Diplomarbeit

Comparison of four treatment options for the clinical improvement of hypertrophic scars

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Eidesstattliche Erklärung

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Abstract

Background: Hypertrophic scars may interfere with a patient´s self-esteem and often feature pruritus and pain, therefore they may also become an aesthetic issue. Since there are many options for the treatment of hypertrophic scars, patients have a variety to select from.

Objective: The aim of this clinical trial is to point out which of the four treatment options, medical needling, fractional CO2 laser treatment, silicone sheets and silicone gel, is most effective as a primary endpoint and which one has the best cost/outcome/patient satisfaction ratio as a secondary endpoint.

Methods: 100 female subjects aged 18 – 65 years, with hypertrophic scars after cesarean section will be recruited. Forty patients with scars older than one year, will be randomly assigned to group1 (fractional CO2-laser) and group2 (medical needling) and 60 patients with scars younger than one year old will be randomly assigned to group 3 (silicone gel roller), group 4 (silicone sheets) and group 5 (control group). Time from baseline to follow up is 24 weeks. In this time patients of group 1 and 2 receive 3 treatments and patients of group 3 and 4 will use topical treatment for 18 weeks. Improvement will be evaluated using the Vancouver scar Scale, POSAS, 3D-Photography, Best cost/outcome ration and a 5-stage scale for scar improvement.

Results: Up to now, 4 patients completed the study. One patient was in group 1, two patients in group 2 and one patient in the control group. No patients of group 2 and 3 finished the study yet. The first patient treated with needling showed no difference in the score of the VSS, but an improvement of 38,5% in the score of the POSAS. The second patient treated with needling showed an improvement of 16,7% in the VSS and an improvement of 12,8% in the POSAS. The patient treated with fractional CO2 laser showed an improvement of the VSS of 9,1% and 7% of the POSAS. The score of the VSS of the patient in the control group stayed the same, whereas the score of the POSAS increased 16,8%.

Conclusion: Although treatment with fractional CO2 laser and needling show promising results in this first part of the study, more patients are needed to receive significant results.

Zusammenfassung

Einführung: Hypertrophe Narben stellen für viele Patienten ein Problem dar. Nicht nur Schmerz und Juckreiz zählen zu den unangenehmen Aspekten einer Narbe, sondern für viele Patienten ist besonders der ästhetische Faktor belastend. Heutzutage gibt es zahlreiche Therapieoptionen für die Behandlung hypertropher Narben und Patienten müssen sich aus dieser großen Auswahl für eine oder mehrere entscheiden.

Fragestellung: Das Ziel der Studie ist einerseits herauszufinden, welche der vier Behandlungsmethoden, nämlich medizinisches Needling, fraktionierter CO2-Laser, Silikonpflaster und Silikongel, die effektivste ist und andererseits das beste Kosten-Nutzen-Patientenzufriedenheits-Verhältnis darstellt.

Methoden: 100 weibliche Teilnehmerinnen zwischen 18 und 65 Jahren, mit hypertropher Kaiserschnittnarbe werden rekrutiert. 40 Patientinnen mit Narben, die älter sind als ein Jahr werden den Gruppen 1 (fraktionierter CO2-Laser) und 2 (medizinisches Needling) zugeteilt. 60 Patientinnen mit Narben, die jünger sind als ein Jahr werden den Gruppen 3 (Silikonpflaster), 4 (Silikongel) oder 5 (Kontrollgruppe) zugeteilt. Die Zeit vom Erstbesuch bis zum Follow-Up beträgt 24 Wochen. Patienten aus den Gruppen 1 und 2 erhalten in dieser Zeit 3 Behandlungen, Patienten aus den Gruppen 3 und 4 verwenden ihre Mediznprodukte für 18 Wochen. Ergebnisse werden anhand des VSS, POSAS, 3D-Fotografie, bestes Kosten-Nutzen-Verhältnis und anhand einer 5-stufigen Skala zur Verbesserung der Narbe ermittelt.

