Improvement of disfiguring skin conditions by laser therapy
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1 GENERAL INTRODUCTION AND AIMS OF THE THESIS
INTRODUCTION

In this thesis, therapies are described for scars, benign dermal tumours and port-wine stains. While these three types of skin conditions could not be more unalike, they have two things in common. First of all, they can be disfiguring and may affect quality of life. Secondly, they can be treated with laser therapy.

Disfiguring skin conditions

Disfiguring skin conditions, whether congenital or acquired, are visible skin conditions that force a patient to deal with an altered body appearance. In addition to physical and functional difficulties that may come with skin disorders, a patient may also have to deal with psychosocial problems.1-3 These psychosocial and psychological problems can have a major impact on a patients’ quality of life regardless of the type of skin condition.4 Various studies have been performed to assess the quality of life in patients with the disfiguring skin conditions that are dealt with in this thesis. 4-10 Especially for scars and port-wine stains, research on psychosocial problems related to the skin condition has been done, but also for dermal tumours like fibrofolliculomas, a quality of life assessment study was performed.11 Nowadays, there is more awareness for the psychosocial and psychological problems that come with disfiguring skin conditions. Apart from these quality of life studies, continuous research is performed to improve the therapeutic options for these skin conditions. Currently, especially laser therapy is being highlighted as a treatment option.

Laser therapy

Laser is the acronym for Light Amplification by Stimulated Emission of Radiation. While the theoretic foundations for the laser had already been established by Albert Einstein in 1917, it was not until 1960 that the first operating laser was actually developed by Theodore Maiman. He used a ruby crystal to emit red light with a wave length of 694 nm.12 Shortly after, the first physician to utilize a laser on humans was Goldman in 1963.13 He introduced the dermatologic application of laser technology, and ever since, a broad variety of improved and specialized laser types has been developed for a wide range of applications. In 1983, Anderson and Parrish introduced the concept of selective photothermolysis, a theory that described target specific destruction with minimal collateral thermal injury and thus less tissue damage.14 With this concept, cutaneous laser surgery was able to develop into the therapeutic option that it is for many skin conditions nowadays.

Many different lasers using various wavelengths have been developed in the past decades. The lasers that are currently being used can be divided into ablative and non-ablative lasers. The ablative laser used in the research described in this thesis, is the 10600 nm carbon dioxide (CO₂) laser. The CO₂ laser was developed in 1964, making it one of the earliest gas-mediated lasers.15 To this day, the CO₂ laser has proven useful in industrial applications as well as in different types of medical uses. It operates with infrared light at a wavelength of 10600 nm, which is very well absorbed by water molecules. Laser energy will convert into heat, which causes evaporation of the water molecules. This ablative effect makes the laser an accurate surgical
device. Moreover, coagulation of surrounding tissue limits blood loss. The CO\textsubscript{2} laser can be used in pulsed or continuous wave (CW) mode. The concept of pulsed laser treatment is to enable the tissue to cool down between pulses, therefore creating less accumulating heat resulting in less surrounding tissue damage. In 2004, fractional photothermolysis was introduced. Soon after, ablative fractional laser therapy (AFLT) was developed. Microscopic treatment zones (MTZ) are created while the tissue surrounding each column is spared, thus resulting in rapid epidermal repair (within 24 hours) with reduced downtime. Since this development, numerous studies on various skin conditions have been performed using ablative fractional lasers.

The non-ablative lasers that were used in the research for this thesis are the pulsed dye laser (PDL) at a wavelength of 595 nm, and the neodymium: yttrium-aluminum-garnet (Nd:YAG) laser at a wavelength of 1064 nm. The dye laser was first introduced in 1966 and in the 1980’s, the first PDL system was introduced. With a wavelength of 577 nm, penetration was only superficial, and in the following decades the 585 nm and 595 nm PDL systems were developed for deeper tissue penetration. Nowadays, the 595 nm pulsed dye laser is regarded the gold standard in the treatment of vascular lesions such as port-wine stains, and is, together with the 585 nm PDL, also the most frequently used laser in the treatment of hypertrophic scars.

The Nd:YAG laser was developed in 1964 and in the 1980’s it was first used for dermatologic applications such as pigment and hair removal and for the treatment of vascular lesions. In 2003, the long-pulsed Nd:YAG system was introduced in the treatment of deeper situated vascular lesions. Since then, only a small amount of studies on the Nd:YAG laser in the treatment of vascular lesions was performed. Consequently, evidence for this laser in the treatment of port-wine stains is still lacking.

