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Effects of Ultrasound Therapy on Pain Intensity of Patients with Knee Osteoarthritis - A systematic Review of Evidence

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The knee is the major weight bearing joint of the body. It is therefore expected that the knee more than most joints of the body will be more prone to the development of Ostearthritis (OA). Literature appears unsettled regarding the most preferred treatment parameters and the effects of ultrasound in the management of knee OA. This study systematically reviewed randomized controlled trials (RCTs) on the effects of ultrasound in the management of knee OA. Electronic bibliographical databases such as PubMed, Cochrane, PEDro and Google Scholar were searched using MeSH terms and Key terms where applicable. The PICO format was used to define study eligibility while methodological quality of studies was assessed using the PEDro scale. High-quality RCTs with PEDro score ≥7 and large sample sizes ≥70 were considered level 1 evidence while lower-quality RCTs with smaller sample size were considered level 2 evidence. A total of 577 studies were generated from the search strategy; only 5 of the articles met all the inclusion criteria and were selected for this review. About 80% of these studies recruited patients with bilateral knee OA and were aged ≥ 40 years. Most of the studies (80%) had sample size that ranged between 30 and 89 and had fair/good methodological quality. Based on the PEDro scores and sample size, only one study provided level 1 evidence. The most utilized ultrasound parameter was an intensity ≥1W/cm2, 1MHz frequency, for 5-10mins/session, 5 days/week and for total duration of 2 weeks. Ultrasound at an intensity ≥1W/cm2, 1MHz frequency, for 5-10mins/session, up to 5days/week and for total duration of 2 weeks is effective for the enhancement of functional recovery in patients with knee osteoarthritis

Key words: Ultrasound, Knee Osteoarthritis, Pain Intensity, Functional Recovery, Systematic Review

INTRODUCTION

Osteoarthritis (OA) has been defined as "a heterogeneous group of conditions that leads to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone and at the joint margins" (Altman et al, 1986). It is a degenerative joint disease that involves the cartilage and many of its surrounding tissues that leading to damage and loss of articular cartilage as

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well as remodeling of subarticular bone, osteophyte formation, ligamentous laxity, weakening of periarticular muscles, and, in some cases, synovial inflammation (Cooper et al, 2014). These changes may occur as a result of an imbalance in the equilibrium between the breakdown and repair of joint tissue (Dulay et al, 2015). Joint pain, stiffness, and limitation of movement are the primary symptoms of OA (Litwic, 2013). Disease progression is usually slow but can ultimately lead to joint failure with pain and disability (Dulay et al, 2015). Knee OA constitutes 83% of the global disease burden for OA (Vos et al, 2010).

In 1961 WHO accepted the Kellgren and Lawrence system of classification of the severity of knee osteoarthritis. The classification ranges from grade 0 to 4; with grade 0 described as an OA that presents with no radiographic evidence and grade 4 characterized with marked joint space narrowing, severe sclerosis, large osteophytes and definite bony deformity (Kohn et al, 2016). Cross-sectional imaging methods, such as magnetic resonance imaging (MRI), can visualize joint structures in more detail and continue to undergo evaluation to determine if they will provide a means by which the definition of OA can be refined.

According to Zhang and Jordan, (2010), the prevalence of OA varies depending on the definition of OA, the specific joint(s) under study, and the characteristics of the study population. The age standardized prevalence of radiographic knee OA in adults aged ≥ 45years was 19.2% among the participants in the Framingham Study and 27.8% in the Johnston County Osteoarthritis Project (Lawrence et al, 2008). In the third National Health and Nutrition Examination Survey (NHANES III), approximately 37% of participants age >60 years or older had radiographic knee OA.

