and active life expectancy - old age free of disability. One of the methods that is known to defy ageing is through the use of antioxidants, which act by eliminating the by-products of oxygen and food metabolism called 'free radicals'. However, there is no sufficient evidence to support this claim and still needs further investigation. Aside from this, another method that has anti-ageing effect is caloric restriction.

In a pilot study on Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE), it was revealed that overweight adults who decreased their caloric intake by 20 to 30 percent showed a lower fasting insulin levels and core body temperature. These two indicators are linked to improved longevity in animal models. On the other hand, another effect of ageing is the alteration in hormone levels responsible for supporting and maintaining good metabolism, immune function, sexual reproduction, and growth. Hence, some anti-ageing therapies are geared towards regulating the level of hormones that decline in the advancing years. However, some of these off-label use of hormone replacement therapy are associated with several health risks such as endometrial problems and heart diseases in women (National Institute on Ageing, 2016).

With the increasing demand for different anti-ageing possibilities, the emergence of cryotherapy has been thought to benefit a greater population. In fact, some of the methods that utilize the technology behind cryotherapy such as cryo-facials which last for 10 – 25 minutes can help remove dead skin cells to revitalize the skin. Furthermore, cryotherapy is also known to facilitate the healing process of damaged tissues, improve blood circulation and metabolism, increase serotonin levels and boost the function of an individual's immune

system (Keenan,2015). Aside from cryo-facials and neuromodulation is another method known to remove one of the most common signs of ageing, which is wrinkles. Before, this procedure is only done through cryosurgery, which was then associated with possible permanent damage to nerve function. With recent studies and advancement in technology, it was found out that same desired effect can be achieved by using moderate temperature. Hence, leading to the utilization of focused cold therapy (FCT) to reduce dynamic facial wrinkles by inducing temporary muscle relaxation as it blocks the impulse conduction of motor nerves without the use of neurotoxins (Wong & Giausseran, 2014). Cryotherapy to Defy the Ageing Process References: 1. Keenan, C. (2015, October 22). View. Retrieved July 25, 2016, from Las Vegas Review Journal:

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(2016). Global Health Observatory. Retrieved July 25, 2016, from World Health Organization: http://www.who.int/gho/mortality_burden_disease/life_tables/situation_trends/ en/ In addition, temperature also plays a vital role in maintaining the normal function of a physical system. Several studies show that high temperature can affect metabolic rates and increase the rate of biochemical reactions responsible for the ageing process as it facilitates oxidative and/or DNA damage. In fact, both poikilotherms and homeotherms showed a clear trend for lower temperature being associated with longer lifespans in wild populations and in laboratory conditions wherein even slight changes in temperatures for long periods of time can influence longevity. Hence, cryotherapy, which induces a decrease in body temperature that equates to a decrease in molecular disorder, has the potential to slow down the ageing process and improve life expectancy (Keil, Cummings, & de Magalhães, 2015).

Localised Cryotherapy in sports recovery and treating athletes

Athletes and individuals who engage in physical activities and strenuous routines are prone to develop musculoskeletal sports injuries, which may result from accidents, improper use of equipment and poor training practices including failure to do warm-up and stretching exercises. Some of the most common types of sports injuries are muscle sprains and strains, ligament or tendon tears, joint dislocation and bone fracture that can eventually affect an athlete's performance. In addition, sports injuries can either be acute or chronic. Acute injuries occur suddenly while a person performs an activity. On the contrary, chronic injuries may result from over use of certain areas of the body over a long period of time. Both acute and chronic sports injuries are associated with disabling symptoms such as pain, swelling and limited mobility (National Institute of Arthritis and Musculoskeletal and Skin Diseases, 2016). The moment a person acquires injury, the body reacts by releasing chemicals from

damaged cells. This triggers an inflammatory response wherein the blood vessels of the injured area become dilated to increase blood flow, thereby, carrying nutrients to the damaged tissues. Minor injuries, such as sprains and strains, are initially managed with PRICE (Protection-Rest-Ice-Compression-Elevation) therapy. (National Health Service UK, 2015). However, in severe cases, some sports injuries such as those that can damage the anterior cruciate ligament (ACL) and medial collateral ligament (MCL) of the knees may require reconstruction surgery and rehabilitation to restore normal function and mobility (American Academy of Orthopaedic Surgeons, 2009). Application of ice or cold pack as the third element of PRICE therapy, is known to decrease inflammation as it helps constrict blood vessels. Hence, cryotherapy, which utilizes cryo cabins with temperatures ranging from−110°Cto−140°C, can potentially facilitate recovery of body parts affected by various types of sports injuries. Such benefit is also brought about by the alteration of serum mediators of inflammation and serum muscle enzymes.

