

Therapeutic Ultrasound: Physiological Role, Clinical Applications and Precautions

Asmaa Aly Saber¹, Aly Saber²

¹Department of Physical Therapy, Port-Fouad General Hospital, Port-Said, Egypt

²Department of General Surgery, Port-Fouad General Hospital, Port-Said, Egypt

Email address:

Soma_1_25_2008@yahoo.com (A. A. Saber), Alysaber54@gmail.com (A. saber)

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Abstract: *Background:* Sound travels in waves that transport energy from one location to another. Ultrasound is the name given to sound waves that have frequencies greater than 20000Hz. It's too high pitched for human hearing, but many animals, such as dogs, cats and bats can hear ultrasound. As the ultrasound waves travel through tissues, they are partly transmitted to deeper structures, partly reflected back to the transducer as echoes, partly scattered, and partly transformed to heat. The amount of echo returned after hitting a tissue interface is determined by a tissue property called acoustic impedance which is an intrinsic physical property of a medium defined as the density of the medium times the velocity of ultrasound wave propagation in the medium. *Physiologic effect of US:* The thermal therapeutic ultrasound include increased tissue temperature, hyperdynamic tissue metabolism, increased local blood flow, increased extensibility of collagen fibers, and reduced viscosity of fluid elements in the tissue. The nonthermal mechanisms include ultrasonic cavitation, gas body activation and mechanical stress or frequency resonance nonthermal processes. *Therapeutic effects of US:* Therapeutic ultrasound is delivered in two modes; the continuous mode in which the delivery of ultrasound is non-stop throughout the treatment period and the pulsed mode in which the delivery of ultrasound is intermittently interrupted. Essential treatment parameters for therapeutic ultrasound include frequency, intensity, treatment mode, treatment time. *Clinical applications:* US in damaged muscle accelerates the repair process due to the decrease in the response and number of inflammatory cells and increases the proliferation and differentiation of muscle cell lines together with the formation of the connective tissue, improving mechanical resistance in the early stages. US is used also in chronic pain syndrome, tissue repair and wound healing and extra and intracorporeal shock wave lithotripsy. *Cancer therapy:* High-intensity focused ultrasound is a noninvasive therapy that makes entire coagulative necrosis of a tumor in deep tissue. HIFU ablation can destroy all proliferating tumor cells and their feeding blood vessels at the same time; this may break interdependent vicious cycle of tumor angiogenesis and tumor growth. *Conclusion:* Applications of ultrasound in medicine for therapeutic purposes have been an accepted and beneficial use of ultrasonic biological effects for many years. While therapeutic ultrasound is safe for treating many clinical conditions, it may cause substantial bioeffects and patients should be fully informed of possible benefits and risks.

Keywords: Ultrasound, Therapeutic, Physiological Role, Clinical Applications, Precautions

1. Background

Sound is the rapid motion of molecules and these molecular vibrations transport energy from a transmitter, a sound source like a voice, to a receiver like an ear. Sound travels in waves that transport energy from one location to another. When the molecules get closer together, this is called compression, and when they separate, this is called

rarefaction. This mechanical motion, the rapid back and forth motion, is the basis for calling sound a mechanical wave or a mechanically propagated wave. There are sound frequencies below and above what man can hear. The lowest frequency classification in the acoustic spectrum is infrasound that has a frequency range less than about 20 Hz. Audible sound is what human beings hear and has an approximate frequency range between 20 Hz and 20 kHz. The ultrasound frequency range starts at a frequency of about 20 kHz [1]. The normal

human sound range is from 16 Hz to something approaching 15-20,000 Hz (in children and young adults). Beyond this upper limit, the mechanical vibration is known as ultrasound and the mechanical vibration at increasing frequencies is known as sound energy. The frequencies used in therapy are typically between 1.0 and 3.0 MHz (1 MHz = 1 million cycles per second) [2].

Ultrasound is the name given to sound waves that have frequencies greater than 20000Hz. It's too high pitched for human hearing, but many animals, such as dogs, cats and bats can hear ultrasound. Therefore, ultrasound is not different from the normal audible sound in its physical properties except in that man cannot hear it. Ultrasound wave moves as a pressure wave through a medium causing mechanical disturbance within that medium and when the medium is a patient, the wavelike disturbance is the basis for use of ultrasound as a diagnostic tool. Appreciation of the characteristics of ultrasound waves and their behavior in various media is essential to understanding the use of diagnostic ultrasound in clinical medicine [3]. Sound waves are longitudinal waves consisting of areas of both compression and rarefaction. Particles of a material or tissues when exposed to a sound wave will oscillate about a fixed point rather than move with the sound wave itself. As the energy within the sound wave is transferred to the material, it will cause oscillation of the particles of that material [4].

