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Ultrasound in the management of osteoarthritis: part I: a review of the current literature

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Background: *Ultrasound has been widely used in clinical settings for the management of various ailments but many authors still question its efficacy. An accumulating body of literature demonstrates that ultrasound evokes a broad spectrum of bioeffects which may be therapeutically beneficial in the management of a variety of clinical conditions.*

Objective: *A critical review the current research investigating the use of therapeutic ultrasound in the treatment and/or management of osteoarthritis. Specific emphasis is placed on interpreting the literature in the context of its strengths and weaknesses, with particular attention placed on study protocols and technical parameters used in the trials. Relevant basic science is also introduced and meaningful inter-study comparisons are highlighted with suggestions for future research.*

Design: *Literature Review.*

Methods: *A Pubmed search of the literature was performed from 1985 to present using the key words "ultrasound" and "osteoarthritis" retrieved a total of 313 publications. Experimental, clinical and animal studies that directly assessed applications of therapeutic ultrasound in the clinical management of osteoarthritis and/or its underlying physiologic mechanisms were accepted. Studies that evaluated ultrasound in combination with other modalities were accepted but their conclusions were interpreted in the context of their methodological strengths and limitations.*

Results: *A total of 17 articles met our search criteria; one study was excluded due to poor methodology. Of a total of five review papers, two concluded that ultrasound had positive therapeutic effects, two did not demonstrate any benefit and one was inconclusive. The remaining*

Contexte : *Bien que l'ultrason soit beaucoup utilisé dans des conditions cliniques pour la gestion des malaises divers, plusieurs auteurs remettent toujours en question son efficacité. Une recherche de plus en plus étoffée démontre que l'ultrason déclenche une gamme étendue d'effets biologiques qui pourraient être favorables sur le plan thérapeutique dans le cadre du traitement de diverses conditions cliniques.*

Objectif : *Une recension critique de la recherche actuelle, qui étudie l'application de l'ultrason thérapeutique dans le traitement ou la gestion de l'arthrose. Plus particulièrement, on met l'accent sur l'interprétation des travaux dans le contexte de ses forces et faiblesses, accordant une attention particulière aux protocoles et aux paramètres techniques utilisés dans les essais. De la science fondamentale pertinente est également incorporée et des comparaisons claires sont surlignées comportant des suggestions pour la recherche à venir.*

Format : *Analyse des documents.*

Méthodes : *Une recherche de l'analyse effectuée dans les publications en médecine (Pubmed) à partir de 1985 jusqu'à aujourd'hui, en utilisant les mots clés « ultrason » et « arthrose », a généré 313 articles en tout. On a inclus les études expérimentales, les études cliniques en plus de celles effectuées sur les animaux, qui ont directement évalué l'application d'ultrasons thérapeutiques dans le cadre du traitement clinique de l'arthrose ou des mécanismes physiologiques sous-jacents. Les études qui ont évalué l'ultrason, conjugué à d'autres modalités, ont été admises, mais leurs conclusions ont été interprétées dans le contexte de leurs forces et faiblesses méthodologiques.*

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nine studies consistently reported that ultrasound has therapeutically beneficial effects on pain and functional outcomes. Five studies reported that ultrasound has positive cartilage healing properties and one experimental study demonstrated increased intra-articular absorption of high molecular weight molecules (hyaluronan) using ultrasound phonophoresis. Only one randomized controlled trial reported no effect on pain or active range of motion when ultrasound is used in combination with exercise.

Conclusions: Ultrasound demonstrates the ability to evoke a broad range of therapeutically beneficial effects which may provide safe and effective applications in the management of osteoarthritis.
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key words: ultrasound, osteoarthritis.