In a study conducted to determine the effectiveness of cryotherapy in athletic recovery, it was revealed that CT can increase the levels of anti-inflammatory cytokine interleukin (IL)-10, and decrease the levels of proinflammatory cytokine IL-2 and chemokine IL-8. This process is also supported by a decrease in the intracellular adhesion molecule-1. Furthermore, cold stimulation also improves athletes' recovery by exerting positive effects on muscular enzymes creatine kinase and lactate dehydrogenase (Banfi, Lombardi, Colombini,&Melegati,2010). On the other hand, high-intensity and high-duration exercises can also induce metabolic stress and increase temperature, which may eventually cause structural damage and muscle soreness. Hence, exposure of the affected area to cold temperature immediately following the exercise, can reduce the energy demand of the muscles and provide temporary analgesic and anti-inflammatory effects (White & Wells, 2013). On the contrary, in another study focusing on the effects of cryotherapy on muscle recovery and inflammation after muscle damaging exercise, it was revealed that thoughit cannot significantly alleviate strength decrement and muscle soreness, a mitigation in plasma chemokine ligand 2 was noted after a 20-minute cryotherapy (Crystal, Townson,Cook, & LaRoche, 2013).

In addition, a study by Hubbard and Denegar showed that cryotherapy can be effective in decreasing pain related to soft tissue injury. However, further investigation is still needed to evaluate its effectiveness Athletic Recovery Through Cryotherapy Biblography: American Academy of Orthopaedic Surgeons. (2009, September). Ortho Info. Retrieved August 11, 2016, from American Academy of Orthopaedic Surgeons Banfi, G., Lombardi, G., Colombini, A., & Melegati, G. (2010). WholeBody Cryotherapy in Athletes. Sports Medicine, 509 517. Dambros, C., Martimbianco, A. L., Polachini, L., Lahoz, G., Chamlian, T., & Cohen, M. (2012). Effectiveness of cryotherapy after anterior cruciate ligament reconstruction. Acta Ortopédica Brasileira, 285 290. National Health Service UK. (2015, February 25). Retrieved August 11, 2016, from NHS choices: http://www.nhs.uk/conditions/sportsinjuries/pages/treatment.aspx National Institute of Arthritis and Musculoskeletal and Skin Diseases. (2016, February). Health Information. Retrieved August 11, 2016, from National Institute of Arthritis and Musculoskeletal and Skin Diseases: http://www.niams.nih.gov/health_info/sports_injuries/#ra_2 White, G., &

Wells, G. (2013). Coldwater immersion and other forms of cryotherapy: physiological changes potentially affecting recovery from high intensity exercise. Extreme Physiology and Medicine compared to other rehabilitation techniques (Hubbard & Denegar, 2004). Aside from facilitating athletic recovery, patients with sports injuries who required surgery may also benefit from cryotherapy. In a study conducted in Brazil, patients who underwent cryotherapy combined with an exercise protocol immediately after ACL reconstruction, experienced less pain and an improvement in the range of motion of the affected knee. As a result, decreased intake of pain medications, reduced length of hospital stay and an improvement in the quality of life were noted among postoperative patients (Dambros, Martimbianco, Polachini, Lahoz, Chamlian, & Cohen, 2012).

Benefits of Localized Cryotherapy

The wide range of applications of cold therapy has long been recognized for thousands of years. In fact, the therapeutic benefits of cold temperature, particularly its analgesic and anti-inflammatory effects, were discovered by the ancient Egyptians and the Greek physician Hippocrates (Dawber & Cooper, 2001). Such intervention has evolved from the simple application of ice packs to the development of cutting edge equipment which utilizes the concept involving the effects of cold temperature in stimulating different body responses. Eventually, this idea has led to the emergence of different methods of cryotherapy, which is known to alleviate pain and inflammation commonly associated with various health conditions.