As the ultrasound waves travel through tissues, they are partly transmitted to deeper structures, partly reflected back to the transducer as echoes, partly scattered, and partly transformed to heat. The amount of echo returned after hitting a tissue interface is determined by a tissue property called acoustic impedance which is an intrinsic physical property of a medium defined as the density of the medium times the velocity of ultrasound wave propagation in the medium. Air-containing organs such as the lung have the lowest acoustic impedance, while dense organs such as bone have very high-acoustic impedance. The intensity of a reflected echo is proportional to the difference in acoustic impedances between two mediums. If two tissues have identical acoustic impedance, no echo is generated. Interfaces between soft tissues of similar acoustic impedances usually generate low-intensity echoes. Conversely interfaces between soft tissue and bone or the lung generate very strong echoes due to a large acoustic impedance gradient [5].

2. Physiologic Effect of US

Ultrasound may induce thermal and non-thermal physical effects in the target tissues and it is incorrect to assume that only one effect is present at any time and that physical therapy treatment may be classed as either thermal continuous wave exposure or nonthermal pulsed exposure. The reality is that both two effects are not separable and indeed it is rarely true that one class of effects may be ignored completely [2]. The physiological effects of thermal therapeutic ultrasound include increased tissue temperature, hyperdynamic tissue metabolism, increased local blood flow,

increased extensibility of collagen fibers, and reduced viscosity of fluid elements in the tissue. However, in terms of local blood flow the current evidence is conflicting. Some researchers stated that therapeutic ultrasound increased the blood flow in the skin, muscle and artery [6]. Other thermal effects of ultrasound on tissue may be in the form of vasodilation of local tissue from the skin surface to muscle, reduction in muscle spasm, and pro-inflammatory response. It is postulated that thermal effects of ultrasound occur with elevation of tissue temperature to 40–45°C for at least 5 minutes while excessive thermal effects with higher ultrasound intensities may cause relative damage to the tissues [6, 7]. The mechanism of thermal effects leading to vasodilation can be attributed to the direct reflective activation of vascular smooth muscles via skin temperature receptors, suppression of the sympathetic nervous system through indirect activation of local spinal reflexes, and increases in the local release of inflammatory chemical mediators, and the compound effect would result in dermovascular dilation [6, 8]. By reducing the vasoconstrictor activity and elevating the vasodilator activity, activating intramuscular circulation is usually set up and in turn, these sequelae dilate intramuscular arterioles and capillaries, increasing the flow of oxy-Hb-rich arterial blood and accelerating intramuscular oxygen distribution and blood circulation [6].

Ultrasonic energy causes soft tissue molecules to vibrate from exposure to the acoustic wave. This increased molecular motion generates frictional heat and consequently increases tissue temperature. This increased temperature, named thermal effects, is thought to cause changes in nerve conduction velocity, increase in enzymatic activity, changes in contractile activity of skeletal muscles increase in collagen tissue extensibility, increase in local blood flow, increase in pain threshold, and reducing muscle spasm [9, 10].

Therapeutic ultrasound can induce effects not only through heating, but also through nonthermal mechanisms including ultrasonic cavitation, gas body activation and mechanical stress or frequency resonance nonthermal processes [11]. Many researches have reported that the nonthermal effect of ultrasound is accumulated upon both cellular and molecular aspects of tissues [12]. It was demonstrated that there is a direct relationship between the absorption of ultrasound and amount of protein in the tissue and when the concentration of protein increased, the absorption of ultrasound increased. In normal tissue, the absorption of ultrasound energy varies depending on the amount of protein in the tissue. In 1980, Love and Kremkau demonstrated that by eliminating extracellular tissue structures such as collagen, fibrin and elastin, and then placing only the cells in tissue culture media maintained at 37°C, they could treat cells at therapeutic levels without significant increases in temperature less than 0.5°C for more than 10-minute [13].