Ergebnisse: Bis jetzt haben 4 Patientinnen die Studie beendet. Eine Patientin in Gruppe 1, zwei Patientinnen in Gruppe 2 und eine Patientin in der Kontrollgruppe. Die erste Patientin wurde mit medizinischem Needling behandelt und zeigte eine Besserung des POSAS um 38,5% und keinen Unterschied im VSS. Die zweite Patientin, welche mit Needling behandelt wurde, zeigte eine Besserung des VSS um 16,7% und eine Besserung des POSAS um 12,8%. Die Patientin, welche mit Laser behandelt wurde, zeigte eine Besserung des VSS um 9,1% und eine Besserung des POSAS um 7%. Die Werte des VSS, der Patientin in der Kontrollgruppe, blieben gleich, wobei der POSAS sich um 16,8% verschlechterte.

Fazit: Die Resultate, der Behandlung mit medizinischen Needling und fraktioniertem CO2-Laser sind vielversprechend, dennoch sind weitere Patientinnen nötig, um signifikante Ergebnisse zu erhalten.

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1 Introduction

Scars develop due to injuries of the skin going along with destruction of the collagen network. The quality of scar tissue is of inferior quality to normal skin. It is composed of different types of collagen. Hypertrophic scars are raised fibrous lesions that typically do not expand beyond the boundaries of the initial injury (1). They originate due to an excessive production of collagen, mainly type 3 collagen, after skin injuries involving deep layers of the dermis. The risk for developing hypertrophic scars increases with the mechanical tension of a healing wound. Usually hypertrophic scars are reddish and thick. They feature pruritus and pain and may also become an aesthetic issue (2). Various treatment options may be useful to improve the quality of scars. Clinical studies have been conducted to show statistically significant improvement of scar pliability or elevation of hypertrophic scars (3) and of scar quality in hypertrophic burn scars (4) after treatment with fractional CO_2 laser. Another study proposing medical needling in combination with topical vitamin A showed significant improvement of scars (5). Silicone gel is able to decrease the elevation of scars (6) and showed significant improvement in scar height, pain, pigmentation, pliability, pruritus and vascularity of the scars (7). Silicone gel sheeting was found effective in reducing scar thickness and improving the pliability of the scar tissue (8).
Other treatment options for hypertrophic scars are compression therapy, intralesional corticosteroid injections and cryotherapy.
Individual studies for each method mentioned above have already proven the positive effects of those treatments. In our study, we will compare the effects of fractional CO_2 laser and needling on one hand and the effects of silicone sheeting and silicone gel rollers on the other. The aim of this clinical trial is to point out which of the four treatment options is most effective as a primary endpoint and which one has the best cost/outcome/patient satisfaction ratio as a secondary endpoint.

1.1 Definition and types of a scars

A scar is defined as fibrous tissue, that replaces normal skin after injury and is the final state of wound healing (9). Although all scars consist of collagen, their clinical appearances differ. Generally, scars can be classified in three different types: atrophic scars, keloids and hypertrophic scars. Atrophic scars are sunken lesions of the skin, often forming small dents or pits. This form of scaring is typically associated with acne or chickenpox, but also surgical interventions can lead to atrophic scaring. Keloids and hypertrophic scars, are both raised fibrous lesions, but while hypertrophic scars remain within the confines of the original wounds, keloids can grow indefinitely large. Sadly, most of the literature found on scar development and treatment, does not distinguish between these two types of scars.