The knee is the major and most complex weight bearing joint of the body (Bennell et al, 2019). It is therefore expected that the knee more than any other joint in the body will be more prone to the development of OA. Heidari et al, (2011) reported that about 13% of women and 10% of men aged 60years and above had symptomatic OA of the knee. The prevalence of OA especially knee OA is expected to increase due to the aging of our population and the increasing rate of obesity and overweight in the general population (Leyland et al, 2016). With this rise in the prevalence of OA especially knee OA, several studies have investigated several treatment modalities such as ultrasound (Tascioglu et al, 2010; Zhou et al, 2018), resistant exercise (Jan et al, 2008; Vincent and Vincent, 2012), combination therapies (Mascarin et al, 2012; Park and Hwangbo, 2015) and others (Tangadulrat et al, 2019; Odole et al, 2019).

Although some studies (Cakir et al, 2014; Yang et al, 2011; Alfredo et al, 2020) have shown that the use of ultrasound is effective for pain reduction in patients with knee OA, other studies found no such effects (S˘varcova et al, 1988; Falconer, 1992). Literature also appears unsettled regarding the most preferred ultrasound treatment parameters for people with knee osteoarthritis. Given the need for a systematic appraisal of literature in the face of conflicting reports (Ekechukwu et al, 2020) as well as the lack of a consensus regarding an empirically supported ultrasound therapy parameters for people with knee OA, the impetus for this study was gained. This study reviewed randomized controlled trials on the effects of ultrasound in the management of knee OA.

Methods

Search Strategy

In adherence to the Preferred Reporting Items for Systematic Reviews and MetaAnalysis (PRISMA) guidelines, studies were identified by a search of the electronic databases of PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), the Physiotherapy Evidence Database (PEDro) and google scholar. Two reviewers (NIE and ENE) independently screened all abstracts obtained and retrieved randomized control trials involving patients with knee osteoarthritis treated with the use of ultra sound with a comparable control. The reference lists and bibliographies of identified systematic reviews were also scanned and reviewed.

Eligibility criteria

Using the PICO method to define the four major components of the topic

P (Patient): Adults with knee osteoarthritis

I (Intervention): Ultrasound (pulsed and/or continuous modes)

C (Control): Any other treatment means for the management of knee osteoarthritis as well as placebo.

O (Outcome): primary outcome pain; secondary outcomes – range of motion, walking distance, function etc

Inclusion criteria

Only Randomized Clontrolled Trials on knee osteoarthritis that used ultrasound as a means of pain management that were published between January 1, 2009 and December, 2019 were selected and reviewed. Primary studies comparing ultrasound therapy with any other treatment method as well as ultrasound with a placebo group were included provided ultrasound was an additional therapy for the experimental group. Only studies that included patients with knee osteoarthritis of kellengren-Lawrence grade 1 and above were included in this review.

Exclusion criteria

Studies that met the inclusion criteria but with reports that indicated previous surgery on the knee or arthroscopy to the knee joint were excluded. Also, primary studies where the participants had confounding co-morbidities such as rheumatoid arthritis or any other obvious autoimmune disorders were excluded.

Study Quality Appraisal

The quality of the RCTs was assessed using the PEDro quality appraisal tool. Answers to the quality appraisal items were defined as yes and no. It consists of 11-items but only the scores of items 2-11 are summed and that stands for the total score of the study's methodological quality. A score of one was given to each yes and

