

Pulsed Electromagnetic Fields and Osteoarthritis: A Case Where the Science and its Application Do Not Always Concur

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Abstract

Introduction: Osteoarthritis, a highly prevalent disabling joint disorder often resistant to amelioration, is not always amenable to surgery and/or pharmacologic interventions. One non-pharmacological modality, pulsed electromagnetic field therapy has shown promise in numerous laboratory studies but its clinical application remains controversial.

Objective: This work was undertaken to re-examine the evidence base detailing the rationale for and the potential efficacy of applying pulsed electromagnetic fields in the context of treating osteoarthritis pain and dysfunction.

Methods: All related English language literature located in the entire ACADEMIC SEARCH PREMIER, SCOPUS, GOOGLE SCHOLAR, WEB OF SCIENCE, CINAHL and PUBMED databases up to May 31, 2017 using the key words, pulsed electromagnetic fields and osteoarthritis were retrieved and reviewed.

Results: The available basic and clinical research studies in this field published over the last few years, while numerous, are not always in agreement. Basic studies more consistently imply there is high value in continuing to explore the potential of applying pulsed electromagnetic fields to ameliorate pain and dysfunction associated with disabling osteoarthritis, as well as to foster cartilage regeneration. But actual clinical studies while largely positive, do not show consistently positive outcomes.

Conclusion: Given the strong scientific basis for treating osteoarthritis with short duration dosages of pulsed electromagnetic wave forms, it is concluded more carefully construed well-designed sham controlled prospective studies are indicated.

Keywords: Articular Cartilage; Disability; Osteoarthritis; Pain; Pulsed Electromagnetic Fields

Introduction

Osteoarthritis, a highly prevalent destructive joint disease produces progressive pathological changes in the articular cartilage lining of synovial joints, as well as the subjacent bone and surrounding joint tissues. Associated with high levels of disability, including unrelenting bouts of pain and functional impairments, osteoarthritis remains highly challenging to treat. Indeed, many pharmacologic interventions as well as some surgical approaches developed to ameliorate the disability have not proven to be universally efficacious or indicated, and even if they are, they do not necessarily modify the complex osteoarthritic process in a favourable way [2]. A specific search for an effective safe approach to relieving osteoarthritic pain and disability, while positively influencing the underlying joint pathology, which is not subject to spontaneous repair [3] is hence strongly indicated in this regard [4].

In this respect, basic experimental studies conducted since 1989 have shown the application of biophysical stimuli in the form of low energy pulsed electromagnetic fields that employ wave frequencies from the lower end of the electromagnetic spectrum [5] to be potentially efficacious in the context of treating osteoarthritis non-invasively [6-8]. However, despite efforts to support the proposed applica-

tion of pulsed electromagnetic field therapy as a novel intervention for preserving osteoarthritic joint integrity [1,2], the clinical efficacy of this physical form of external intervention in the context of osteoarthritic joint damage and pain remains contentious.

Aims

In recognition of the possible utility of pulsed electromagnetic field applications for ameliorating osteoarthritic disability, especially through its pain alleviating potential and its cartilage and bone cell mediating properties [3,4], this work examines the current status of this electrotherapeutic modality for treating osteoarthritis.

Methods

To achieve the goals of this work, a broad comprehensive literature scan providing an updated review of all published English language research or English language abstracts published in peer reviewed journals on this topic was undertaken.

To maximize topic coverage, the PUBMED and MEDLINE (1985-May 31, 2017) databases, along with SCOPUS, WEB OF SCIENCE, AMED, CINAHL, GOOGLE SCHOLAR, COCHRANE, and ACADEMIC SEARCH COMPLETE databases were searched using the key words: articular cartilage, osteoarthritis, pain, and pulsed electromagnetic fields. The articles selected had to be focused on the association between pulsed electromagnetic fields and some aspect of joint biology or osteoarthritic pathology. No other forms of electrical energy were studied, even those claiming to be classified as magnetic fields, but were not focused exclusively on pulsed electromagnetic fields were excluded.