1.2 Hypertrophic Scars

1.2.1 Clinical characteristics

The typical clinical appearance of a hypertrophic scar is a raised fibrous lesion within the confines of the original wound and a tendency to regress spontaneously. They are to be distinguished from keloids, which grow beyond the original wound boundaries and have no tendency to regress. The coloring is often erythematous at first, later becomes a brownish-red and pales with time (1). Hypertrophic scars usually develop 4-8 weeks following wounding. They have a rapid growth phase of up to 6 months, often followed by a regression over several years. Surgical scars are often linear, whereas inflammatory and ulcerating lesions often produce papular or nodular scars (2). Often the scars feature pruritus and pain (1). A previous study reported that the most common and distressing complications in burn patients who developed hypertrophic scars were abnormal appearance (75.2%), pruritus (73.3%) and pain (67.6%) (10). The majority of hypertrophic scars develop in anatomic areas with high tensions, such as shoulders, neck, presternum, knees and ankles (11)(12).

1.2.2 Histology

Hypertrophic scars consist primarily of type III collagen (13). Collagen fibers in hypertrophic scars are fine and randomly organized. The tissue of hypertrophic

scars contains distinct nodules consisting of myofibroblast and collagen filaments. Hypertrophic scars have a higher density of blood vessels compared to normal skin. Small blood vessels are oriented vertically in the scar tissue and around the nodules. Furthermore hypertrophic scars show an overproduction of multiple fibroblast proteins, which could either indicate a pathological persistence of wound healing signals or a failure of the downregulation of wound healing cells (14)(15)(16).

1.2.3 Epidemiology

According to literature, incidence rates of hypertrophic scarring vary from 40% to 70% following surgery to up to 91% following burn injury, depending on the depth of the wound. (2)
Studies have shown, that the incidence of hypertrophic scaring after orthopedic surgery on limbs is about 40% (15), and also about 40% after c-section (18). Excessive scaring occurs mostly in younger patients aged between 11 and 30 years (19)(20). Further epidemiological facts are hard to obtain, since most studies do not distinguish between hypertrophic scars and keloids, although there are several risk factors discussed, that may promote the development of hypertrophic scarring.

1.2.4 Risk factors for hypertrophic scarring

1.2.4.1 Age

As mentioned above, hypertrophic scars develop typically in younger patients aged between 11 and 30 years old. This may be related to delayed cellular proliferation, changes in ECM production and composition, and an altered cytokine and inflammatory response. With aging, the epidermal turnover becomes slower, the cellular activity decreases in the epidermis and dermis and therefore the proliferation of collagen decreases, which then rather results in dermal atrophy than hypertrophy. The inflammatory response in elder patients is delayed and the remodeling phase is distinct from the one in younger patients: There is a decrease in collagen fiber bundle density and type 1 collagen is more disorganized. (21)(22)

1.2.4.2 Bacterial Colonization

Whereas Infection is a known risk factor for excessive scarring, there is the hypothesis that the mere colonization of the wound with bacteria may also play a role in hypertrophic scarring. The suggested pathomechanism is, that bacterial toxins stimulate and prolong the inflammatory phase of wound healing and therefore promote the development of hypertrophic scars.(21)(23)

1.2.4.3 Stretch

As already mentioned hypertrophic scars typically develop in anatomic areas with high tensions. Studies have shown, that stretch during wound healing has a positive effect on the proliferation phase and angiogenesis and also leads to a reduction of apoptosis. (21)(24)
Another study describes the connection between the increased transition of fibroblasts into myofibroblasts in wounds exposed to mechanical tension, which can play a role in the formation of hypertrophic scars (25). Another study showed that the reduction of the tension acting on the surgical wound after c-section, due to the use of paper tape, could reduce the development of hypertrophic scars. (18)

1.2.4.4 Protective factors in hypertrophic scar formation

Besides avoiding risk factors such as infection and mechanical tension, studies suggest, that chemotherapy and smoking play a protective role in hypertrophic scarring.
Since chemotherapy reduces proliferation and collagen production, it has a negative effect on the genesis of hypertrophic scars. A study, observing the development of hypertrophic scars after TRAM (Transverse Rectus Abdominal Muscle flap) during chemotherapy, showed a decrease of hypertrophic scar formation. Since the chemotherapy was administered during the remodeling phase, chemotherapy seems to have a positive effect on scar maturation.(21)(26)
Besides from its well known negative effects, like delayed wound healing and complications during wound healing, smoking may have a protective effect on hypertrophic scarring. Smoking leads to a recued migration of neutrophils into the

wound, reduced production of proinflammatory cytokines and reduced collagen production and therefore decreases hypertrophic scar formation.(21)(27)(28)

