Ultrasound stimulation of mandibular bone defect healing
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Chapter 7

Summary
Ultrasound is a high frequency sound wave (> 20,000 Hz) that is used in medicine for diagnostic and therapeutic purposes. When applied to tissue, the high frequency pressure waves will exert a vibrating force onto the tissue. Higher ultrasound intensities may cause heating of tissue because the energy of the vibrations is converted into heat. These vibrations and local heating are considered stimulate healing of damaged tissue. Since the first therapeutic ultrasound application in 1932, ultrasound therapy has evolved within the physiotherapy practice mainly to treat soft tissue disorders. Until today, controversy remains with regard to the effects of ultrasound on soft tissue healing.

In the past, there have also been attempts to stimulate bone fracture healing with ultrasound. Since bone exists by virtue of physiological mechanical loading, ultrasound pressure waves would act as an alternative for this physiological loading in case of a fracture. Ultrasound would, therefore, act as an extra stimulus for a fracture to heal.

The first experiments to stimulate bone fracture healing with ultrasound failed, however, because the ultrasound intensities that were used were too high. Bone has a higher density than soft tissue, and is easily overheated during ultrasound application. Later (1950 - 1970), it became clear that ultrasound could stimulate bone fracture healing by using ultrasound with lower intensities that would prevent overheating. After animal experimental work, indicating that ultrasound could stimulate fracture healing under certain circumstances, the first prospective randomised double blind clinical trials were published in the nineties. The results of these studies indicated that the healing time of fresh tibial and radial fractures could be reduced by 38% after ultrasound was applied. Here, low intensity pulsed ultrasound was used with an intensity of 30 milliwatts per square centimetre, 20 minutes a day, by placing a transducer onto the skin across the fracture. It also became clear that slow or non-healing fractures could be healed by the application of ultrasound. Furthermore, it seemed that the effect of ultrasound is not limited to fracture healing, but that bone healing after osteotomy or osteodistraction could be stimulated as well.

A substantial part of the maxillofacial surgery practice deals with bone and bone healing. It is, therefore, interesting to assess whether ultrasound can stimulate bone healing in the maxillofacial region. If so, ultrasound could be beneficial in the healing of facial fractures, healing of bone defects after reconstructive surgery or osteodistraction, and in the osseointegration of dental implants. Based on the assumption that the process of bone healing of the facial bones and the extremities is essentially the same, the potential of ultrasound to stimulate maxillofacial bone healing was investigated in a literature review (Chapter 2). Although most of the existing literature deals with bone of the
extremities, there are indications that mandibular bone is responsive to ultrasound as well. It was, therefore, concluded that there may be a potential for ultrasound to stimulate maxillofacial bone healing.

Maxillofacial procedures often involve the mandible. Especially the reconstruction of bone defects can pose challenging technical problems. Therefore, the experimental work described in this thesis has been carried out to explore whether ultrasound therapy can be used to stimulate bone defect healing in the mandible. The research comprised an animal experimental and a clinical part.

The model used to conduct the animal experiments was the rat mandibular defect. This model consists of a round bicortical defect, drilled through the ramus of the mandible. The model was chosen because of its obvious advantages: the operative procedure is relatively simple, and the alveolar nerve as well as chewing ability remain preserved. Furthermore, the mandibular defect model has been extensively used and described in the literature.

Microradiography was used as the method to measure bone growth into the rat mandibular defect. The reason for using this technique rather than histology was that histological sections only represent one part of the defect. Moreover, histology is relatively time consuming and expensive. Microradiography has been described previously, but it had not yet been applied to measure areas of bone growth into rat mandibular defects. In chapter 3, high resolution microradiography was compared to traditional histology and it was found that both were accurate in measuring defect widths. The microradiography technique may also be used to measure a defect’s area in addition to its width. Therefore, microradiography was used in the subsequent three experiments to measure the area of bone growth into a rat mandibular defect.