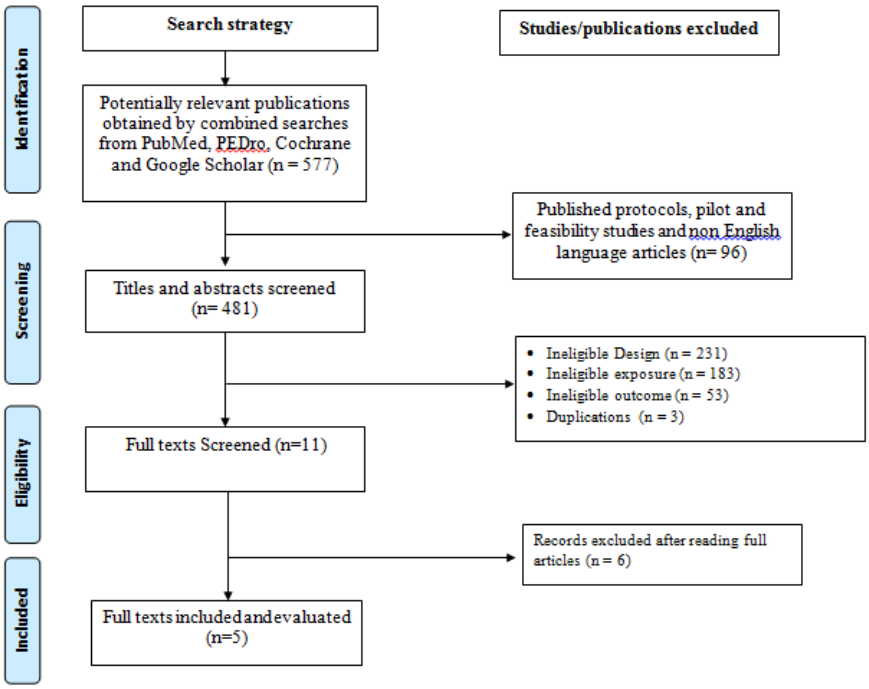

Figure 1: PRISMA Diagram

zero to no. The overall score was reported as a tally of all yes out of 10 based on the applicable answers for each study

Any study with PEDro score greater than or equal to 7 and with sample size greater than or equal to 70 was judged to have level 1 evidence while studies with PEDro scores less than 7 and/or sample size less than 70 were judged as studies with level 2 evidence (Hamzat and Ekechukwu, 2015).

RESULTS

Flow of studies through the review

The initial searches identified a total of 577 potential relevant papers. The flow of papers through the process of assessment of eligibility is approximately represented with reasons for exclusion of papers at each stage of the process as shown in Figure 1.

Characteristics, Outcome Measures and Treatment Protocols of Included Studies

A total number of 577 articles were generated from the search strategy; 5 articles fulfilled all the criteria and were selected for this review. Most of the studies (80%) had participant of age 40 years and above as well as recruited participants with bilateral knee osteoarthritis (Yildiz et al, 2015; Yegin et al, 2016; Mascarin et al, 2012; Tascioglu et al,2010). Visual Analogue Scale (VAS) was used in all the studies selected as primary outcome to measure pain intensity pre and post intervention. Also, all (100%) of the studies used WOMAC questionnaire and 10% used the Leguense scale as secondary outcome measures. To classify osteoarthritis, the Kellengren-Lawrence scale was used in most (80%) of the studies, and 60% of the studies were rated 2-3. All (100%) of the studies used the continuous mode of ultrasound while only 40% of the studies used the pulsed mode at a pulse width of either 1:4 or 1:5. All (100%) of the studies used a treatment head of 1MHz, mostly 5cm^2 in size. The treatment intensities varied between 0.8-2W/cm^2 at 3-10mins/session for a total of 10-24 sessions in total. There was an improvement in pain and functional potentials in the intervention groups compared to the control as shown in Table 1.

Quality Appraisal of Included Studies

Only 20% of the studies included in this review had a Pedro rating of 10 (Luksurapan and Boonhong, 2013), while 40% of the RCTs scored 5 on the Pedro Scle (Yildiz et al, 2015 and Yegin et al, 2016). In the same vein, 20% of the primary studies were rated 7 and 6 on the Pedro scale for quality appraisal (Mascarin et al, 2012 and Tascioglu et al, 2010 respectively). The average quality rating of all the studies included in this review was 6.6 as shown in Table 2.

