Effects of ultrasound therapy on mcl injuries

The medial collateral ligament (MCL) is one of the most frequently injured ligaments of the knee joint. Fortunately, most patients who sustain MCL injuries are able to achieve their previous level of activity without the need for surgical treatment. However, the most severe injuries, especially those involving multiple ligaments, may require operative repair. This study will explore the effectiveness of a conservative treatment, namely ultrasound therapy and exercise therapy, in the treatment of MCL injuries of the knee joint. In a review by Phisitkul, James, Wolf, and Amendola (2006), treatment with early range of motion (ROM) exercises and progressive strengthening has been shown to produce very good results.

Ultrasound therapy has been a widely used and well-accepted physical therapy modality for musculoskeletal conditions for many years. Wong, Schumann, Townsend, and Phelps (2007) performed a survey about the use of ultrasound by physical therapists who are orthopaedic specialists, and found that ultrasound therapy is a popular adjunct in orthopaedic physical therapy and that it is perceived as important. However, the lack of studies confirming its benefits has led many to question this traditional view. Indeed, many studied which explored the effectiveness of ultrasound therapy failed in establishing a definite conclusion. Nevertheless, it cannot be assumed that this lack of evidence implies that ultrasound therapy is ineffective, and thus further research is needed to establish the adequacy of its use.

This study aims at answering the following crucial questions: In patients with MCL injuries of the knee, can ultrasound improve pain, disability and general recovery? Is it more effective than exercise therapy in improving symptoms?

An answer to these questions will help to better direct physiotherapy treatment for these patients, and thus optimize recovery.

Subsequent chapters will discuss the current literature available on the subject, followed by the methodology used in this study. The results are then presented and analysed. The interpretation of results in the context of previous research will be discussed in the discussion chapter, including the strengths and limitation of the study.

Literature Review

Ultrasound therapy has become commonly used in soft tissue injuries (Speed, 2001). Research carried out in the past few decades regarding the effects of ultrasound on body tissues will be discussed below. My aim is to review the research available from the past years in attempt to find conclusive and consistent results regarding the effects of ultrasound, and thus to justify the use of ultrasound in the clinical setting, specifically to treatment of medial collateral ligament injuries.

As will be discussed in this chapter, when ultrasound enters the body, it is thought to exert an effect on it through thermal and non-thermal mechanisms (Robertson, Ward, Low, & Reed, 2006, p. 266). Some of these effects may stimulate healing; however others may be dangerous and may cause damage.

Thermal effects of ultrasound

As ultrasound waves travel trough body tissues, they cause oscillation of particles, thus converting sonic energy into heat energy. The amount of heat produced will greatly depend upon the intensity given and the rate of energy absorption, but also on certain tissue properties, such as the heat capacity, efficiency of heat transfer, and the tissue distribution and space (Robertson, Ward, Low, & Reed, 2006, p. 266). Some authors have suggested pre-heating the area of treatment to achieve a greater increase in tissue temperature (Draper et al 1998a).

Living tissue will be affected by an increase in temperature in various different ways. According to Speed (2001), the thermal effects of ultrasound include an increased extensibility in tissues, enhanced blood flow, pain modulation, decreased joint stiffness and muscle spasm, together with a mid inflammatory response. These could explain why a temporary increase in range of motion is observed after ultrasound treatment (Draper et al., 1998b; Knight et al., 2001). Hayes, Merrick, Sandrey and Cordova (2004) studied the extent of heating in tissue at 2. 5cm depth and found that 3MHz ultrasound was more effective in heating the tissues at this depth than 1MHz, reaching a temperature of 40 degrees Celsius after 4 minutes. Unfortunately the production of heat may place the patient at risk of a skin burn if applied incorrectly (Robertson, Ward, Low, & Reed, 2006, p. 290).