In the next section of this introduction, the three types of skin conditions dealt with in this thesis will be described along with their current therapeutic options.

**Scars**

Scars are commonly seen after healing of skin injury in patients of all ages, and can be caused by any kind of trauma, including physical trauma, infections, burns or surgery. Scars can be normotrophic, atrophic or hypertrophic, and often pigmentary changes occur during scar formation. Although most scars do not pose a health risk, they can be highly disfiguring resulting in decreased quality of life. For the improvement of dyschromic or hairless scars, medical tattooing is described. Also, medical make up can help in the concealment of scars. Pruritus, pain and functional impairment are common physical symptoms of scars and can be a reason for patients to seek treatment. Various therapies have been proposed in the treatment of disfiguring or symptomatic scars, such as corticosteroids, 5-fluorouracil, bleomycin, silicone gel sheeting, pressure therapy, radiation, cryotherapy and surgery. However, little evidence on the efficacy is available due to a lack of (randomized) controlled trials.

Since the introduction of lasers in dermatology, many uncontrolled studies have been performed showing lasers to be effective in the treatment of scars. For the treatment of hypertrophic scars, pulsed dye laser therapy is still considered to be the
gold standard. This is also explained by the lack of evidence for other lasers, as only a few randomized controlled trials have been performed. Recently, a randomized trial was performed with the non-ablative fractional laser for hypertrophic scars. Although the therapy was safe, no clinical efficacy was shown for this laser on hypertrophic scars. For atrophic (acne) scars, however, multiple randomized controlled studies have shown the newer ablative fractional carbon dioxide (CO\textsubscript{2}) laser to be effective. This type of laser is now considered the gold standard for treating (facial) atrophic acne scars although the most effective settings are still not known. For other scars of different aetiology, evidence on the effect of ablative fractional laser therapy is still lacking.

**Benign dermal tumours**

Benign dermal tumours appear in various shapes and forms. Trichoepitheliomas for example are benign neoplasms that usually present as multiple skin-coloured or translucent papules of 2-5 mm on the face or upper trunk, with a predilection for the nose, and can also present in multiplicity. Milia are yellowish to pearly white, benign, superficial keratinous cysts, that are generally smaller than 3 mm and may arise either spontaneously (primary milia) or secondary to various processes, usually in the head and neck area. Eruptive vellus hair cysts are other cosmetically bothersome skin tumours which often cause recurrent inflammation. They present as multiple, smooth papules affecting the mid chest, face, neck, axillae, buttocks and/or extremities. The papules are small, 1-2 mm, and mostly skin-coloured or variably pigmented. Syringomas are benign ductal adnexal tumours. They appear as multiple small, soft papules with a skin-coloured to slightly yellowish or translucent colour and is usually confined to the uppermost dermis. Syringomas usually affect the periorbital areas and may be eruptive.

The presence of these benign but multiple dermal tumours can have a large impact on a patient’s quality of life. The treatment of choice for these tumours is (electro-) surgery, but also cryotherapy and laser surgery have been proposed as treatment options for improving the appearance of benign dermal tumours. Especially in patients with a large number of dermal tumours, laser ablation is a practical alternative for conventional surgery. Advantages are speed of the procedure and lack of bleeding. By drilling holes with the 10600 nm CO\textsubscript{2} laser, dermal tumours like fibrofolliculomas, eruptive vellus hair cysts, syringomas, trichoepitheliomas, milia and steatocystoma multiplex have been treated, all with varying results.

Clinical results are often disappointing because of post-inflammatory pigmentary changes, scarring, or due to a high recurrence rate. Conventional laser ablation lacks standardization and results depend largely on the physicians’ surgical skills. Due to intra- and interphysician treatment differences, the variation between lesions created with conventional laser drilling, although performed with the same settings, is too high to result in reproducible results.

**Port-wine stains**

Port-wine stains (PWS) are benign congenital vascular malformations characterized by ectatic blood vessels situated mainly in the superficial dermis. These birthmarks
occur in 0.3-0.5% of infants and initially appear as flat, pink to red patches. Due to progressive vascular ectasia, they may gradually progress into hypertrophic, red to purple lesions. By the fifth decade of life, nearly two-thirds of patients with PWS develop nodules and hypertrophy, worsening the appearance and occasionally causing spontaneous bleeding. Unfortunately, there is no evidence available to date whether prevention of PWS progression is possible. Since most port-wine stains seem to occur in the head and neck region, they often have a stigmatizing effect, and they negatively influence the quality of life, as demonstrated in several studies. For this reason, treatment is often wanted.