One of the effects of cryotherapy that is attributed to its promising benefits is vasoconstriction that reduces the circulation to the affected area. Vasoconstriction slows down the body's metabolism and reduces its demand for oxygen. Aside from this, cold application or cooling below 68°F (20°C), also helps retain the heat in our body and reduce acetylcholine production. Thus, relieving congestion and muscle spasm. On the other hand, the analgesic effect of cold therapy is related to its counterirritant action, its influence on the nerve endings, and its ability to reduce metabolic activity. During a cold therapy, the skin temperature drops almost immediately, which is subsequently followed by a decrease in subcutaneous temperature. However, structures beneath the subcutaneous layer are much less efficiently cooled. As a result, the patient experiences cold perception followed by aching or burning sensation and cutaneous anesthesia (Pfiedler Enterprises, 2014). Unlike cryotherapy(WBC), localized cryotherapy aims to target specific parts of the body. Hence, it does not require the use of complex equipment such as cryo cabin or cryogenic chambers to facilitate a cost-effective and equally safe treatment. Aside from this, since only the affected areas are exposed to extreme temperature, localized cryotherapy can be applied for longer periods to allow deeper penetration and a more effective cooling. In fact, in a study published in the American Journal of Sports Medicine, prolonged superficial cryotherapy reduces post-traumatic microvascular dysfunction, inflammation, and structural impairment secondary to closed soft tissue injury. These effects were due to the effect of cryotherapy in restoring functional capillary density, repairing tissue damage, decreasing intramuscular pressure, and reducing the number of adhering and invading granulocytes (Schaser, Disch,

Stover, Lauffer, Bail, & Mittlmeier, 2007). One of the methods increasing fast in popularity is localized cryotherapy. This method is geared towards facilitating recovery from injuries as well as reducing cellulite formation. In fact, cryotherapy is one of the essential components of the first aid treatment for musculoskeletal injuries known as R.I.C.E therapy - Rest, Ice, Compression and Elevation. This premise is further supported by the results of research studies showing the benefits of cryotherapy in both acute and rehabilitative phases of soft tissue injury which proved its ability to reduce metabolism, decrease the inflammatory reaction and induce local analgesia (Galiuto, 2016). Benefits of Localized Cryotherapy Biblography: Dawber, R., & Cooper, S. (2001). The history of cryosurgery. Journal of the Royal Society of Medicine, 196 - 201. Galiuto, L. (2016). The Use of Cryotherapy in Acute Sports Injuries. Annals of Sports Medicine and Research, 1060. Ingargiola, M. J., Motakef, S., Chung, M. T., Vasconez, H. C., & Sasaki, G. H. (2015). Cryolipolysis for Fat Reduction and Body Contouring: Safety and Efficacy of Current Treatment Paradigms. Plastic and Reconstructive Surgery, 1581-1590. Pfiedler Enterprises. (2014). Retrieved November 10, 2016, from Pfiedler Enterprises:

http://www.pfiedler.com/ce/1107/files/assets/common/downloads/Localized%20temperatur e%20therapy.pdf Schaser, K., Disch, A., Stover, J., Lauffer, A., Bail, H., & Mittlmeier, T. (2007). Prolonged superficial local cryotherapy attenuates microcirculatory impairment, regional inflammation, and muscle necrosis after closed soft tissue injury in rats. The American Journal of Sports Medicine, 93 -102. Aside from treating sports injuries, cryotherapy also offers promising benefits in fat reduction and body contouring. This procedure is referred to as cryolipolysis or cool sculpting or fat freezing. Cryolipolysis is a safe treatment, which is considered as a compelling alternative to liposuction and other invasive methods of reducing localized adiposities. This idea is supported by the results of a research study which revealed that cryolipolysis can lead to an average fat reduction ranging from 14.67 percent to 28.5 percent, as measured by calipers or 10.3 percent to 25.5 percent, as measured by ultrasound. However, the same study also showed that cryotherapy has no significant impact on lipid levels and liver function tests (Ingargiola, Motakef, Chung, Vasconez, & Sasaki, 2015).

Cryotherapy in Biohacking

For several years, cryotherapy has been utilized to treat sports injuries among athletes and to relieve pain and inflammation among patients with rheumatism. Hence, such intervention was noted to bring a significant impact in improving the quality of life of many patients around the globe. Aside from this, recent advancement in technology has led to the discovery of more complex applications of cryotherapy such as its potential benefit in the emerging trend of biohacking. Biohacking is a self-driven biological experiment geared towards applying scientific principles to find alternative methods related to DNA sequencing, microbial screening, environmental monitoring, and improving healthcare services and delivery (Seyfried, Pei, & Schmidt, 2014). The concept behind biohacking is comparable to computer hacking. Instead of altering the computer system, biohacking cracks the code of how the human body is programmed to function and to respond to different stimuli.