Physical effects of ultrasound

Cavitation

Cavitation is “ the formation of tiny gas bubbles in the tissues as a result of ultrasound vibration” (Robertson, Ward, Low, & Reed, 2006, p. 267). Johns (2002) explains how as sound waves travel through the tissues, the characteristic compression and rarefaction causes microscopic gas bubbles present in the tissue fluid to contract and expand. Injury to the cell may occur when these gas bubbles expand and collapse rapidly. Nevertheless, cavitation has been found to occur only when using high intensities, and thus it is unlikely to occur in vivo with therapeutic levels (Nyborg, 2001). However according to a review by Baker, Robertson, and Duck (2001), there are a few studies which suggest the existence of in vivo cavitation. Baker and his colleagues argue that these studies were not replicated and that results obtained may have been due to difficulty with the analysis of B-scan imaging, which were used to measure cavitation. A recent study investigated the method by which cavitation is detected. The wavelet approach was identified as a new tool for studying bubble cavitation (Zhou, 2008). Cavitation becomes clinically relevant during ultrasound applications in water, as bubbles that form between the skin and the treatment head may block transmission of ultrasonic waves (Ward & Robertson, 1996).

Acoustic streaming

Acoustic streaming may be described as a flow of liquid caused by a generation of pressure along the axis of the beam of energy and on any other structures which reflect it (Robertson, Ward, Low, & Reed, 2006, p. 268). There are two types of acoustic streaming: microstreaming and bulk streaming (Duck, as cited in Baker, Robertson & Duck, 2001). Bulk streaming occurs in any fluid and develops as the ultrasound beam is propagated, while microstreaming occurs at a microscopic level and is formed as eddies of flow flanking to an oscillating surface (Robertson, Ward, Low, & Reed, 2006, p. 268).

Unfortunately bulk streaming is much less mechanically powerful, with microstreaming being the only type of acoustic streaming which is able to stimulate cell activity and change membrane permeability (Duck, as cited by

Baker, Robertson, & Duck, 2001). Microstreaming can produce stress on the cell membrane and wash away any molecules and ions which accumulate outside the cell membrane (Robertson, Ward, Low, & Reed, 2006, p. 268). According to Duck (as cited by Baker, Robertson, & Duck, 2001), only bulk streaming occurs in vivo, because microstreaming only occurs secondary to cavitation. In vitro studies show increased growth factor production by macrophages (Young and Dyson, 1990a), increased calcium uptake (Mortimer and Dyson, 1988), increased secretion and degranulation of mast cell (Fyfe and Chahl, 1984) and increase cell membrane permeability (McCance and Huether, as cited by Baker, Robertson, & Duck, 2001) by microstreaming. This however will have minimal relevance in the clinical setting if one assumes that cavitation will not occur. Nevertheless, Manasseh, Tho, Ooi, Petkovic-Duran, and Zhu, (2010), suggest that microstreaming which occurs secondary to cavitation will play a role in the action of microbubbles in therapeutic ultrasound.

Standing waves

Standing waves are formed when reflected sound waves are superimposed with incident waves, and are characterized by high pressure peaks, the antinodes and zones of low pressure known as nodes (Robertson, Ward, Low, & Reed, 2006, p. 267-8). Ter Haar and Wyard (1978) put forward that blood cell stasis may occur with ultrasound, with cells forming at half wavelength intervals in the blood vessels at antinodes. These results match those by Dyson, Pond, Woodward, and Broadbent (1974). The latter studied the effect of a stationary wave on blood cell stasis and endothelial damage in blood vessels of chick embryos. The cells form bands half a wavelength apart inside blood vessels. They suggest that under optimum conditions, the minimum intensity of less than 0. 5 Wcm-2 at 3 MHz with continuous irradiation is required for stasis to occur. Damage to some endothelial cells of vessels in which stasis has occurred was revealed by an electron microscope. Thus, it is suggested that the treatment head is continuously moved during the treatment to minimize the formation of standing waves (Robertson, Ward, Low, & Reed, 2006, p. 268).

