Ultrasound stimulation of mandibular bone defect healing
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Chapter 6

General discussion
The central question of this thesis was whether ultrasound therapy can be used to stimulate bone defect healing in the mandible. The literature provides information suggesting that low intensity ultrasound pressure waves can stimulate the bone healing process in different circumstances such as fresh fractures,\textsuperscript{1-3} delayed unions,\textsuperscript{4} non unions,\textsuperscript{5,6} osteotomies,\textsuperscript{7} osteodistraction,\textsuperscript{8-10} and osteoradionecrosis.\textsuperscript{11} This has been observed in both animal\textsuperscript{12-15} and human studies.\textsuperscript{1-9} However, these investigations mostly concern fractures of the long bones of the extremities. Stimulation of maxillofacial bone healing by ultrasound may be possible if the maxillofacial bone is susceptible to the ultrasound signal. However, only limited evidence is available that supports the susceptibility of this bone to ultrasound signals. Evidence that the cells of the mandibular bone respond to ultrasound was reported in an in vitro study which showed that human mandibular osteoblasts could be stimulated by ultrasound to proliferate and produce angiogenesis-related cytokines.\textsuperscript{16} In mandibular fractures in rabbits, eight days of ultrasound treatment (five minutes each day, 0.2 - 0.6 W cm\textsuperscript{-2}) stimulated fracture consolidation, as compared to non-treated controls.\textsuperscript{17} In a paper concerning the treatment of four mandibular fractures in humans, ultrasound treatment appeared to decrease pain and promote callus formation.\textsuperscript{18} Another study found that osteoradionecrosis of the mandible could be treated with some success using 3 MHz ultrasound at 1.0 W cm\textsuperscript{-2}.\textsuperscript{11} In case of mandibular lengthening by distraction osteogenesis in rabbits, it was possible to stimulate the regenerate maturation with daily ultrasound treatment.\textsuperscript{19}

Based on the assumption that bone healing involves the same processes in the long bones as in the maxillofacial skeleton, it was investigated whether mandibular bone defect healing can be stimulated with low intensity pulsed ultrasound. The ultrasound field variables and treatment regime used in the animal experiments were identical as used in the commercially available SAFHS device, because favourable results have been obtained by its treatment.\textsuperscript{6} Furthermore, the device is approved by the American Food and Drug Administration (FDA) for the treatment of certain fractures of the extremities.\textsuperscript{20,21}

The pressure field as used to stimulate bone healing is characterised by being of high frequency, low intensity, and pulsed. Because of the convenience of treatment, the safety record, and self treatment possibility, the therapeutical application does not seem to be a problem in the maxillofacial area.

The animal experimental work described in this thesis suggests that daily low intensity pulsed ultrasound treatment does not stimulate bone growth into a through-and-through circular mandibular defect in rats, both in ‘plain’ defects and in defects covered with osteoconductive membranes.
The results from the human clinical trial suggest that daily ultrasound given during a consolidation period of 31 days does not produce a difference in early bone formation within the distraction gap between the ultrasound and the placebo group. Because no stimulating effect of ultrasound on bone defect healing in the mandible could be established, it is tempting to suggest that ultrasound therapy has no value in maxillofacial surgery. However, reviewing the literature, there are possible explanations that would fit the ‘negative’ results presented in this thesis with the predominantly ‘positive’ results in the existing literature. These explanations may offer directions for further research efforts that would more clarify the value of ultrasound to stimulate maxillofacial bone healing.

The first explanation that would match the results of this thesis with the existing literature may relate to the susceptibility of mandibular bone to the type of ultrasound and treatment regime. The ultrasound field variables and treatment regime used in the animal experiments presented in this thesis were identical as those used in the commercially available SAFHS device. These variables were chosen because bone appeared sensitive to this type of ultrasound field. However, differences in treatment regimes (treatment time, treatment period) or differences in field variables (frequency, intensity, pulse duration) may be related to differences in the effect of ultrasound on bone healing or the cells involved in bone healing. For example, in rabbits, osteochondral defects of the patella healed earlier and with less degenerative changes at follow up when treated with low intensity pulsed ultrasound. It was found that a treatment time of 40 minutes per day increased the histological quality of the repair cartilage as compared to a treatment time of 20 minutes a day. When the same low intensity ultrasound is applied in cases of mandibular lengthening by distraction in rabbits, daily 20 minutes treatment on one side of the mandible produced more regenerate maturation than alternating daily 20 minutes treatment on both sides. Differences in ultrasound field variables may alter the tissue response as well. It must be noted that, despite the differences in treatment regimes or ultrasound field variables, the overall picture in the literature is one of bone healing stimulation, with a relatively minor emphasis on the importance of differences in field variables. However, this does not exclude that there may be an optimal combination of variables for mandibular bone, but this has not been established yet.