To examine these data, this body of research was carefully scanned, and then accepted studies were categorized into basic laboratory versus clinical study perspectives, regardless of study design. Key factors that embodied certain aspects of this topic were tabulated to depict selected findings, but no meaningful synthesis was clearly possible, due to the diversity of approaches employed, in both realms, notwithstanding the fact that several authors have attempted to synthesize the clinical data on numerous occasions over the recent past with varying results. The results that follow focus firstly on findings from laboratory investigations, followed by those that have examined the clinical efficacy of pulsed electromagnetic fields. Table 1 shows the chronology of most of the available clinical studies, regardless of research design, and the overall outcome in the context of pain. The various parameters influencing the outcome of pulsed electromagnetic applications are shown in Box 1.

Key Findings

Laboratory Experiments

The application of low frequency, low energy pulsed electromagnetic fields to ameliorate osteoarthritis processes has proceeded for some time either in the context of an array of cell culture studies, animal models [9-12], cartilage [13-17] and bone explants [18]. Despite a lack of consensus in explaining the mechanisms underpinning the observed outcomes of this body of research, most of these experiments have pointed to the ability of low frequency electromagnetic fields to positively impact joint morphology [2], chondrocyte function [14], and pathology [19], regardless of employed frequency [20], and duration [21].

That is, the application of low frequency pulsed electromagnetic fields to cartilage and surrounding joint structures affected in early osteoarthritis appear to be protected from excess destruction [9,15,17,22,23] important DNA synthetic mechanisms in both existing as well as newly formed chondrocytes are activated [12,24], proteoglycan synthesis is enhanced [25], and local cartilage catabolic factors are diminished [12]. The waves may also heighten anabolic cell functions, ion exchange, cellular enzymatic activation mechanisms [26], while hastening or fostering cartilage repair [27] in a dose dependent manner [11,17,21].

In addition to impacting articular cartilage and its constituents in a favourable manner, bone, a key structural component implicated in osteoarthritis has been shown to be favourably affected by the application of pulsed electromagnetic fields [5,28]. This ability of pulsed electromagnetic fields to promote bone healing [11,29], may also help reduce cartilage destruction and preserve its integrity indirectly, along with helping to delay the need for revision surgery [30,31].

Additional benefits of pulsed electromagnetic fields in the context of osteoarthritis include enhanced collagen production [32], ligamentous tissue healing [33,34], tendon stem cell regeneration [35], the reduction of genes associated with disc degeneration [36], short term pain and stiffness after surgery [37] and nerve regeneration [38-40]. Muscle spasm, disability and function may also be impacted favourably [41,42], as may pain attributable to nerve root compression [43]. According to Kumar, et al. [44] muscle and nervous tissue regeneration might also be evidenced in response to pulsed electromagnetic field therapy, inflammation and pain may be substantively alleviated [2,45,46], and healing promoted [47] even in the late disease stages [20].

Mechanisms explaining the effectiveness of applying pulsed electromagnetic fields to joint tissues include, but are not limited to their potential to favorably activate chondrocyte cell receptors and transcriptional processes [48], calcium and other ion concentrations that stimulate DNA transcription [49], and chondrocyte proteoglycan synthesis [22]. Other mechanisms include reductions in chondrocyte cell death [50], and changes in receptor activity that stimulate secondary messenger systems favorably [51], and nitric oxide signaling [52].

In short, laboratory experiments over the past 40 years systematically show the application of low frequency fields to cartilage explants, or chondrocytes or both can potentially influence one or more features of the osteoarthritic disease process in a positive way. Consequently, one would anticipate that the careful application of these experimental findings to the clinical realm would support the basic theory that low frequency pulsed electromagnetic fields can potentially exert powerful anabolic biophysical effects on tissues and structures implicated in osteoarthritis, and in doing so can relieve symptoms of pain attributable to cartilage destruction, and along with this, the ability to function physically. If not, it may be possible to find errors either in the context of these basically passive laboratory experiments or in those conducted in the clinical setting or both.