The gold standard for treating port-wine stains is the pulsed dye laser (PDL). However, multiple treatments are required and only a minority of patients achieves total clearance of the PWS. Moreover, hypertrophic PWS respond poorly to PDL treatment. To further improve resistant PWS, variation of PDL wavelength and/or pulse duration has been proposed. Also, studies have been performed to show the effectiveness of multiple PDL passes or of different treatment intervals. For hypertrophic PWS, multilayer PDL treatment or a combination treatment with PDL and Nd:YAG laser has been proposed. No evidence for Nd:YAG laser alone in the treatment of hypertrophic PWS is available to date.

**AIMS OF THE THESIS**

Treatment of disfiguring skin conditions remains challenging as long as optimal improvement is not possible, and patients continue to experience a decreased quality of life due to their skin disorder. In scars, fractional laser therapy has been proposed as a treatment option, and in this thesis the effectiveness will be reviewed and assessed. Furthermore, the lack of standardization in (laser) therapy for benign dermal tumours impedes reproducibility and comparison of results. In this thesis, an attempt was made to standardize treatment settings. In port-wine stains, pulsed dye laser therapy has been the gold standard for many years. In this thesis, innovations in laser therapy for resistant port-wine stains is debated and investigated. Laser therapy for the treatment of various types of scars has been a focus of effort since its introduction in the dermatologic field. Although many studies have been performed using laser therapy for hypertrophic scars, no systematic review was performed to show the effectiveness. Chapter 2 is the first study to assess the overall effectiveness of laser and light therapy in achieving improvement of hypertrophic scars over 6 months of age, compared to conventional or no treatment. Since the introduction of fractional photothermolysis, many uncontrolled studies have been performed using ablative or non-ablative fractional lasers in the treatment of scars. Chapter 3a is the first randomized controlled trial to assess the efficacy and safety of the ablative fractional 10600 nm CO2 laser compared to no therapy in the treatment of scars. Chapter 3b describes four cases of adverse events after ablative fractional CO2 laser therapy for atrophic scars. Although benign, small dermal tumours can be a burden for patients when they are multiple and located on visible areas such as the face. Ablative laser therapy is a practical
alternative for conventional surgery and has been described in several case series. To overcome the lack of standardization of these treatments, timed exposure settings can be used. In Chapter 4, the histological differences of skin treated with timed exposure ablative CO$_2$ laser is compared to skin treated with conventional CO$_2$ laser.

Laser therapy has been the gold standard for the treatment of port-wine stains since the introduction of selective photothermolysis in the early 1980’s. The many different innovations in laser techniques and applications, and new experimental modalities, are put down in Chapter 5. One of those innovations in laser techniques is multiple pass laser therapy. With consecutive passes, or pulse stacking, it was thought that recalcitrant port-wine stains would better respond to PDL treatment. However, the few studies describing this technique were inconclusive and no randomized trials were available. In Chapter 6, a randomized trial comparing single pass to double pass PDL in the treatment of port-wine stains is presented. For hypertrophic port-wine stains, other treatment modalities have been proposed since they rarely respond well to PDL therapy. Little is known about development of hypertrophy in port-wine stains. The aim of Chapter 7a was to assess the prevalence and patient characteristics of hypertrophic port-wine stains. In Chapter 7b is discussed if early start of laser treatment and regular intermittent maintenance of treatment could attribute to the prevention of aesthetically and mechanically disturbing hypertrophy in port-wine stains. As a treatment option for deeper situated vascular anomalies the Nd:YAG laser has been described, while it has also been proposed in the treatment of recalcitrant port-wine stains. The aim of Chapter 8 was to evaluate the safety and efficacy of the Nd:YAG laser in the treatment of hypertrophic PWS and to assess the results of Nd:YAG laser therapy on colour and hypertrophy after a long-term follow up.

In Chapter 9, all chapters of this thesis are summarized. The thesis concludes with a general discussion on the main findings, and future considerations on the use of lasers in dermatological practice are discussed (Chapter 10).

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