Ultrasonic cavitation and gas body activation are closely related mechanisms which depend on the rarefactional pressure amplitude of ultrasound waves. Ultrasound transmitted into a tissue may have rarefactional pressure

amplitudes and this high rarefactional pressure can act to initiate cavitation activity in tissue when suitable cavitation nuclei are present, or directly induce pulsation of pre-existing gas bodies, such as occur in lung, intestine, or with ultrasound contrast agents. Cavitation and gas body activation primarily cause local tissue injury in the immediate vicinity of the cavitation activity, including cell death and hemorrhage of blood vessels [11]. Acoustic microstreaming is defined as the physical forces of the sound waves that provide a driving force capable of displacing ions and small molecules [14] and causes the unidirectional movement of fluids along cell membranes with the result of the mechanical pressure changes within the ultrasound field [12].

Early studies investigating the gross effects of acoustic streaming and cavitation on cells showed growth retardation of cells *in vitro*, increases in protein synthesis, and membrane alterations. Combined, these results may suggest that ultrasound first “injures” the cell, resulting in growth retardation, and then initiates a cellular recovery response characterized by an increase in protein production [12]. Microstreaming may alter cell membrane structure, function and permeability which has been suggested to stimulate tissue repair [15]. Effects of cavitation and microstreaming that have been demonstrated *in vitro* include stimulation of fibroblast repair and collagen synthesis, tissue regeneration [6].

The combined effects of cavitation and microstreaming include a temporarily increase in uptake of calcium ions by fibroblasts exposed to therapeutic levels of ultrasound and increase collagen synthesis by fibroblasts and this effect is highly significant for cell membrane permeability changes [16,17]. Stimulation of protein synthesis by fibroblasts, and the increased release of growth factors from mast cells and macrophages are due to direct effect of both cavitation and microstreaming. Another clinically significant change in membrane function resulting from acoustic streaming is serotonin release from platelets. In addition to serotonin, platelets contain chemotactic factors that promote the migration of cells essential for tissue repair [18].

The frequency resonance hypothesis differs from acoustic streaming and cavitation at the basic levels. First, acoustic streaming relates to the movement of objects from one place to another as a function of the force of the wave. In terms of ultrasound therapy, phonophoresis is commonly used to move medication transdermally. Second, cavitation relates to the oscillation of microscopic gas bubbles that may, in turn, affect the cell or cellular process. However, the frequency resonance hypothesis relates to the absorption of ultrasound by proteins and protein complexes that may directly result in alterations to signaling mechanisms within the cell, either by inducing a conformational shift or by disrupting a multimolecular complex [11, 19, 20].

3. Therapeutic Effects of US

Ultrasound has been developed not only as a diagnostic imaging modality but also as a therapeutic maneuver in

which energy is deposited in tissue to induce various biological effects. Medical uses of ultrasound for therapeutic purposes began to be explored in the 1930s. Early applications were tried for various conditions using the mechanism of tissue heating [11]. By the 1970's, the use of therapeutic ultrasound was established for physiotherapy and research continued on more difficult applications in neurosurgery and for cancer treatment [21] and subsequently, the development of therapeutic ultrasound has accelerated with a wide range of methods [11, 22]. The potent application of ultrasound for therapeutic efficacy also carries the risk of unintentional adverse bioeffects which can lead to significant even life threatening patient injury [11].

Therapeutic ultrasound is delivered in two modes; the continuous mode in which the delivery of ultrasound is non-stop throughout the treatment period and the pulsed mode in which the delivery of ultrasound is intermittently interrupted [23]. Essential treatment parameters for therapeutic ultrasound include frequency, intensity, treatment mode (i.e., duty cycle), treatment time, and treatment area. The frequency of therapeutic ultrasound ranges from 1 to 3 MHz, with 3 MHz used specifically for the treatment of superficial tissues, and 1 MHz aimed to treat deeper tissues. In addition, the combination of intensity and duty cycle in ultrasound produces thermal and/or nonthermal (i.e., mechanical) effects [6, 24]. The therapeutic effects of ultrasound are generally divided into: thermal and non-thermal. In thermal mode, ultrasound will be most effective in heating the dense collagenous tissues and will require a relatively high intensity, preferably in continuous mode to achieve this effect. The non-thermal effects of ultrasound are now attributed primarily to a combination of cavitation and acoustic streaming. There appears to be little by way of convincing evidence to support the notion of micromassage though it does sound rather appealing [12].