In chapter 4.1 a placebo controlled single blind study is described in which it was assessed if ultrasound can stimulate bone growth into a rat mandibular defect. Either low intensity pulsed ultrasound or placebo was applied 20 minutes a day on the skin across the defect under general anaesthesia. An additional control group with only the defect was included. After two and four weeks of ultrasound/placebo application, no additional bone growth into a “plain” rat mandibular defect as an effect of ultrasound could be demonstrated. Presumably, the fast soft tissue ingrowth into the defect had blocked the slow bone growth from the defect rims. This phenomenon may have masked an ultrasound effect. Therefore, an attempt was made to stimulate bone growth in a different model, where soft tissue ingrowth was prevented. First, it was attempted to stimulate bone growth with ultrasound into a rat mandibular defect covered by an expanded polytetrafluoroethylene (e-PTFE) membrane.
(Chapter 4.2). The experimental design was similar to the previous experiment. After two and four weeks, no effect of ultrasound on the amount of bone defect healing was observed. Since the membranes appeared to block most of the ultrasound, it was concluded that this was the reason why no effect was seen. Therefore a second attempt was undertaken, by using collagen membranes that do not block ultrasound (Chapter 4.3). However, still no effect of ultrasound on the amount of bone formation into the mandibular defects was seen.

The maxillofacial region is very well blood perfused, and, therefore, is considered to have an optimal healing capacity. This might explain why ultrasound did not have an additional effect on the bone defect healing. As a consequence, a randomised clinical trial was set up to evaluate if bone healing of the mandible could be stimulated in a relatively compromised healing situation. In the severely resorbed, atrophic mandible it was investigated whether ultrasound could stimulate early bone formation within a bone gap after an osteodistraction procedure (Chapter 5). The results (after 31 days) indicate that ultrasound does not appear to affect the early bone formation, which seemed to be in an initial state, within the distraction gap. Possibly an effect would have been found after a longer period of bone healing.

The results of the experimental work presented in this thesis suggest that ultrasound does not stimulate bone growth into mandibular defects, with or without the use of osteoconductive membranes. This finding is not in accordance with the literature concerning ultrasound, fracture healing, and the healing of bone defects. In the literature, in most instances a positive effect is reported. There are, however, explanations that might fit the ‘negative’ results of the experimental work into the ‘positive’ results of the current literature.

A first explanation may be that the bone of the mandible is not responsive to the field characteristics of the ultrasound that is usually applied to the bone of the extremities. Variations in ultrasound frequency, intensity, pulse duration, and applied scheme may result in different effects than those found with the applied ultrasound field.

A second explanation may be related to the perfusion of the head and neck region. Ultrasound pressure waves have piezo-electric effects and effects on the cell membrane. Also, the formation of vessels is influenced by stimulating the production of certain proteins excreted by bone cells. When vessel formation is stimulated, transport of blood (and hence of oxygen and nutrients) is facilitated and healing is, therefore, stimulated as well. The head and neck region is well perfused and is considered to have an optimal healing capacity. This raises the question as to whether ultrasound can stimulate bone healing in a region where the healing capacity is already optimal. The clinical trial was set up with the idea...
that ultrasound might stimulate bone healing under suboptimal circumstances. In the severely resorbed mandible in the elderly, blood perfusion is considered to be compromised. The results indicate that ultrasound does not affect the early bone formation inside the distraction gap in the severely resorbed mandible. After 31 days, the bone formation seems to be just beginning and it may be that the effect of ultrasound was evaluated too early.

A final explanation may be related to the characteristics of the animal and human model used in the experiments. It has been explained in the literature that bone exists by virtue of mechanical loading (Wolff’s Law). When a fracture occurs, the affected body part will not be used, and thus mechanical loading will be virtually absent. In the animal experiments presented in this thesis, however, there was no fracture of the mandible. Instead, the model consisted of a bone defect. By using this model, the functional capacity of the mandible remains preserved and, as a consequence, the mandible remains mechanically loaded during defect healing. Similarly, during the mandibular distraction procedure in the clinical study, no discontinuity of the mandible has been introduced. The mandible was still loaded to some extent during the healing phase. For this reason, ultrasound may not have shown to be effective in these cases.

It is difficult to reveal which explanation would be most feasible. It may also be that unknown factors are of influence.

Based on the literature, it seems to be reasonable to assume that ultrasound has an effect on bone cells during bone healing, but that a possible observed effect may be related to the mechanical and circulatory conditions at the site.

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, either with or without the use of osteoconductive membranes.
2. Low intensity pulsed ultrasound does not seem to have an effect on the early bone formation in the vertically distracted, severely resorbed mandible.

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 reveal which of these possibilities is the most plausible, additional research is needed. For now, it is not recommendable to apply ultrasound in maxillofacial surgery to stimulate bone defect healing. In situations where mechanical loading or blood perfusion
is limited, as for example in the case of mandibular fractures or osteoradionecrosis, ultrasound might have an effect. 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.