The second reason may be related to the perfusion and healing capacity of the head and neck region. Because the mechanism as to how ultrasound stimulates bone healing is not entirely clear, it is difficult to predict in which case
ultrasound will or will not stimulate bone healing. It has been reported that the pressure wave serves as a surrogate for physiological stresses in bone, which stimulate bone formation. Apart from piezo-electric and membrane effects, part of the ultrasound effect seems to be related to angiogenesis. In ischaemic tissues, where blood perfusion is limited, ultrasound can promote neovascularity and neocellularity. In dogs with an ulnar osteotomy, daily 20 minutes ultrasound treatment with the SAFHS device for 8 weeks produced an increase in blood flow around the osteotomy site after 2 - 3 days and this increase lasted for two weeks as compared to the non treated controls. Ultrasound can also stimulate the production of angiogenesis-related cytokines (Interleukin-8, fibroblast growth factor and vascular endothelial growth factor) in human mandibular osteoblasts, which indicates that ultrasound may stimulate angiogenesis.

This may explain why the stimulation of bone healing with ultrasound is apparent in compromised healing situations such as delayed and non-unions of the extremities, the healing of scaphoid fractures, and osteoradionecrosis of the mandible. These compromised healing situations are thought to be related to a relatively poor blood supply due to anatomical predisposition, vascular disease, treatment (medication, radiation) or habit (smoking). Thus, an important factor in the ultrasound stimulation of bone healing seems to be related to angiogenesis. This raises the question as to whether an already optimal healing tendency (read: optimal blood perfusion) can be influenced by ultrasound. The head and neck area of the body is well blood perfused and can, therefore, be considered to have an optimal healing capacity. This would imply that the additional effect of ultrasound treatment of mandibular bone in healthy individuals is expected to be minimal. This may explain why no effect of the ultrasound treatment on osteoconduction was measured in the presented studies. The rats used were mature, healthy, and had no known disorders that could compromise angiogenesis/bone healing. However, there are contra arguments to this theory. In healthy rabbits with an apparent optimal perfusion of the head and neck region subjected to mandibular lengthening by osteodistraction, low intensity pulsed ultrasound therapy seemed to accelerate the regenerate maturation in the distraction gap.

The third explanation that would place most of the results of the experimental work presented in this thesis into perspective, may be related to the types of animal and human models used. It has been explained that bone remodels according to functional demands (Wolff’s law) which means that bone exists by virtue of mechanical loading. When a fracture occurs, the bone will not be used as it would have been used before and, therefore, this stimulus by
physiological loading will be absent. The healing of a fracture is largely dependent on blood supply and stability. Recent insights indicate that the gap size, hydrostatic pressure and micro-movement between the fractured bone parts are fundamental factors influencing fracture healing. It has been proposed that ultrasound therapy serves as a substitute for the physiological loading, and therefore would give an additional incentive for a broken bone to heal. It seems that ultrasound waves exert pressure on the cellular level where bending of the bone-cells membrane alters its ionic permeability and, eventually, its metabolism. Thus, in case of a bone fracture, there is absence of physiological loading and presence of a certain micro-movement at the fracture site.

In case of a bone defect without bone discontinuity, the situation is reversed. In the mandibular defect-model described in this thesis, physiological use of the mandible is preserved, because there is no discontinuity (read: fracture) of the mandibular bone. Accordingly, there is no micro-movement that may be influenced by ultrasound. This may explain why ultrasound treatment may not have had an effect on the bone healing in the rat mandibular defects with or without the use of osteoconductive membranes. This reasoning may also be applied to the human distraction experiment. During and after the operative procedure, the continuity of the mandible remains preserved. After the operative procedure, the patients can still use their mandible for eating and speaking, albeit limited. This means that the mandible remains subjected to mechanical forces, similar to physiological use of it. In other words, the differences between a bone injury with (fracture) or without (defect) loss of continuity may account for the fact that no effect was seen of ultrasound therapy on bone defect healing.

It is difficult to suggest which of the above explanations may be the most applicable and it may also be that there are unknown factors involved. For now, it is reasonable to assume that ultrasound pressure waves do influence the cells involved in the bone healing process, but that this influence may be related to mechanical and circulatory conditions at the site of bone injury.

Conclusions

The conclusions of the experimental work presented in this thesis are:

1. Low intensity pulsed ultrasound is not effective in stimulating bone growth into a rat mandibular defect, with or without the use of osteoconductive membranes.
2. Low intensity pulsed ultrasound does not seem to stimulate early bone healing in the severely resorbed vertical distracted mandible.
Future perspectives
This thesis focused on a small area in the field of ultrasound and bone healing that had not been explored before. The animal experimental work indicates that ultrasound does not stimulate mandibular bone defect healing with or without the use of osteoconductive membranes in healthy animals. This may be related to the ultrasound field variables used, to an optimal healing tendency of the head and neck region, or to limitations of the animal model. To differentiate between these possibilities, additional animal experiments may be pursued repeating the experiments using other ultrasound field variables, using a compromised bone healing model such as for example, irradiated mandibular bone, or developing other maxillofacial bone healing models with the emphasis on bone discontinuities (for example developing a mandibular fracture model). More importantly, unravelling the mechanism of action as to how ultrasound stimulates bone healing in certain cases may eventually predict if, and if so, when, ultrasound may be of value in maxillofacial surgery.

The human experimental work indicates that in case of the severely resorbed distracted mandible, a longer consolidation period before the biopsy may be taken into account to ensure an intact biopsy, or a different method should be used to measure the amount of bone fill in the distraction gap. In this way it may be possible to assess more accurately if ultrasound can accelerate regenerate-maturation in the vertical distracted severely resorbed mandible.

References