Table 1. Summary of Study Characteristics, Outcome Measures and Treatment Protocols of Included Studies

Studies	Location	Intervention (s)	Control	Affected Side	KL grade	Rx head area / PW	Outcome (Outcome Measure)	Treatment Parameters							Results
								F(MHz)	I (W/Cm^2)	D/S (min)	TD (weeks)	TF (days/wk)	N	Age	
Yildiz et al, 2015	Turkey	I_1 = C-UTS I_2 = P-UTS	Placebo (CG)	bilateral	2 & 3	$5cm^2$ / 1:5	Pain (VAS); ROM; Function (LFI); QoL (SF-36)	1	1.5	5	2	5	90	40-65	- Sig.↑ knee ROM in both UTS groups - at M2, VAS & Lequesne scores of CG Sig. > both C-UTS (P < 0.01) and P-UTS (P < 0.05)
Yegin et al, 2016	Turkey	C-UTS	Sham	bilateral	2	$5cm^2$	Pain (VAS, WOMAC, LFI, SF-36); Function (Morning stiffness; 6MWD, SF-36)	1	2	8	2	5	65	40-70	- Sig improvement in all pain scales (VAS, WOMAC, Lequesne, SF-36), morning stiffness and 6MWD in IG (p<0.05), but only in VAS, WOMAC and SF-36 in CG (p<0.05). -Sig better improvement in IG than CG
Tascioglu et al, 2010	Turkey	I_1 = C-UTS I_2 = P-UTS	Placebo	bilateral	2 and 3	5cm diameter / 1:4	Pain (VAS, WOMAC); ROM; 20mWT	1	2	5	2	5	82	54-70	- Sig. improvements in the VAS & WOMAC in all groups. - The ↓ in VAS and WOMAC Significantly higher in P-UTS than CG.
Luksurapan & Boonhong, 2013	Thailand	C-UTS	PhP	Not specified	1-3	Not specified	Pain (VAS, WOMAC); Function (WOMAC)	1	1.0	10	2	5	46	26-78	- Sig improvement in VAS & WOMAC in both groups (P<0.001). - PhP > C-UTS (though non-significantly)
Mascarin et al, 2012	Brazil	C-UTS	C_1=KT; C_2=TENS	bilateral	nil	5cm diameter	Pain (VAS); Function (WOMAC); ROM (Goniometer); FEC (6MWT)	1	0.8	3-4	12	2	40	≥45	Sig. improvements in 6-MWD for C-UTS & KT (14.1± 22.5% and 19.8 ± 21.7% respectively). - All treatments ↓pain and ↑ WOMAC

KL = Kellengeen-Lawrence; Rx = Treatment; PW = Pulse width; F = Frequency; I = Intensity; D/S = Duration per session; TD = Total treatment duration; N = Number of participants; IG = Intervention group; CG = Control group; C-UTS = Continuous Ultrasound; P-UTS = Pulsed Ultrasound; LFI = Lequesne functional index, VAS = Visual Analogue Scale; ROM = Range of Motion; QoL = Quality of Life; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; 6MWD = Six Minutes Walk Distance; SF = Short form; 20mWT = Twenty meters walking time; KT = Kinesotaping; TENS = Transcutaneous electrical nerve stimulator; FEC = Functional exercise capacity; 6MWT = Six minutes walk test.

Table 2. Summary of Quality Appraisal of Included Studies

Research Studies	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	SCORE
Yildiz et al,2015	√	√	√	√	x	x	x	√	x	√	x	5
Yegin et al,2016	√	√	x	√	x	x	x	√	x	√	√	5
Tascioglu et al,2010	√	√	√	√	√	x	x	√	x	√	√	7
Luksurapan and Boonhong,2013	√	√	√	√	√	√	√	√	√	√	√	10
Mascarin et al, 2012	√	√	x	√	x	x	√	√	√	√	x	6
Average Score												6.6

Key: Q1 = Eligibility criteria, Q2 = Random allocation, Q3 = concealed allocation, Q4 = Similar Baseline, Q5 = Blinding of all subjects, Q6 = Blinding of therapists, Q7 = Blinding of Assessors, Q8 = Adequate follow up, Q9 = Intention to treat, Q10 = Between group comparison, Q11 = Point and Variability measures