The effect of ultrasound on repair of body tissues

According the following research, ultrasound therapy may have an effect on cells involved in repair of body tissues, including:

Levels of prostaglandins and leukotrienes

Leung, Ng, and Yip (2004) performed a randomized, case-control study to study the effect of ultrasound during the acute inflammation of soft-tissue injuries. They measured the levels of leukotriene B4 and prostaglandin E2 in the medial collateral ligament of rats and found that pulsed ultrasound (1: 4) applied for five minutes at different durations and intensities may stimulate acute inflammation by increasing the levels of the above mentioned leukotriene and prostaglandin.

Release of fibroblast from macrophages

Young and Dyson (1990a) studied if ultrasound therapy can increase the release of fibroblast mitogenic factors from macrophages in vitro, and assessed fibroblast proliferation over five days. This study showed an increased secretion of already formed fibroblasts in macrophages at 0. 75 MHz ultrasound, which may be caused by permeability changes. On the other hand, at 3 MHz frequency, ultrasound appeared to encourage both the synthesis and secretion of fibroblast mitogenic factors. The reason why these two frequencies cause different effects may be explained by the different physical mechanisms involved. Williams (as cited in Young, 2002, p. 217), argues that cavitation is more liable to occur at lower frequencies, while at a higher frequency heating is more likely.

Platelets and Î²-thromboglobulin

Williams, Chater, Allen, Sherwood, and Sanderson (1978) investigated the effect of ultrasound on platelets and established that more Î²-thromboglobulin, a platelet specific protein, was released by ultrasound therapy. They suggest that this protein is released both by the disruption of platelets by cavitation and by other aggregating agents liberated in parallel with it which cause a release reaction in the adjacent platelets. This however, has not been proved to happen in vivo.

Histamine release from mast cells

Fyfe and Chahl (1984) suggest that ultrasound applied in the therapeutic range causes a significant increase in degranulated mast cells and thus an increase in histamine release, in rats. They suggest the possibility that ultrasound increases the permeability of mast cells to calcium causing them to degranulate, resulting in an increase in local blood flow. On the other hand, when Hogan, Burke, and Franklin (1982) investigated the change in blood flow in rat muscle on insonation, they found that arterioles vasoconstrict transiently in response to insonation, but improve perfusion after long-term treatment.

Increase membrane permeability to calcium

Change in the permeability of membranes to calcium has been demonstrated when using therapeutic ultrasound. According to Al-Karmi, Dinno, Stoltz, Crum, and Matthews (1994), applying ultrasound for two minutes will cause a significant boost in ionic conductance in the presence of calcium ions, thus confirming that calcium ions influence the biological effects of ultrasound. Dinno et al. (1989) also used a frog skin model to study the effect of ultrasound on membranes. They argue that the increase in the concentration of calcium ions inside cells which occurs after the application of ultrasound, may decrease the permeability of gap junctions and uncouple cells in the way by which cells differentiate. Therefore, they concluded that ultrasound can affect cell differentiation and consequently histogenesis, and thus its use should be avoided over embryonic tissue.

Growth factor secretion

Ito, Azuma, Ohta, and Komoriva (2000) applied ultrasound to a co-culture system of human osteoblastic and endothelial cells and studied their effect on growth factor secretion. Their study showed that ultrasound increases the levels of platelet-derived growth factor. This may be the reason for improved fracture healing rate with ultrasound treatment, as discussed later.

Fibroblasts and Collagen synthesis

Ramirez, Schwane, McFarland, and Starcher (1997), conducted an investigation to determine the effect of ultrasound on the rate of cell proliferation and collagen synthesis by using cultured fibroblasts form the Achilles tendons of neonatal rats. They found an increase in collagen synthesis and rate of thymidine incorporation and DNA content after ultrasound treatment, suggesting that ultrasound stimulates the synthesis of collagen in tendon fibroblasts and cell division after injury. In a more recent study Chiu, Chen, Huang, and Wang (2009), studied the effect of ultrasound on the proliferation of human skin fibroblasts at different frequencies. They applied ultrasound for three minutes daily for three days and found an increase in fibroblast proliferation by both 1 and 3 MHz frequencies, with less stimulation when using 0. 5 MHz frequency. Chiu et al., also took into account temperature changes and found a change of only one degree Celsius after insonation, thereby implying that the results observed where due to non-thermal effects.