Résultats : *Au total, 17 articles ont répondu à nos critères de recherche, une étude a été exclue en raison des lacunes de sa méthodologie. À partir d'un ensemble de cinq articles de synthèse, deux articles ont conclu que l'ultrason possède des effets thérapeutiques positifs, deux n'ont démontré aucun avantage alors qu'un article était peu concluant. Les neuf études restantes ont constamment démontré que l'ultrason a des effets bénéfiques sur le plan thérapeutique sur la douleur et sur les résultats fonctionnels. Cinq études ont indiqué que l'ultrason possède des qualités de guérison du cartilage et une étude expérimentale a démontré une augmentation de l'absorption intra-articulaire des molécules à masse moléculaire supérieure (hyaluronane) en se servant de la sonophorèse. Un seul essai clinique comparatif randomisé a montré qu'il existe aucun effet sur la douleur ou sur l'amplitude actif des mouvements lors de l'utilisation de l'ultrason combiné avec de l'exercice.*

Conclusion : *L'ultrason démontre la capacité d'évoquer une gamme étendue d'effets bénéfiques sur le plan thérapeutique qui pourrait fournir des applications sécuritaires et efficaces pour le traitement de l'arthrose.*
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mot clés : ultrason, arthrose.

Introduction and Background

Osteoarthritis is considered to be the most common rheumatologic disease which affects more than 80% of the population above 55 years.[1] It is a complex, multi-faceted condition that has been characterized by various criteria including pathogenesis (mechanical, biological), morphology (articular cartilage, subchondral bone) and clinical features (joint pain, stiffness, tenderness, loss of ROM, crepitus and inflammation/effusion).[2] This ensemble of clinical and pathologic entities is often referred to as the osteoarthritic complex (OAC).

Ultrasound has been employed for over six decades with few documented cases of adverse effects.[3,4] It has demonstrated a long-standing record of safety and efficacy in numerous clinical applications.[5] Reports describing the physical, chemical and biologic effects of ultrasound date as far back as the early 1920's[6] and, since then, extensive research describing its mechanisms and bioeffects has been published.

The volume of research specifically evaluating the use of ultrasound in the treatment and management of osteoarthritis is sparse. While some clinicians still reject its use, there is an accumulating body of experimental, human and animal research demonstrating that ultrasound can evoke a broad profile of systematic bioeffects which may be useful in the management of many clinical conditions,[4] including osteoarthritis.

In spite of the accumulating research, incongruity exists between the study designs and the conclusions drawn from them. The primary challenge in interpreting the existing literature lies in the inadequate technical and biophysical applications of ultrasound in these studies. Inconsistent ultrasonic output parameters (intensity, frequency, dose) and application techniques (insonation locations, tissue char-

acteristics, treatment area) profoundly impact energy (dose) delivery and tissue absorption profiles, precluding meaningful inter-study comparisons. Furthermore, from a methodological standpoint, many of these studies evaluate ultrasound in combination with various adjunct modalities (massage, exercise) yet proceeded to offer conclusions on the efficacy of ultrasound alone.

Standardization and comparability of results between studies is further compromised in light of the broad subject variability (inclusion criteria) and inconsistent application of outcome measures (functional, disability and pain).[7] Despite these acknowledged limitations, a growing foundation of basic clinical, experimental and animal research demonstrates that ultrasound has positive therapeutic benefits which may be useful in the treatment and management of osteoarthritis.

Objective

The objective of this paper is to critically review the existing literature investigating the use of therapeutic ultrasound in the treatment and/or management of osteoarthritis. A specific emphasis is placed on interpreting the literature in the context of its strengths and weaknesses, with particular attention placed on study protocols and technical (waveform) parameters employed in the trials. Relevant basic science is also introduced and meaningful inter-study comparisons are highlighted with suggestions for future research.

Search Methods

A Pubmed search of the literature was performed from 1985 to present using the key words "ultrasound" and "osteoarthritis." Basic experimental, clinical and animal studies that specifically investigated applications of therapeutic ultrasound in osteoarthritic populations were targeted. Studies that evaluated therapeutic ultrasound in combination with other modalities (massage, exercise) were accepted but their conclusions were interpreted within the context of their strengths and limitations.

Our literature search retrieved 313 total articles which were then examined for relevance to the application of therapeutic ultrasound in the management of osteoarthritis. The majority of retrieved articles were related to some aspect of ultrasound imaging; accordingly, the search list was further filtered by the keyword of "ultrasonography." The resulting 59 references were individually examined for relevance, leading to a further 42 exclusions; 26 papers discussed various applications of ultrasound imaging, 9 described non-ultrasound interventions, 3 evaluated non-osteoarthritic populations, 2 assessed phonophoresis in non-osteoarthritic populations, 1 discussed ultrasound in the context of osteoporosis and another on bone repair. Figure 1 summarizes the search methods employed in this study.