Table 3. Summary of Level of Evidence of RCTs using Pedro Scores and Sample Size

Variables	**Categories**	**Studies**	**f**	**%**
Pedro Scores	Excellent (9-10)	Luksurapan and Boonhong,2013	1	20
	Good (6-8)	Tascioglu et al,2010; Mascarin et al, 2012	2	40
	Fair (4-5)	Yildiz et al,2015; Yegin et al,2016	2	40
	Poor (0-3)	None	0	0
Sample Size	< 30	-	0	0
	30 - 59	Mascarin et al, 2012; Luksurapan and Boonhong, 2013	2	40
	60 - 89	Yegin et al, 2016; Tascioglu et al, 2010	2	40
	≥ 90	Yildiz et al,2015	1	20
Level of evidence	Level 1	Tascioglu et al, 2010	1	20
	Level 2	Mascarin et al, 2012; Luksurapan and Boonhong, 2013; Yegin et al, 2016; Yildiz et al,2015	4	80

Level of Evidence of RCTs using Pedro Scores and Sample Size

Twenty percent of the studies included in this review had an excellent score on the Pedro scale (9 – 10) while other RCTs were good (6-8) or Fair (4 – 5) in quality. Most of the primary studies (80%) had sample sizes between 30 – 89 persons with knee OA. Using the Pedro scale and sample size, only one study (Tascioglu et al, 2010) was classified to have level 1 evidence while other studies had level 2evidence as illustrated in table 3.

DISCUSSION

Ultrasound is sound with a frequency greater than 20,000 cycles per second (20 KHz) (Peterson, 2012). Generally, therapeutic ultrasound has a frequency between 0.7 and 3.3 megahertz (MHz) to maximize energy absorption at a depth of 2 to 5 cm of soft tissue (Londeen, 2013). Ultrasound has a variety of physical effects that can be classified as thermal or non-thermal effects. These effects are both useful for addressing the pathology of Osteoarthritis. Acoustic streaming, microstreaming, and cavitation, which may be capable of altering cell membrane permeability and cell functioning, are the nonthermal effects of ultrasound (Lentacker et al, 2014); whereas the increase in tissue temperature constitutes the thermal effect of ultrasound (Gupta and Srivastava, 2018). Continuous ultrasound is generally used to produce thermal effects, whereas pulsed ultrasound is used for nonthermal effects (Xin et al, 2016). Osteoarthritis is a peri-articular degenerative disease common among older adults. Ultrasound, unlike most commonly used pharmacological agents among people with osteoarthritis due to the considerable gastrointestinal and cardiac side effects of these pharmacological agents (Maniar et al, 2018) has been well tolerated especially among older adults.

All the studies in this review assessed pain intensity using the visual analogue scale while WOMAC had the greatest utility for assessing functional potential. Although VAS is basically a rating scale (Sung and Wu, 2018), it is unarguably, the most utilized outcome measure for assessing pain intensity not only among OA cohorts but also among other populations with musculoskeletal disorders (Pathak et al, 2018) both for clinical and research purposes. The Western Ontario Mc-Master Universities Osteoarthritis Index (WOMAC) has also been reported to be a commonly used outcome measures among patients with OA (Celik et al, 2019). The WOMAC scale has been commonly used to assess pain and joint stiffness among OA patients in most studies (Kamel, 2018; Lu et al, 2018). Lequesne scale was also used in some of the studies reviewed to assess pain and maximum walking distance and daily activities of their participants. Although in some studies, walk tests (the 6MWT and 20mWT) were used to assess walking distance while goniometry was used to asses joint stiffness or range of joint motion.