This can be explained by the increase in protein synthesis found to occur in fibroblasts after ultrasound treatment. Harvey, Dyson, Pond and Grahame (1975) suggest that therapeutic ultrasound at 3 MHz frequency and at an intensity of 0. 5 – 2. 0 Wcm-2, can directly stimulate protein synthesis in fibroblasts, without any other cells acting as mediators. In fact they attributed this to membrane-associated changes. Nevertheless, the increase in fibroblast proliferation may occur as a result of the effects of ultrasound on macrophages, which release fibroblasts mitogenic factors (Young & Dyson, 1990a), as previously discussed.

Ultrasound not only stimulates fibroblasts to produce more collagen (Ramirez et al. 1997), but the collagen produced also has a higher tensile strength and is better organized and aggregated. Okita et al. (2009) studied joint mobility and collagen fibril arrangement in the endomysium of immobilized rat soleus muscle, and showed that therapeutic ultrasound may prevent changes in joint mobility and collagen fibril movement which occur with immobility. In contrast, when Larsen, Kristensen, Thorlacius-Ussing and Oxlund (2005) studied the influence of pulsed ultrasound at 3 MHz frequency and different intensities, on the mechanical properties of healing tendons in rabbits, they found greater extensibility after insonation with higher intensities, however there was no significant change of the point of rupture when the tendons were loaded, suggesting that pulsed ultrasound did not improve the mechanical properties of the healing tendons.

Angiogenesis

Therapeutic ultrasound may also affect the rate of angiogenesis. Young and Dyson (1990b) considered the formation of new blood vessels in full-thickness lesions of flank skin in adult rats and found that by day 5 post-injury, ultrasound treated wounds had developed a greater number of blood vessels, and were thus at a more advanced stage in the repair process. However by the seventh day, there was no significant difference between the groups.

Therapeutic mechanism

On the basis of these conflicting results, two schools of thought were developed. The ‘ evidence-based’ or ‘ factual’ school considers heat as the only effect of ultrasound therapy and thus emphasise the use of high doses and give little value to low intensity and pulsed treatment. This view is found in most American writing about this subject. On the other hand, the other school of thought is largely European, and is more involved in the biological and mechanical effects of pulsed low-intensity treatments (Robertson, Ward, Low, & Reed, 2006, p. 269).

Robertson, Ward, Low, & Reed, (2006, p. 269) suggest that clinical studies may be used to investigate which doses produce better outcomes. In vitro studies can provide a dose-response relationship which may provide information about the most effective dose. Nevertheless, effects demonstrated in vitro, such as cavitation and acoustic streaming have not yet been shown to occur in vivo, since it is difficult to produce doses in vivo which are comparable to dose in vitro. They argue that in vitro, ultrasound is applied to only a thin layer of cells, and thus the noted changes do not necessarily occur when applied to a much larger volume of tissue in vivo. Moreover, in vitro the energy is confined to a very small volume and thus the power density will be much higher than in vivo.

Therapeutic effects of Ultrasound

Ultrasound therapy has been claimed effective in a wide range of clinical conditions, however there are still difficulties in establishing the effectiveness of ultrasound with certainty and in identifying a dose-response relationship, if there is any. Some of the alleged effects of ultrasound include promotion of fracture healing, soft tissue healing, articular cartilage repair, pain relief, increase local blood flow, change the extensibility of scar tissue and for the diagnosis of a stress fracture, and will be discussed below.