Clinical Experiments

Contrary to the aforementioned preclinical related literature, the various attempts implemented to examine the clinical outcomes of the application of pulsed electromagnetic fields over the past 30 years have tended to produce quite variable results. Not only are there an array of both negative as well as positive findings, when using comparable approaches, but meta analyses conducted to ascertain whether the treatment is superior to placebo have arrived at conflicting conclusions.

However, this situation, may not be that surprising, if we consider the challenges in trying to synthesize a highly inconsistent array of studies that are not necessarily well designed at the outset, nor reflective of best practices. In addition, the fact that the widely applied definitions of this form of magnetism may generate differential responses, rather than those specific responses evoked in experimental models, should not come as a surprise. Moreover, the use of placebo applications that may inadvertently yield favourable physical effects, along with co-interventions that may mask unique treatment effects [eg 53] adds to the complexity in resolving the effects of pulsed electromagnetic fields for treating osteoarthritis. Other issues that may account for discordant meta analytic findings are the limited number of such studies that have examined similar protocols, their variable sample sizes [53,54], different outcome assessments, and diverse application approaches and dosages [55].

Mixing pulsed electromagnetic field application studies with shortwave diathermy studies [66], and finding positive overall results by selecting only high-quality studies even though negative outcomes are evident in selected studies [66] along with placebos used that may have emitted an active current, the failure to discern results that are anticipated based on laboratory research is not surprising either.

The manifold meta analytic conclusions that prevail are also confusing because when viewed individually the data base of most prevailing studies include more positive reports, than not, even when potentially active placebo treatments are applied, suggesting the method does have some unique effects. Most positive studies reported in the literature that were randomized used double blind assessors with very few exceptions, thus strengthening the case for unique pulsed electromagnetic field effects. For example, the studies by Nikolakis, *et al.* [51], Piptone and Scott [56], Trock, *et al.* [57], and Battisti, *et al.* [58] all suggested the application of this biophysical intervention is able to significantly attenuate the magnitude of the disability accompanying osteoarthritic joint disease.

In this respect, Wuschech, *et al.* [59] too found pulsed electromagnetic field therapy delivered as a sinusoidal magnetic field that varied between 4 - 12Hz twice a day for 5 min for 18 days useful as a complementary treatment in patients with osteoarthritis. In addition, Gobbi, *et al.* [60] found therapeutic pulsed electromagnetic fields applied for 4 hours per day for 45 days significantly improved the osteoarthritis samples' symptoms and function as well as activity for up to one year after initial exposure.

Moreover, Bagnato, *et al.* [61] who recently conducted a double blinded placebo controlled trial of pulsed electromagnetic fields among 60 cases with knee osteoarthritis suffering from moderate to severe pain using a commercially available pulsed electromagnetic field machine generator similarly found a decrease in the experimental subject's pain, plus increases in pain tolerance and 26% stopped taking medications. As well, most subjects receiving the treatment exhibited improved physical capacity after one month of exposure for a treatment duration of 12 hours per day. Contrary to several negative meta analytic assessments [eg 64,66,67], these aforementioned results have been replicated for patients with early knee osteoarthritis [62], for cases with post-operative knee pain [63], for selected cases reviewed on a case by case basis [65], and for high-quality studies subjected to a meta analytic process [66].