All the studies but one (Mascarin et al, 2012) used the Kellegren-Lawrence (KL) classification system to categories the severity of knee OA in their studies. This system ranges from 0 to 4 and grades knee OA severity into 4 categories where grade 1 represents “doubtful narrowing of the joint space with possible osteophyte formation” (Kellgren and Lawrence, 1957; Schiphof et al, 2008) and this coincides with grade B of the International Knee Documentation Committee (IKDC) classification system defined as having a joint space that is greater than 4mm, but with the presence of small osteophytes, slight sclerosis, or femoral condyle flattening (Hefti et al, 1993; Irrgang et al, 2006). The KL grade 2 is defined as “possible narrowing of the joint space with definite osteophyte formation” and this aligns with having a joint space between 2 and 4mm going by the IKDC system. The third grade of the KL classification refers to a “definite narrowing of joint space, moderate osteophyte formation, some sclerosis, and possible deformity of bony ends” while the last grade represents “large osteophyte formation, severe narrowing of the joint space with marked sclerosis, and definite deformity of bone ends”. These third and fourth grades are the equivalence of joint spaces that are less than 2mm (IKDC); and a joint space narrowing that is greater than 75% with additional secondary features (Fairbank system and Brandt system) respectively (Kohn et al, 2016). Majority of the studies included in this review recruited patients with KL grades 2 or 3. This implies that these patients had a non-speculative knee OA.

Most of the studies in this review used the continuous and/or the pulsed mode of ultrasound as their intervention at an intensity ≥1W/cm^2, 1MHz frequency, for 5-10mins/session, 5days/week and for total duration of 2 weeks. These interventions resulted in improved outcomes. The continuous mode of ultrasound operates using the thermal effects of ultrasound (Wang et al, 2018). Here, high-frequency alternating electrical current is delivered to the transducer for throughout the treatment time and this causes heat to build up. Ultrasound heats tissues with high ultrasound absorption coefficients (eg scars, tendons, ligaments, joint capsules, and fasciae) more than those with low absorption coefficient (eg muscles, adipose tissues) (Cortela et al, 2016). It is also suitable for tissues with high blood circulation and the highest temperature is generally produced at soft tissue–bone interfaces where reflection is greatest (Nell and Myers, 2010). These descriptions suit the knee joints a great deal, hence the therapeutic benefits of ultrasound in chronic knee pathologies such as OA. The thermal effect of continuous ultrasound accelerates metabolic rate (Dziedzic and Hammond, 2010), reduces or controls pain and muscle spasm (Ebadi et al, 2012), alters nerve conduction velocity (Suganthirababu et al, 2019) and

increases circulation (Morishita et al, 2014); these ultimately result in pain reduction and tissue healing (Yadollahpour et al, 2014).

Pulsed ultrasound is produced when the high-frequency alternating electrical current is delivered to the transducer for only a limited proportion of the treatment time, as determined by the selected duty cycle (Polak et al, 2016). The studies included in this review used a duty cycle of 1:4 or 1:5. This implies that ultrasound is only delivered to the tissue for about 20-25% of the time and so does not give enough time for heat build-up. Thus, pulsed ultrasound utilizes the non-thermal effects of ultrasound. These non-thermal effects are the result of the mechanical events produced by ultrasound, including cavitation, microstreaming, and acoustic streaming (Izadifar et al, 2017). Pulsed ultrasound with low average intensity has been shown to increase intracellular calcium levels (Tassinary et al, 2018) and to increase skin and cell membrane permeability (Yu et al, 2012). It is also known to have increased mast cell degranulation and the release of chemotactic factor and histamine (Çalık et al, 2020). Pulsed ultrasound also promotes macrophage responsiveness and increases the rate of protein synthesis by fibroblasts and tendon cells (Ennis et al, 2016). Furthermore, low-intensity pulsed ultrasound has been observed to stimulate proteoglycan synthesis by chondrocytes (cartilage cells) (Yuan et al, 2014). Pulsed ultrasound appears to facilitate tissue healing and functional recovery better than continuous ultrasound (Tascioglu et al, 2010), although these differences in these studies were not significant. More randomized clinical trials on the comparative efficacies of these two ultrasound modes are therefore recommended.

Conclusion

Continuous or pulsed ultrasound (duty cycles 1:4 or 1:5) at an intensity ≥1W/cm^2, 1MHz frequency, for 5-10mins/session, up to 5days/week and for total duration of 2 weeks is effective for pain reduction, promoting tissue healing and enhancement of functional recovery in patients with knee osteoarthritis.

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