Fracture healing

Ultrasound has been proposed to promote the processes involved in fracture healing and thus increase its rate. Sun et al., (2001) investigated the effects of low-intensity pulsed ultrasound on bone cells in vitro, and found a significant increase in osteoblast cell counts and a significant decrease in osteoclast cell count after stimulation, suggesting a positive effect on the bone-healing process. Nolte et al., (2001) also studied the in vitro effects of low intensity ultrasound. The latter used foetal mouse metatarsal rudiments and found an increase in length of the calcified diaphysis, which was significantly greater in the ultrasound treated groups compared to the untreated groups, after 7 days. Therefore they concluded that low-intensity ultrasound directly affects osteoblasts and ossifying cartilage, with consequential more active ossification.

Cyclooxygenase-2 regulates the production of Prostaglandin E2 by osteoblasts, both of which are thought to be an essential part of fracture healing (Zhang et al., 2002). Ultrasound stimulation has been found to increase cyclooxygenase-2 expression and to promote bone formation in osteoblast via various signalling pathways (Tang et al., 2006). Together with prostaglandins, nitric oxide is a crucial mediator in early mechanically induced bone formation. Reher et al., (2002), investigated the effect of ‘ traditional’ (1MHz, pulsed 1: 4) and a ‘ long-wave’ (45 kHz, continuous) ultrasound on nitric oxide induction and prostaglandin E2 production in vitro, on human mandibular osteoblasts. A control group was set which was treated with sham ultrasound. They found a significant increase in both induced nitrate and prostaglandin E2 production. Long wave ultrasound was found to be more effective than the traditional ultrasound.

Other studies suggest that ultrasound may have an effect on the regulation of genes necessary for osteogenesis. Suzuki and his colleagues (2009) studied the typical osteoblastic cell line in the presence or absence of daily low intensity pulsed ultrasound stimulation at 1. 5 MHz frequency, and 30 mW/cm2 intensity, for 20 minutes, for 2 weeks. They concluded that stimulation with these parameters directly affected osteogenic cells, leading to mineralized nodule formation, thus low intensity pulsed ultrasound therapy is likely to have an influence on the activities of osteoblasts in alveolar bone.

Clinical studies gave controversial conclusions in this area. In a review, Busse et al., (2002) concluded that evidence form randomised controlled trials suggest that low intensity pulsed ultrasound therapy may significantly reduce the time of fracture healing for non-operatively treated fractures. Five years later, Walker, Denegar, and Preische, (2007) confirmed this finding through another review. Moreover, Della Rocca (2009) reviewed studies about the effects of low-intensity pulsed ultrasound treatment in fracture healing and found a large body of animal and cellular research which shows this to be beneficial in simulating faster normal fracture healing. However, from a review to of randomised controlled trials to determine the effectiveness of low intensity pulsed ultrasound in fracture healing, Busse et al., (2009), concluded that the evidence available has a moderate to very low quality and provides conflicting results.

Pain relief

There are a very small number of studies which investigate the effectiveness of ultrasound in pain relief. Nevertheless, assuming that ultrasound promotes healing and resolves inflammation, pain should consequently decrease. Levent, Ebru, and Gulis (2009), used a randomised controlled trial to study the effect of ultrasound therapy in knee osteoarthritis. They applied ten sessions of five minutes of continuous ultrasound at 1 MHz to the experimental group and sham ultrasound to the control group to act as a placebo. They assessed pain by a visual analogue scale (VAS) and found that the decrease in pain in the experimental group is statistically significantly more than the control group. Thus they concluded that therapeutic ultrasound can be used effectively as a pain relief modality in patient suffering from knee osteoarthritis.

An earlier review by Brosseau et al., (2001), did not show ultrasound as clinically important for pain relief in people with patellofemoral pain syndrome. However, they were unable to draw a conclusion regarding its use due to methodological flaws and limitations in the studies included in this review.

Soft tissue injuries

Wilkin, Merrick, Kirby and Devor (2004) studied the effect of pulsed ultrasound applied once daily for a week, on the healing of skeletal muscle in eighty rats. The results suggest that pulsed ultrasound as administered did not accelerate or improve regeneration of skeletal muscle tissue after contusion. Similarly, Markert, Merrick, Kirby and Devor (2005), using a randomized controlled trial with rats, found no evidence that specific continuous ultrasound and exercises protocols enhance skeletal muscle tissue regeneration following contusion injury.