4. Clinical Applications

4.1. Skeletal Muscle

Ultrasound therapy in damaged skeletal muscle accelerates the repair process due to the decrease in the response and number of inflammatory cells and increases the proliferation and differentiation of muscle cell lines together with the formation of the connective tissue, improving mechanical resistance in the early stages [23]. In the muscle treated with ultrasound, an aligned and more regular disposition of the collagen fibers and myotubes is observed, allowing for increased functionality [25]. In the healthy skeletal muscle tissue, low-intensity ultrasound therapy produces neither damage nor histological alterations to the muscle fibers and connective tissue as well as no foci of inflammation, fibrosis or necrosis could be observed [23].

4.2. Chronic Pain Syndromes

4.2.1. Low Back Pain

According to the recommended diagnostic triage, three

types of low back pain can be defined:

- non-specific low back pain;
- back pain with nerve root symptoms; and
- back pain resulting from serious pathology such as malignancy, fracture, ankylosing spondylitis and infection [9, 26].

Chronic non-specific low-back pain is considered as one of the main causes of disability in the adult population around the world. Therapeutic ultrasound is frequently used by the physiotherapists in the treatment of low-back pain and is one of the most widely used electro-physical agents in clinical practice. No high quality evidence was found to support the use of ultrasound for improving pain or quality of life in patients with non-specific chronic low-back pain. There is some evidence that therapeutic ultrasound has a small effect on improving low-back function in the short term, but this benefit is unlikely to be clinically important [27].

4.2.2. Chronic Pelvic Pain

Chronic pelvic pain syndrome is associated with many symptoms, such as pelvic pain, irritative and obstructive voiding symptoms, and sexual dysfunction. Several biological mechanisms have been reported for explanation of chronic pelvic pain syndrome such as infection, immunological abnormality, neurological dysfunction, psychosocial problems, and endocrine disorders [28]. Results demonstrated that transperineal ultrasonic therapy is highly effective for CP, especially in relieving prostate pain. With its advantages of safety, easy operation, and high acceptability, low intensity ultrasound was recommended for a wider clinical application. Transrectal low intensity ultrasound has also been previously reported to be effective in improving clinical symptom of chronic pelvic pain syndrome [29].

4.3. Tissue Repair & Wound Healing

The application of ultrasound during the inflammatory, proliferative and tissue repair phases is not only of value because it changes the normal sequence of events, but also because it has the capacity to stimulate or enhance these normal events and thus increase the efficiency of the repair phases [4]. During the inflammatory phase, ultrasound has a stimulating effect on the mast cells, platelets, white cells with phagocytic roles and the macrophages [30]. The ultrasound application induces degranulation of mast cells, causing the release of arachidonic acid which itself is a precursor for the synthesis of prostaglandins and leukotrienes which in turn act as inflammatory mediators [31]. Ultrasound has a stimulative effect during the proliferative phase and scar production through the fibroblasts, endothelial cells and myofibroblasts [4] therefore ultrasound does not change the normal proliferative phase, but maximises its efficiency – producing the required scar tissue in an optimal fashion and low dose pulsed ultrasound increases protein synthesis and several research groups have demonstrated enhanced fibroplasia and collagen synthesis [32]. The application of therapeutic ultrasound can influence the remodeling of the scar tissue by enhancing the appropriate orientation of the newly formed

collagen fibres, increasing tensile strength and enhancing scar mobility [33, 34].

4.4. Shock Wave Lithotripsy

4.4.1. Extracorporeal Shock Wave Lithotripsy

Extracorporeal shockwave lithotripsy is a widely used ultrasound therapy, relying on nonthermal mechanisms for its efficacy and patient benefits. The development of safer treatment protocols for lithotripsy is a prime example of the potential value of research on risk mitigation for optimizing the patient risk/benefit profile in therapeutic ultrasound [11].

4.4.2. Intracorporeal Lithotripsy

Lithotripsy is also performed by minimally invasive probes which are advanced to the stone directly. Intracorporeal lithotripsy is the favored treatment for many patients, for example for very large stones, and many different methods and techniques have been reported. The stone may be imaged for guidance by external ultrasound or fluoroscopy, or by ureteroscopic, endoscopic or laparoscopic methods [11].