Results

A total of 17 articles met our search criteria; one study[8] was excluded due to methodological concerns, as scored on the Jadad rating scale.[9] This study failed to report the ultrasound output parameters (intensity, frequency) used in the trials.

Of the remaining 16 papers, five were reviews; two of these reviews reported positive therapeutic effects (decreased pain, increased ROM) of ultrasound on osteoarthritis,[10,11] two were unfavourable[7,12] and one inconclusive.[13]

The Cochrane Database Review[7] is perhaps the most prominent and widely cited of these reviews. The authors of the Cochrane review concluded that "Ultrasound therapy appears to have no benefit over placebo or short wave diathermy for patients with knee OA"; however, they also acknowledged the studies' limitations by stating that "These conclusions are limited by the poor reporting of the characteristics of the device, of the population, of the OA, and therapeutic application of the ultrasound and low methodological quality of the trials included."

Falconer et al.[10] reviewed the effectiveness of therapeutic ultrasound in the treatment of selected musculoskeletal conditions. These authors reported sufficient evidence to support the use of ultrasound in the reduction of pain and increase of joint range for acute periarticular inflammatory conditions and osteoarthritis. The authors emphasized, however, that they could not discount the placebo response or subject bias and suggested the results are inconclusive, requiring further well-designed clinical trials.

Puett and Griffin[12] published a review on the efficacy of non-medicinal, non-invasive therapies in hip and knee osteoarthritis, concluding that there was no support in the literature for pre-exercise ultrasound use. Their conclusion was based on one study.[14] Our review incorporates an additional 14 publications since 1993 that were not included in the Puett and Griffin review.