Takakura et al. (2002) investigated the effect of low-intensity pulsed ultrasound on the rate of healing of injured medial collateral ligaments of rat knees and found a significant improvement in the mechanical properties on the twelfth day, which however was lost by the twenty-first day. Nevertheless they also observed a larger mean fibril diameter in the ligaments treated with ultrasound, concluding that low intensity pulsed ultrasound enhances the early healing of medial collateral ligament injuries.

Ebenbichler et al., (1999) investigated the effect of ultrasound in the treatment of calcific tendinitis. This study suggests better outcomes with ultrasound treatment. Since only patients with calcific tendinitis diagnosed by diagnostic imaging were included in the study, results are more valid than if numerous shoulder pathologies with different cellular process were included. This study was included in the review by Alexander et al., (2010). The latter carried out a review from various electronic databases and identified eight randomised controlled trials out of a total of seven hundred and twenty seven, which met their inclusion criteria. All the studies reviewed focused on shoulder musculoskeletal disorders. They concluded that statistically significant improvements were observed generally in studies which used higher levels of total energy and those who used longer exposure times. They noted favourable outcomes when at least 2, 250J per treatment session was applied. This is further suggested by the frequency resonance hypothesis, which suggests that the mechanical energy produced by the ultrasound wave may be absorbed by proteins, altering the structure of individual proteins or changing the function of a multi-molecular complex. Thus it may affect enzymatic proteins, inducing temporary conformational shifts, and thus alter the enzyme activity and cell function. This hypothesis implies that different frequencies will cause unique resonant or shearing forces which will therefore have specific effects at cellular and molecular levels (Johns, 2002). Thus further reviews should address different parameters used in different studies, in attempt to establish effective doses.

Blood flow

Noble, Lee, and Griffith-Noble (2007) applied ultrasound at 3 MHz frequency and 1 Wcm-2 for 6 minutes to assess its effect upon cutaneous blood flow by laser Doppler flowmetry. They also measured skin temperature. They concluded that cutaneous blood flow increased significantly with ultrasound even though no significant changes in temperature had occurred. Nevertheless, blood flow changes in skeletal muscles have not yet been established. Robinson and Buono (1995), investigated the effect of continuous ultrasound on blood flow using 1. 5 Wcm2 intensity for 5 minutes and found no significant change in skeletal muscle blood flow.

Wound healing

Other authors have studied the healing rates varicose ulcers by ultrasound and found more marked healing of insonated ulcers (Dyson, Franks, & Suckling, 1976). However more recent studies suggest that ultrasound does not have an influence on the acceleration of healing or final stage of the wound healing (Dolibog, Franeki, Taradai, Blaszczak, & Cierpka, 2008). Different findings may be attributed to the different nature of the injuries studied and the different way by which the effectiveness of ultrasound is assessed.

Diagnosis of stress fractures

Romani and his colleagues (2001), were some of the few people who investigated the effectiveness of ultrasound therapy in the diagnosis of stress fractures. They used 1 MHz of continuous ultrasound therapy in twenty-six subjects with pain in the tibia since less than 2 weeks. Each subject completes a visual analogue scale after each different intensity was applies to assess the pain response to ultrasound. An MRI was taken to ascertain the diagnosis. However none of those who were found to have a stress fracture by MRI were correctly diagnosed by ultrasound.

Following this review of literature, it is suggested that there may be a specific therapeutic window for ultrasound therapy. Conflicting results were obtained, possibly due to the different doses and frequencies used in various studies, indicating the need for further future research to identify the most effective parameters. Fortunately, none of the studies reviewed mentioned any negative effects on patients, making ultrasound a relatively safe modality when precautions are taken, and thus would make an important physiotherapy modality if its use is justified.