Additionally, contrary to a meta-analysis by McCarthy, *et al.* [67], when the intervention efficacy was evaluated for function, a significant improvement was observed eight weeks following treatment initiation, with a standardized mean difference of 0.30 (95% CI 0.07, 0.53) [66]. Importantly, too, even though osteoarthritis is a progressive disease, no significant adverse effects over the time period of two years was noted for a sub group of knee osteoarthritis cases with early symptomatic knee osteoarthritis [60]. In other research pulsed electromagnetic field applications improved an osteoarthritis patients' daily life function [63,68,69], even though Dundar, *et al.* [70] found no useful outcome for the additional use of pulsed electromagnetic fields when added to conventional therapy in cases with knee osteoarthritis. These results were at odds however, with those of Iammarrone, *et al.* [71], Adravanti, *et al.* [63], and Iannetti, *et al.* [72], Sutbeyez, *et al.* [41] and Erikson, *et al.* [73] among others listed in Table 1, and were not based on a direct comparison between active and sham pulsed electromagnetic fields.

In short, despite a sound scientific basis for applying non-invasive pulsed electromagnetic fields to alleviate osteoarthritis pain and function, and an array of studies supporting its clinical value, the clinical evidence base in this regard, while more promising than not, remains contentious, and is generally not among recommendations made to treat osteoarthritis conservatively. Yet, negative studies, while disproving either the underlying explanatory theory[ies] as to why pulsed electromagnetic fields can favorably influence joint tissues affected by osteoarthritis, or the actual value of the application of this modality or both, do not however commonly indicate or carefully explore any alternate explanation for these findings to guide practice. Moreover, most studies in the clinical realm did not measure direct joint tissue effects, did not necessarily apply optimal dosages, or did not account for the possible errors incurred in home based treatment applications, among others [18]. The role of competing treatments [53] and acknowledging that there is likely to be a ceiling level as to how much improvement can be expected even in controlled studies of this type, especially if there is substantive joint destruction or a competing modality was independently successful was not discussed in any report. To continue this research and arrive at a meaningful consensus further exploration, using well-conceived experimental strategies and optimal dosages to test hypotheses regarding symptom relief, functional improvements, and cartilage regeneration are clearly warranted. As well the costs of not using a possibly valuable osteoarthritis treatment that may have regenerative effects cannot be underestimated, for example increased surgical costs if pain cannot be relieved by standard methods. Applications employed post surgery can also help speed up the recovery process, and patient autonomy may be enhanced because the treatment can be applied in the patient's home at fairly low cost.

Author	Year	Beneficial (Y/N)	Sample size	Type study*	True control group
Perrot, <i>et al</i> [100]	1994	Y	40	Rc	N
Trock, <i>et al</i> [57]	1993	Y	27	Rc	N
Nicolakis, <i>et al</i> [51]	2002	Y	36	Rplc	N
Pipitone and Scott [56]	2001	Y	75	Rplc	N
Jacobsen, <i>et al</i> [65]	2001	Y	176	Db	N
Thamsberg, <i>et al</i> [18]	2005	N	83	Rc	N
Sutbeyaz, <i>et al</i> [41]	2007	Y	32	Rc	N
Ay, <i>et al</i> [53]	2009	N	55	Rc	N
Kulcu, <i>et al</i> [99]	2009	Y	45	Rc	Y
Ozguclu, <i>et al</i> [91]	2010	N	40	Rc	N
Moldovan, <i>et al</i> [80]	2012	Y	70	Rc	N
Pavlovic, <i>et al</i> [76]	2012	Y	60	Rc	N
Nelson, <i>et al</i> [62]	2013	Y	34	Rpcdb	N
Ianniti, <i>et al</i> [72]	2013	Y	33	Ic	Y
Gobbi, <i>et al</i> [60]	2014	Y	22	Pr	Y
Wuschech, <i>et al</i> [57]	2015	Y	57	Pr	N
Bagnata, <i>et al</i> [61]	2016	Y	66	Rc	N
Dundar, <i>et al</i> [70]	2016	N	40	Rc	N
Battisti, <i>et al</i> [58]	2004	Y	90	Rc	N
Kanat, <i>et al</i> [89]	2013	Y	25	Rc	N
Peroz, <i>et al</i> [66]	2004	Y	25	Rc	N

Table 1: Studies conducted over three decades showing no coherent trend regardless of study design.