4.5. Cancer Sonotherapy

During the last forty five years of research, the cancer therapy using ultrasound may be divided into the four periods of initiation, enthusiasm, pessimism and revival and the ultrasound effects on tumors is studied using ultrasound alone; ultrasound in combination with radiotherapy and ultrasound in combination with chemotherapy. With the first approach the results have varied. In some cases, decreased growth rates or regressions of tumors have been reported; in other cases, either no effect has been observed or growth has been increased. With the second approach, for some tumors, combined treatment has produced greater effects on tumors than has x-ray alone, whereas in other tumors the addition of ultrasound has produced no change. With the third approach, enhancement of the effects of drugs has been observed in melanoma and mouse tumor cells treated with ultrasound and several anticancer drugs. The mechanism of action in most cases has appeared to be absorption heating. The potential of ultrasound to provide local tumor control and to enhance other therapy modes has motivated the current efforts by several groups to further study and understand its actions on malignancies [36]. Ultrasound beam propagates with harmless through living tissues and if the concentrated energy is sufficient, here may be tissue destruction solely within the focal volume, while cells lying elsewhere remain unharmed [37]. Ultrasound energy absorption by living tissue can result in measurable temperature rise and the mechanism for cell killing is primarily thermal causing immediate coagulation necrosis of the targeted volume. The extent of cellular thermal damage is determined both by the temperature achieved, and the length of time for which it is maintained, the higher the temperature, the shorter the time required to produce identical effects [38, 39].

It was proposed that acoustic cavitation of ultrasound waves is the primary mechanism underlying sonochemical

reactions and has potential for use in tumor treatment and some researchers found that the ultrasonically-induced chemical reactions are greatly accelerated when ultrasound is simultaneously applied at frequencies of 1 MHz and 150 kHz. Experimental work reported that the tumor-bearing mice treated with combined dual-frequency ultrasound in continuous mode effectively showed delayed tumor growth and increased the tumor growth inhibition and the researchers concluded that sonodynamic therapy with combined dual-frequency ultrasound in a progressive wave mode can be useful for cancer therapy [40].

4.5.1. Pancreatic Cancer

The high intensity focused ultrasound (HIFU) has been recently investigated as a potential adjuvant and additional therapy for tumor debulking and disease symptom control. Using an extracorporeal approach, it employs focused ultrasound energy to raise the temperature between 56 °C and 100 °C in a targeted tumor while ultrasound beam is transmitted into a pancreatic lesion, leading to a complete destruction of all the targeted pancreatic cancer cells, instead of local tumor removal [41]. The main advantages of HIFU therapy are less invasive with no incision, no scarring, cheap, less pain and short recovery time. These result in an associated reduction in mortality, morbidity, hospital stay, cost and improved quality of life for cancer patients. The purpose of this article is to review recent developments in the use of HIFU therapy for pancreatic cancer, and to discuss its potential in this application [37].

4.5.2. Hepatic Tumour

After treatment using low-frequency ultrasound, the hepatic tumor, hepatocellular carcinoma exhibits a poor parenchymal vascular network with atrophy of the arterioles in the parenchyma and decreased blood perfusion to the tumour bed. Low-frequency ultrasound appears to present a potential minimally invasive and convenient method of tumor treatment. This modality may gain attention in the future as a minimally invasive method for the treatment of hepatic malignant tumors with a copious blood supply and with surgical contraindications [42].

4.5.3. Prostate Carcinoma

HIFU has been used to treat prostate carcinoma at a few medical centers in Europe and Japan for the past decade. Endorectal and transperineal treatment protocols have been evaluated in animals and humans with success rates for the treatment of prostate cancer range from 60% to 80% in clinical studied and patients being disease-free at repeat biopsy and show a reduction of serum PSA values to less than 4 ng/mL. Treatment success correlates highly with pretreatment staging and PSA levels, with more than 90% of patients disease-free and having PSA levels of 4 ng/mL initially to 57% disease-free with PSA levels greater than 4 ng/mL [43].

4.5.4. Renal Tumours

Although high frequency ultrasound (HIFU) in animal

models for renal tumor ablation could exist and have been used to treat these tumors, high frequency ultrasound ablation of renal tumors in humans remains in the early stages of clinical trials. A clinical feasibility study using high frequency ultrasound to ablate renal tumors has been performed and showed histologic evidence of ablation in the treated areas after excision; however [44, 45].