Biohackers tend to experiment on their own bodies to find solutions to certain health problems related to genetic make-up and other circumstances that may have affected their well-being.

Moreover, biohacking also aims to conquer the ballooning costs of research and development by producing accessible and cheap laboratory equipment and methods (Loftrup, 2015). Cryotherapy, which utilizes extremely cold air in a cryochamber or cryosauna, has been used in biohacking to achieve optimum health outcome. Exposure to cold temperature stimulates the sympathetic nervous system as the body perceives a life-threatening situation and activates survival mechanisms. Some of the advantages of cryotherapy that gain attention from biohackers are its benefits on relieving pain and inflammation. Moreover, it also promotes blood circulation that supports cellular processes and reduces damage to organs and tissues (Taylor, 2016). One of the most famous pioneers of biohacking is David Asprey, an American entrepreneur whose goal is to live until the age of 180 years old through his bulletproof concept. Asprey ventures on experimenting with his own body to determine the response to sleep, light, nutrition and supplementation. As Asprey's ideas turn to an industry, his life becomes an open book that influences the lives of millions of people who listen to his broadcasts, read his blogs and subscribe to his social media pages (Conner, 2016). To achieve his personal goal, Asprey established a biohacking laboratory in Victoria, British Columbia in Canada. His facility consists of different equipment such as the cryotherapy chamber to promote longevity. This premise can be supported by the results of several research studies which reveal the potential benefits of cryotherapy in regulating various biochemical processes. In a study published in a Polish journal, it was found out that exposure to ten sessions of three-minute cryotherapy with temperatures ranging from -120 degrees Celsius can suppress oxidative stress by increasing the total antioxidative status (TAS) in plasma (Miller, Mrowicka, Malinowska, Kedziora, & Majsterek, 2011). Aside from this, cryostimulation is also hypothesized to have an immunostimulating effect related to enhanced noradrenaline response The Use of Cryotherapy in Biohacking. Biblography: Conner, C. (2016, September 28). Retrieved October 11, 2016, from Forbes: http://www.forbes.com/sites/cherylsnappconner/2016/09/28/from-idea-to-industry-dave-asp rey-bulletproof/#5e0901b317c0 Li, Y., Browne, R. W., Bonner, M. R., Deng, F., Tian, L., & Mu, L. (2014). Positive Relationship between Total Antioxidant Status and Chemokines Observed in Adults. Oxidative Medicine and Cellular Longevity, 6 pages. Loftrup, J. (2015, May 12). Retrieved October 11, 2016, from Lunds Universitet Magasin: http://www.lum.lu.se/english/biohackers-crack-the-human-bodys-programming-code/ Lubkowska, A., Szygula, Z., Chlubek, D., & Banfi, G. (2011). The effect of prolonged whole-body cryostimulation treatment with different amounts of sessions on chosen pro- and anti-inflammatory cytokines levels in healthy men. Scandinavian Journal of Clinical and Laboratory Investigation, 419 - 425. Miller, E., Mrowicka, M., Malinowska, K., Kedziora, J., & Majsterek, I. (2011). The effects of whole-body cryotherapy and melatonin supplementation on total antioxidative status and some antioxidative enzymes in multiple sclerosis patients. Polski Merkuriusz Lekarski, 150 - 153. Seyfried, G., Pei, L., & Schmidt, M. (2014). European do-it-yourself (DIY) biology: Beyond the hope, hype and horror. Bioessays, 548 - 551. Taylor, M. (2016). Retrieved October 11, 2016, from Living Bulletproof in Australia:

hype and horror. http://www.livingbulletproof.com.au/cryotherapy-biohacking-australia/and can be connected with paracrine effects. In fact, in a study that aimed to determine the effects of cryotherapyin pro- and anti-inflammatory cytokine levels in healthy men, it was noted that twenty sessions of 3-minute cryostimulations per day can significantly increase the level of anti-inflammatory cytokines IL-6 and IL-10 and decrease the Il-1a cytokine level (Lubkowska, Szygula, Chlubek, & Banfi, 2011). Oxidative stress, that leads to the production of free radicals, is known to play a major role in the development of a wide variety of illnesses such as cardiovascular diseases, diabetes, cancer and autoimmune diseases. Inflammation, on the other hand, can lead serious damage to tissues and organ systems. Hence, by suppressing oxidative stress and inflammation through cryotherapy, the risk of developing different health problems can be minimized, thereby promoting longevity (Li, Browne, Bonner, Deng, Tian, & Mu, 2014).