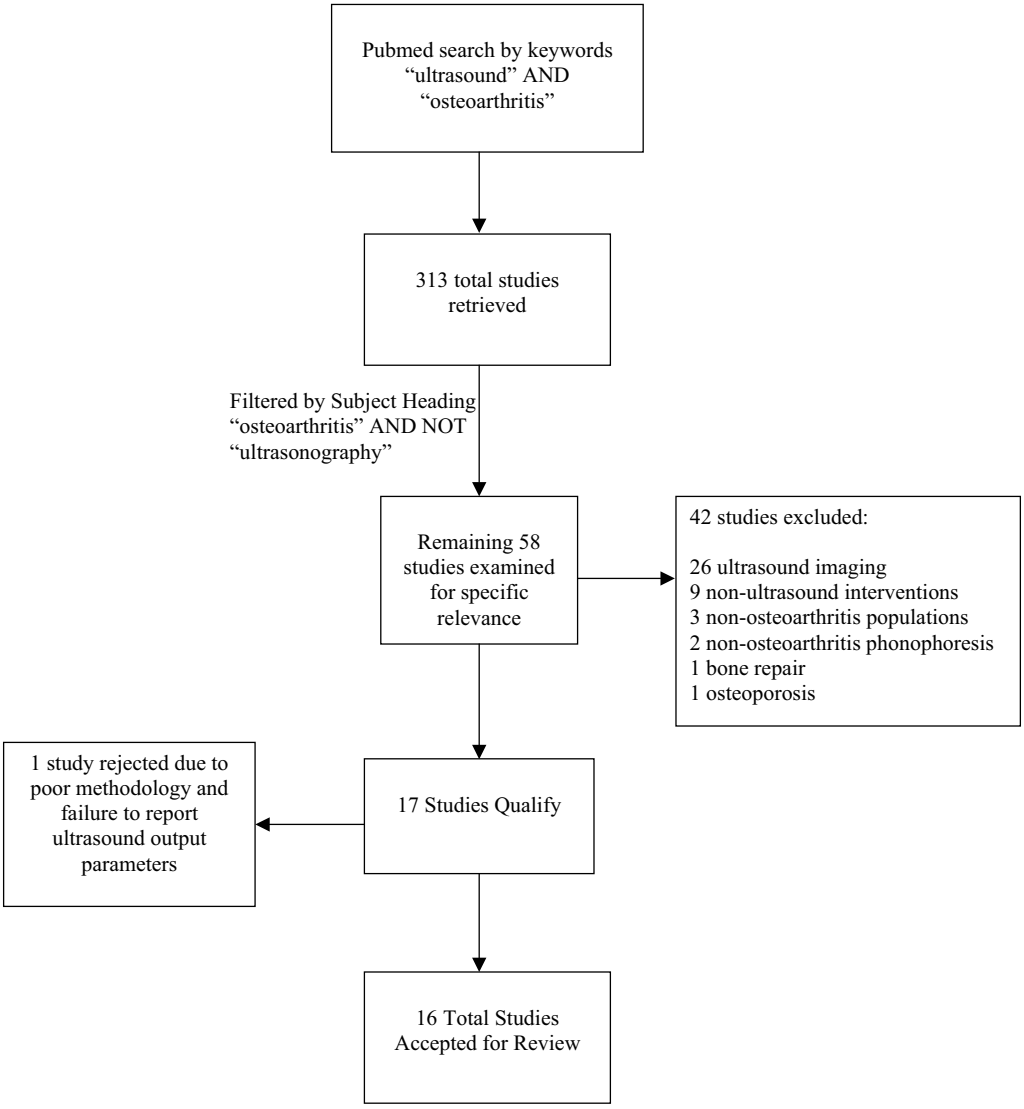

Figure 1 *Flow diagram illustrating the stages of inclusion of studies*

In an additional review, the Philadelphia Panel[13] set out to establish evidence-based practice guidelines for selected rehabilitation interventions in the management of knee pain. The Panel found no evidence supporting the use of ultrasound in osteoarthritis, but cited significant methodological limitations of these studies including lack of outcome measure standardization and high subject variability. They also underscored the innate difficulties in evaluating rehabilitation interventions, in general, due to the confounding impact of psychosocial, physical and occupational factors as well as the difficulty in blinding. One last review of therapeutic modalities used in the treatment of osteoarthritis[11] concluded that ultrasound demonstrated positive therapeutic effects. This review was written in German and the specifications of their search methods or inclusion criteria were not accessible.

Six further studies we retrieved examined the impact of ultrasound on cartilage healing and regeneration. Our search identified four animal trials and two experimental studies, all of which reported positive cartilage enhancing

effects. These studies consistently demonstrate that low intensity ultrasound in the range of 200–400 mW/cm^2 optimally enhances the expression of cartilage matrix-producing proteins.[15,16] Two additional studies report that exposure to pulsed ultrasound enhances cartilage repair in the early stages of experimentally induced osteoarthritis in animals and attenuates joint deterioration in later stages.[17,18] Similarly, two studies using an animal model of osteoarthritis demonstrate increased hyaluronan absorption into rabbit knee joints under the influence of ultrasound phonophoresis[19] while combined ultrasound and hyaluronan injection therapy significantly reduces the severity of OA-induced structural damage to the cartilage and synovium of rabbit knee joints.[20]

Five publications, one controlled trial and four RCTs, evaluated pain and functional outcomes (disability, ambulation speed, ROM, peak flexion/extension torques, isokinetic testing) after ultrasound treatment. In 4 of the 5 trials, ultrasound improved functional outcomes; one study failed to demonstrate any positive effect. A randomized controlled trial[17] investigating the effectiveness of isokinetic strengthening exercise with and without adjunctive ultrasound therapy for bilateral knee OA reported significant improvement in all functional outcomes in the ultrasound-treated groups. Another RCT using similar methodology[18] evaluated the effects of an integrated rehabilitation program using combinations of ultrasound, isokinetic strength exercise and intraarticular hyaluronan injection therapy on functional outcomes in knee osteoarthritis. In this study, both groups receiving ultrasound (pulsed, continuous) exhibited significant improvements in ambulation speed and range of motion; notable improvements in peak muscle torque and disability (Lequesne Index) were also reported. Another RCT[21] demonstrated a threshold 30% decrease in the WOMAC Osteoarthritis Index in almost 50% of subjects (n = 30) after only 10 sessions of ultrasound (1 MHz, continuous wave, 1 W/cm^2); significant improvement was reported in subjective pain scores, knee ROM and 20 meter walking time. Finally, the controlled clinical trial[22] comparing the effectiveness of ultrasound and diathermy in combination with exercise on chronic osteoarthritic knees reported an increase in both functional capacity and peak muscular torque in the ultrasound-only and ultrasound-exercise groups.