*Ic: Intrinsic Control Using Opposite Limb; Pr: Prospective; Rc: Randomized Controlled Trial; Rplc: Randomized Placebo Controlled Trial; Rpcdb: Randomized Placebo Controlled Double Blind Trial; Uc: Uncontrolled Trial

Discussion

Despite a great need to improve our ability to reduce the pain and suffering of osteoarthritis, a highly common disabling joint disease, where many experience inadequate pain relief [74], efforts to validate the efficacy of pulsed electromagnetic fields remain inconclusive despite quite consistent experimental data to support its potential clinical efficacy. In addition, as clearly outlined by Pfeiffer, *et al* [95] more than 15 years ago, even though more positive than negative clinical studies prevail, and the modality is clearly safe to apply, and may be more effective than drugs alone for reducing pain [62,75], even when compared with other modalities [76], very little emphasis has been placed in the general osteoarthritis literature on the potential benefits of this form of therapy, especially in the realm of recommendations by osteoarthritis experts. This exclusion is hard to understand. Moreover, it seems especially disadvantageous to patients and practitioners given that multiple rather than only single post treatment benefits have been observed among older adults with knee osteoarthritis in fairly well designed controlled trials for over 15 years [56,72], even among patients resistant to conventional treatment [56], and a reasonably robust scientific rationale exists to explain their demonstrated clinical effects. In addition, among the positive studies, a majority were found statistically superior to placebos when examined using double blinded methods, even though subjective data collection procedures may be suspect. The use of biochemical and biomechanical validated approaches, and research designs with well defined and validated inclusion criteria plus untreated controls, applied for an adequate time period to groups made up of adequate

sample sizes may help to more clearly highlight the benefits of this approach than is presently discernable. However, when compared or contrasted with the fact that no progress in any realm of pain reduction has occurred in the context of altering the pathology of osteoarthritis for more than 25 years, along with recent reports of the ineffectual use of currently recommended pharmaceutical remedies, and meta analyses that find differing results, the fact that low frequency applications of pulsed electromagnetic fields of short duration may provide pain relief and bone healing that may be the source of osteoarthritis pathology, and has clearly shown that it can impact function, strongly implies this form of treatment option should not be arbitrarily discounted without further research or informed discussions in this author's view.

As emphasised by Glickman-Simon and Pettit [72], multiple weaknesses and limitations in the clinical data base including small sample sizes, [only one study has examined more than 100 cases], the use of potentially insensitive outcome measures [70], differences in clinical history and eligibility criteria across studies and numbers of affected joints, and use of steroid injections, are arguably stronger explanations for failed clinical studies, rather than any lack of intervention efficacy. Others are possible use of co-interventions, lack of adherence or consistency in home based applications, age of subjects, medication profiles, extent of disease progression, nature of the placebo application, limited follow-up study periods, failure to educate the patient about the importance of joint protection, and lack of inflammation control. Indeed, based on experimental findings, as well as outcomes since 1993 that show more positive trends in post-treatment outcomes, regardless of samples and joints studied, co-treatments, type of set-up, equipment brand, stimulation duration, amplitude, frequencies and wave form, it is surprising the modality is not more readily discussed or recommended in day to day primary care practices to any noticeable degree. However, since magnet devices vary highly [56] and the effects of pulsed electromagnetic fields on cartilage cells may vary in accordance with various pulsed field therapy parameters [20,21,63], as well as coil size, wave form and duration, field intensity, and exposure durations [78], and the optimal dosage for alleviating specific clinical problems remains unknown, more robust uniformly structured clinical results may help to reverse this trend. In addition, future studies might examine the degree to which outcomes will tend to vary dependent on whether broad rather than focal areas are stimulated, the initial condition or physiological state of the tissues is more or less damaged, the individual is in poor or good health status, and the exposure to the fields follows only after a wash out period as is the approach in medical studies [78,79]. But no studies to date have adequately examined these and other salient determinants of outcome of patients with varying degrees of osteoarthritis, using a more universally agreed upon dosage, and valid biomechanical and biochemical instrumentation. The observation by Nikolakis, *et al.* [51] that time to peak torque, and steroid need, was reduced in the experimental group, along with gait improvements in the actively treated group, but not the sham group, and that stiffness was reduced 19% in cases already taking medication [18] is of great relevance to reducing impairments in activities of daily living and should be especially acknowledged and explored.