4.5.5. Breast Cancer

High-intensity focused ultrasound (HIFU) is a noninvasive therapy that makes entire coagulative necrosis of a tumor in deep tissue through the intact skin. There are many reports about the HIFU's efficacy in the treatment of patients with breast cancer, but randomized clinical trials are rare which emphasize on the systematic assessment of histological changes in the ablated tumor vascularities [46]. The application of HIFU treatment for breast cancer is performed under ultrasound real-time monitoring. The tumor is continuously irradiated by scanning the tumor, and each irradiation area is closely arranged to form a matrix resulting in damage to the adjacent area overlapping the tumor area to an extent that avoids residual damage to the area as much as possible. Irradiation continues until the tumor is completely contained within the HIFU irradiation range, as indicated by the observation of ultrasonographic changes to the tumor and the pathological changes from before to after irradiation. These findings are used to determine the efficacy of the treatment. After HIFU treatment, the ultrasonogram showed a strong echo in the entire area of the tumor and the absence of a blood supply to the tumor [47].

HIFU ablation can destroy all proliferating tumor cells and their feeding blood vessels at the same time; this may break interdependent vicious cycle of tumor angiogenesis and tumor growth. Not like utilizing bevacizumab and other anti-angiogenic agents in breast cancer, breast cancer cells can escape anti-angiogenic therapy and develop resistance to anti-angiogenic agent, while HIFU ablation can make whole breast cancer tissue coagulative necrosis completely, so it cannot cause tumor resistance to HIFU ablation. It may be a new anti-angiogenic strategy that needs further clinical observation and exploration. This study only included women with early-stage breast cancer single palpable tumors, not included nonpalpable and multifocal breast cancer, but the treatment indications may extend to the above type of breast cancer ultimately with technical progress and the improvement of clinical practice in HIFU ablation [46].

4.5.6. Soft Tissue Tumours

The application of ultrasound in clinics is no longer limited to diagnosis. High intensity focused ultrasound (HIFU) is being promoted as the only completely noninvasive and extracorporeal method to treat primary solid tumors and metastatic disease. The key of HIFU treatment is to deliver the energy required to raise the tissue temperature to a cytotoxic level sufficiently fast such that the tissue vasculature does not have a significant effect on the extent of cell killing (Figure 1). Coagulative necrosis caused by heat

differs in microscopic appearance and host response from the classical ischemic-type coagulative necrosis: heat coagulation favors giant cell reaction with chronic inflammation whereas ischemic-type necrosis causes healing mainly with granulation tissue. In addition, with heat coagulation, the surrounding normal fatty tissue frequently shows histological signs of fat necrosis. The boundary between apparently totally disrupted cells and normal tissue is no more than 50 μm in width [48]. At present, the standard treatment of soft-tissue tumors in the extremities consists of limb-sparing surgery and adjuvant radiation and/or chemotherapy. However, in case of small soft-tissue tumors, HIFU may be used as an alternative treatment, because therapeutic ultrasound energy can penetrate soft tissue with a relatively good sonic window compared with that of deep-seated organs such as the liver or pancreas [49].

5. Hazards and Contraindications of Therapeutic Ultrasounds

While therapeutic ultrasound is safe for treating many clinical conditions, it may cause substantial bioeffects and patients should be fully informed of possible benefits and risks [11].

5.1. Hazards of Therapeutic Ultrasounds

Standing waves is a major cause of burns in sonotherapy and to reduce their damage tissue that may also lead to thrombus formation, the treatment head must be moved continuously across the treatment area. Formation of standing waves can also be prevented by ensuring that no part of the operator's body is in the path of the ultrasound emitted from the applicator, especially, when the ultrasound is being applied to the patient via a water bath. Transient cavitation is another source of burns caused by the pressure changes applied to the tissues by the sound waves. It occurs as a result of collapse of a bubble of gas formed as a result of a mechanical effect. This can be prevented by using intensities of about 3 watt/cm², using a pulsed source of ultrasound, or moving the treatment head during insonation [50].

The ultrasound transducer heads and ultrasound gel are extensively studied and investigated as potential vectors of infection and interesting studies determined the degree of contamination on therapeutic ultrasound transducer heads and ultrasound gel after routine clinical use, and evaluated the efficacy of recommended infection control procedures [4].

Alternatively, the heat can be concentrated by focused beams until tissue is coagulated for the purpose of tissue ablation. Ultrasound heating which can lead to irreversible tissue changes follows an inverse time-temperature relationship. Depending on the temperature gradients, the effects from ultrasound exposure can include mild heating, coagulative necrosis, tissue vaporization. In addition to direct physical mechanisms for bioeffects, there are secondary physical, biological, and physiological mechanisms that

cause further impact on the organism. Some examples are vasoconstriction, ischemia, extravasation, reperfusion injury, and immune responses. Sometimes these secondary effects are greater than the direct insult from the ultrasound [11].