In contrast to these findings, the results of only one RCT we retrieved,[14] which investigated the ability of ultrasound to reduce stiffness and pain in chronic knee contractures secondary to osteoarthritis, was unfavourable. In this study, active exercises were prescribed, preceded by either ultrasound (1MHz, 2.5 W/cm2) or sham ultrasound. No difference in active ROM was observed between groups after 12 treatments spanning a 6 week period.

Discussion

Ten out of the 11 experimental studies we reviewed (excluding the 5 review papers) reported positive outcomes for ultrasound in osteoarthritic populations; these outcomes included decreased pain, increased function and enhanced cartilage repair. Two of the 5 review papers reported sufficient experimental evidence to support the use of ultrasound in specific clinical settings, two reported insufficient evidence and one was inconclusive.

The six studies addressing cartilage repair unanimously support the cartilage-enhancing effects of ultrasound. The frequency and intensity output levels used were consistently in the low intensity ultrasound range (1 MHz, 200–400 mW/cm^2). Treatment frequency and duration varied, however, ranging from 7 minute exposures of pulsed ultrasound, three times weekly for 4 weeks in comparison with daily continuous-wave exposures lasting one week in duration. Accordingly, optimal exposure parameters must be standardized before optimal treatments and clinical protocols can be established.

Five studies we retrieved evaluated the impact of ultrasound on functional outcomes in arthritic joints; four out of the five studies reported positive outcomes. The general concern with these studies is the uniform use of adjunctive modalities with the ultrasound. Of the four positive outcome studies, three studies applied ultrasound in conjunction with modalities including exercise and injections. The lone study[14] which failed to demonstrate any effect specifically investigated the impact of pre-exercise ultrasound on chronic knee contractures secondary to osteoarthritis. In this study, the authors reported no difference between ultrasound and sham-ultrasound but declare dosage, muscle shortening, transience of physiologic effect(s) and the effects of exercise as confounding factors. Moreover, this study failed to employ exercise controls to isolate the effects of ultrasound and, therefore, the interpretation of these conclusions should be restricted to the context of pre-exercise ultrasound only.

The five review publications we retrieved were balanced in their assessment of ultrasound. Falconer et al. report that "pain and range of motion appear to improve following ultrasound therapy in acute periarticular inflammatory conditions and osteoarthritis" while Kladny et al. conclude that ultrasound demonstrates positive therapeutic effects in osteoarthritis. Both studies cite potential limitations of placebo and experimenter expectancy bias. The Philadelphia Panel review looked at the broad scope of knee pain, including osteoarthritis, and concluded that there was a "lack of evidence regarding efficacy" of ultrasound in the treatment of knee pain but qualify this by declaring a lack of outcome standardization and high subject variability. Two further reviews inappropriately concluded that insufficient evidence exists for the use of ultrasound in osteoarthritis.[7,12] Both of these reviews, however, based their assumption on only one trial,[14] which exclusively assessed the impact of pre-exercise ultrasound on knee contractures. Puett et al. emphasized this point by qualifying that "no support exists in the literature for pre-exercise ultrasound treatment." The conclusion of the influential Cochrane Database Review was more critical, however, stating that "Ultrasound therapy appears to have no benefit over placebo or short wave diathermy for patients with knee OA." The Cochrane Review included an additional two studies,[8,23] both of which were excluded from our review. One of these studies[23] predated our search criteria while both studies[8,23] scored poorly on the Jadad Scale due to a failure to report the output parameters used in their trials. Indeed, the authors of the Cochrane Review go on to qualify their conclusion by declaring limitations of poor reporting of the ultrasonic device, study population, inclusion criteria for osteoarthritis, ultrasound application techniques and poor methodological quality of the studies they reviewed.