Box 1. Factors influencing pulsed electromagnetic field outcomes and warranting careful thought when applying modality to improve osteoarthritis outcomes

- Field parameters of amplitude, duration, frequency [20,44]
- Intensity, wave form, number of impulses per train and intervals between trains [44]
- Health and disease status
- Nature of the tissue being stimulated
- Application duration [66]
- Application method [94,107]
- Research design
- Outcomes measured
- Outcome assessment tools
- Co-interventions not controlled for
- Time point of treatment initiation [109]

Possible mechanisms explaining favourable results that should be sought in future studies include reductions in ligamentous damage [34], reductions in inflammation [101], improvements in tendon and tendon-bone healing [102, 103], improvements in cartilage viability, mobility and anti-inflammatory processes [11,50,104]. Others are, swelling and edema [105], pain thresholds [106], stiffness [18,37], diminished inflammation of synovial membranes [44], chronic and acute pain [37,46,47,108,110], and bone structure modelling benefits [50,109].

Conclusion

Despite a voluminous array of laboratory and clinical studies, it is concluded that the question of whether pulsed electromagnetic fields can be favorably employed to ameliorate the pain and disability of osteoarthritis must remain in question. Although some clinically oriented articles referring to the application of pulsed electromagnetic field applications for alleviating osteoarthritis pain and functional disability report significant benefits, the fact that others report no benefits clearly precludes the adoption of any definitive recommendation concerning this form of non-pharmacological treatment. However, given that the electrophysiological application of pulsed electromagnetic fields exhibits powerful anti-inflammatory, pro anabolic microcellular biological effects, plus favorable results in efforts to promote cartilage regeneration [27], chondrocyte growth and proliferation in surgical implants [14], gene expression [93], chondrocyte viability [94], upregulation of growth factors and glycosaminoglycan levels [96], it is concluded more research to examine the clinical utility of pulsed electromagnetic fields may prove highly beneficial.

Moreover, in light of the many design shortcomings observed in the presently reviewed clinical literature on this topic, it is concluded carefully designed clinical research that attempts to eliminate wide differences in the extent of impairments in prospective samples will be helpful. Perhaps, too, more consistent outcomes may be forthcoming through concerted efforts of multiple laboratories to collaborate and test treatment approaches consistent with possible best stimulation practices and mechanisms identified in basic research studies. Employing valid biomechanical and biochemical measurement approaches across different laboratories for diverse samples and joints may similarly help to more firmly establish the nature of any potential benefits of this form of therapy. Researching the possible reasons for negative study findings, as intimated by Ganesan, *et al.* [78], and careful subgroup analyses [79] may be especially helpful in this regard.

Until then, in light of the fact there are more published positive clinical studies than not, and very few side effects have been noted as a result of the application of pulsed electromagnetic fields, clinicians might still want to consider whether pulsed electromagnetic fields may be helpful for purposes of pain relief in selected cases, rather than simply following standard guidelines for osteoarthritis, which now exclude this modality. Bearing in mind those treatment parameters shown to best counter pain [80], and promote healing [39], including the repair of damaged articular cartilage [48] and subjacent joint tissues [81], while reducing inflammation and effusion [76,82], among other physiological benefits [83] will possibly prove especially advantageous to selected patients with low risk. Demonstrating that clinical exposure of affected osteoarthritic joints to pulsed electromagnetic fields can promote cartilage integrity, while reducing articular cartilage catabolic effects [92] will undoubtedly yield far reaching clinical benefits as well.

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