5.2. Contraindications of Therapeutic Ultrasounds

Contraindications to ultrasound therapy have been listed in several publications and most of these lists are based on a general understanding of the principles and practice of ultrasound therapy. Ultrasound physical therapy should not be applied to any patient with obtunded reflexes or to any area with significantly diminished pain sensitivity or heat sensitivity. Ultrasound therapy should not be used in pregnant or potentially pregnant women in any area of the body which for fear of exposure to the fetus and overheating of the fetus therein. The fetus is at particularly high risk during the first trimester, during the period of organogenesis [51]. Ultrasound should not be applied to the eye since the avascular lens has limited ability for removing heat and has a relatively high absorption coefficient. Similarly, any region of significantly diminished blood circulation should not undergo irradiation, except at low intensities where wound healing may be expected [52].

Ultrasound should not be applied to the brain, spinal cord or large subcutaneous peripheral nerves. To avoid the possibility of spinal cord damage, it is advisable to avoid using ultrasound over the vertebral column following laminectomies or when any anaesthetic area is involved. Ultrasound physical therapy should not be applied to the reproductive organs. Care should be taken not to irradiate neoplastic tissues as there is some evidence that inappropriate heating patterns, giving rise to temperatures less than 42°C, may stimulate tumor growth or promote metastases. Care should be taken not to irradiate epiphyseal lines in children. Treatment of acute infection of bone or tissue should not be carried out as the treatment could force areas of pus into surrounding tissue, thereby spreading infection. Ultrasound should not be used in the thoracic area if the patient has a cardiac pacemaker of any kind. Blood vessels in poor condition should not be treated as the vessel walls may rupture as a result of the exposure. Patients suffering from cardiac disease should not receive treatment over the cervical ganglia, the stellate ganglion, the thorax in the region of the heart, or the vagus nerve, as a reflex coronary vasospasm might result [53]. Only low intensities and short treatment times should be used if these patients are treated in other areas since the stimulation of practically any afferent autonomic nerve (especially the vagus nerve) in the body may cause a change in cardiac rate. Patients with thrombophlebitis or other potentially thromboembolic diseases should not be treated since a partially disintegrated clot could result in an obstruction of the arterial supply to the brain, heart or lungs [52, 53].

The following are lists of contraindications and precautions of both pulsed and continuous ultrasound [54].

Table 1. Contraindications and precautions in pulsed ultrasound.

Contraindications	Precautions
<ul style="list-style-type: none"> • Hemorrhagic conditions • Eyes, anterior neck, carotid sinus, reproductive organs • Electronic device • DVT or thrombophlebitis (local) • Malignancy (local) • Pregnancy (local) • Tuberculosis (local) • Recently radiated tissue (local) 	<ul style="list-style-type: none"> • Active epiphysis • Acute injury or inflammation • Damaged or at-risk skin • Infection • Skin disease • Impaired circulation or sensation • Impaired cognition or communication • Plastic or cement implants • Regenerating nerves

Table 2. Contraindications and precautions in continuous ultrasound.

Contraindications	Precautions
<ul style="list-style-type: none"> • Acute injury or inflammation • Hemorrhagic conditions • Impaired circulation or sensation • Impaired cognition or communication • Eyes, anterior neck, carotid sinus, reproductive organs • DVT or thrombophlebitis (local) • Infection or tuberculosis (local) • Malignancy (local) • Recently radiated tissue (local) • Pregnancy (local) • Skin disease (local) e.g. psoriasis, eczema, etc. • Electronic device (local) • Plastic or cement implants (local) 	<ul style="list-style-type: none"> • Active epiphysis • Chronic wound • Damaged or at-risk skin • Regenerating nerves

6. Conclusion

Applications of ultrasound in medicine for therapeutic purposes have been an accepted and beneficial use of ultrasonic biological effects for many years. Low power ultrasound of about 1 MHz frequency has been widely applied since the 1950s for physical therapy in multiple clinical conditions. In the 1980s, high pressure-amplitude shockwaves came into use for other certain clinical conditions such as treatment of chronic pain, intra and extracorporeal shock wave lithotripsy and tumour ablation. While therapeutic ultrasound is safe for treating many clinical conditions, it may cause substantial bioeffects and patients should be fully informed of possible benefits and risks

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