In parallel to the research directly examining osteoarthritic populations, there is a growing body of basic science suggesting that ultrasound enhances healing and may impact various physiologic processes that are foundational to the osteoarthritic condition. In this capacity, ultrasound has demonstrated the ability to enhance tissue healing by means of facilitating protein synthesis[24] and accelerating angiogenesis[25,26] with outputs as small as 100 mW/cm^2 and frequencies of both 0.75 and 3 MHz. It also promotes orderly collagen deposition to increase tissue tensile strength in healing[27,28] with low dose ultrasound (500 mW/cm^2, pulsed mode, 20% duty cycle, 1 MHz, 5 minutes) demonstrating increased effectiveness over high dose ultrasound (1.5 W/cm^2, continuous mode, 1 MHz, 5 minutes). Additionally, animal studies have established that pulsed ultrasound (1 MHz, I_{sata} = 500 mW/cm^2, 5 min, 14 consecutive days) is more effective than continuous wave at enhancing the deposition rate, organization and aggregation of collagen bundles in tendons post-tenotomy, as compared to controls.[29,30] Ultrasound also promotes earlier resolution of inflammation and heightened fibroblast recruitment with waveforms of both 0.75 MHz and 3 MHz (continuous wave, I_{sata} = 0.5 W/cm^2). These collective observations suggest that therapeutic ultrasound may possess significant healing benefits useful for the management of a broad spectrum of pathologies, including osteoarthritis. Furthermore, this foundation of basic science can provide the conceptual basis for further hypotheses and clinical research in this field.

If a therapeutic intervention is to have a reliable and consistent effect, there must be a recognized correlation between dose delivered to tissues and bioeffects. Therefore, an important antecedent to creating effective clinical protocols is the establishment of an accurate dose-response profile for ultrasound. The primary failure in the current literature is the inadequate standardization and reporting of the output waveform parameters and application techniques, both critical determinants of dose. Detailed reporting of these parameters allows for meaningful inter-study comparison and standardization of dose-response characteristics which may be systematically extrapolated to clinically testable hypotheses.

Apart from the waveform frequency, the basic waveform parameters essential to energy (dose) calculations include the average intensity (W/cm2), duty cycle (%) and time of exposure (min). Other parameters that are vital to describing the energy characteristics include pulse frequency (Hz), pulse duration (msec), beam nonuniformity ratio (BNR), pulse average and peak pulse intensities (W/cm2).[31] These parameters were insufficiently documented in the studies we retrieved.

Variations in application technique can have an equally profound impact on dose delivery. The energy density (J/cm2) delivered to the tissues is related to the ratio of the ultrasound head radius to the radius of the treatment area,[32] thus, variations in the size of treatment area significantly impact dose. Furthermore, the insonation location

(local tissue composition, depth of lesion, density of tissue) plays a vital role in the tissue energy absorption profile, with higher frequencies being more readily absorbed superficially.

Conclusion

There is an accumulating body of research suggesting that ultrasound may have the potential to provide significant benefits in the treatment and management of the osteoarthritic complex. In spite of the methodological limitations in the research, each of the retrieved studies does offer valuable data and unique insight into some aspect of ultrasound biophysics that could possibly be exploited in the management of osteoarthritis.

The current literature on ultrasound lacks consistency and its deficiencies have been well documented. To promote future meaningful inter-study comparison and meta-analyses, it is imperative that the research in this field adheres to strict methodologies and meticulous reporting of output parameters and application techniques. In addition, in order to make definitive conclusions on the bioeffects of ultrasound, study designs must isolate the effects of ultrasound by excluding, where possible, adjunctive modalities in their methodology.

An important directive for future research is to elucidate the biologic impact of various ultrasound waveform parameters. For example, while absolute dose calculations currently guide much of our clinical rationale, some authors suggest that other parameters, such as peak pulse intensity, may be a more appropriate correlate to the physiologic bioeffects of ultrasound.[31] Thus, it is critical that future research in this field detail the output parameters to allow for meaningful inter-study comparison.

Nevertheless, there is accumulating evidence to justify significant interest in this technology as a clinical tool. Ultrasound is a generally safe, non-ionizing energy form that is ideal for use in the daily clinical setting due to its cost-effectiveness, portability and ease of use. For these reasons, we must embrace the current literature and strive to further our understanding and application of ultrasound in medicine.

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