1.2.5 Pathophysiology

1.2.5.1 General wound healing

Wound healing proceeds in three steps: Inflammation, proliferation and maturation.
The first step, inflammation, begins right after wounding with the activation of the coagulation cascade. The release of vasoactive mediators and chemotactic factors lead to the immigration of neutrophils and macrophages into the wound. Monocytes infiltrate the wound, transform into activated Macrophages and release growth factors such as platelet-derived growth factor and vascular endothelial growth factor. Those factors initiate the formation of granulation tissue. The proliferation phase starts after 48 to 72 h and lasts for 3–6 weeks. Fibroblasts synthesize reparative tissue, the extracellular matrix (ECM). The newly formed granulation tissue is made of procollagen, elastin, proteoglycans and hyaluronic acid. Its structure serves the closure of the wound and the vascular ingrowth. Myofibroplasts containing actin filaments lead to wound contraction. When the wound is closed, the immature scar transitions into the final maturation phase, where remodeling of the collagen network takes place and the immature type-3 collagen should be transformed into the mature type-1 collagen. The maturation phase can last several months. Various signaling molecules regulate the complex process of wound healing, which is still not completely understood. Although it is known, that a disturbances in the different steps of the wound healing process can contribute to excessive scar formation. (29)(30)(31)

1.2.5.2 Possible pathomechanisms for hypertrophic scarring

1.2.5.2.1 Inflammation

One possible disturbance in the wound healing process and therefore for hypertrophic scarring is inflammation. Studies have shown, that prolonged inflammation may play a role in excessive scar formation, whereas the degree of

the inflammation is a determining factor for the scar to become either hypertrophic or a keloid. (32)(33) But not only the degree and duration of the inflammation, also the expression of different cytokines plays a significant role in excessive scar formation. (34)

1.2.5.2.2 Cytokines and growth factors

Different cytokines and growth factors stimulate angiogenesis, epithelialization and the production of the ECM. As mentioned above, vascularization in hypertrophic scar tissue is increased. Angiogenesis is stimulated by cytokines such as VEGF, FGF, angiopoietin and TGF-b. (29) Reepithelialization is guided by factors like IL-1a, TNF-a, EGF, FGF, TGF and many others, which regulate the activation, migration and proliferation of keratinocytes. Activated keratinocytes increase proliferation and collagen production and since keratinocytes in hypertrophic scar tissue show a prolonged activation and proliferation, alterations in the repithelialization-process may play a role in excessive scar formation. (34)(35)
The production of the ECM plays another significant role in hypertrophic scarring. Optimal wound healing requires a balance between matrix degradation and production. This process is manly influenced by factors such as PDGF, IGF-I, FGF and TGF. (30) A misbalance in this process may lead to excessive production of ECM and therefore to hypertrophic scar formation. Fibroblasts are primarily responsible for the formation of granulation tissue (34). Factors that simulate the migration of fibroblasts are fibronectin, PDGF, NGF, TGF-b and CTGF whereas TGF-b1 and mechanical forces stimulate the differentiation into myofibroblasts. (36)(37)(38) (Myo)fibroblasts also produce collagen, stimulated by many growth factors, such as PDGF, TGF, EGF and CTGFr. (36)
Compared to normal fibroblasts, myofibroblasts produce higher amounts of ECM components. Hypertrophic scar tissue shows higher numbers of fibroblasts and myofibroblasts than normal skin or normotrophic scar tissue, which presumably leads to an overproduction of ECM and collagen. (39)

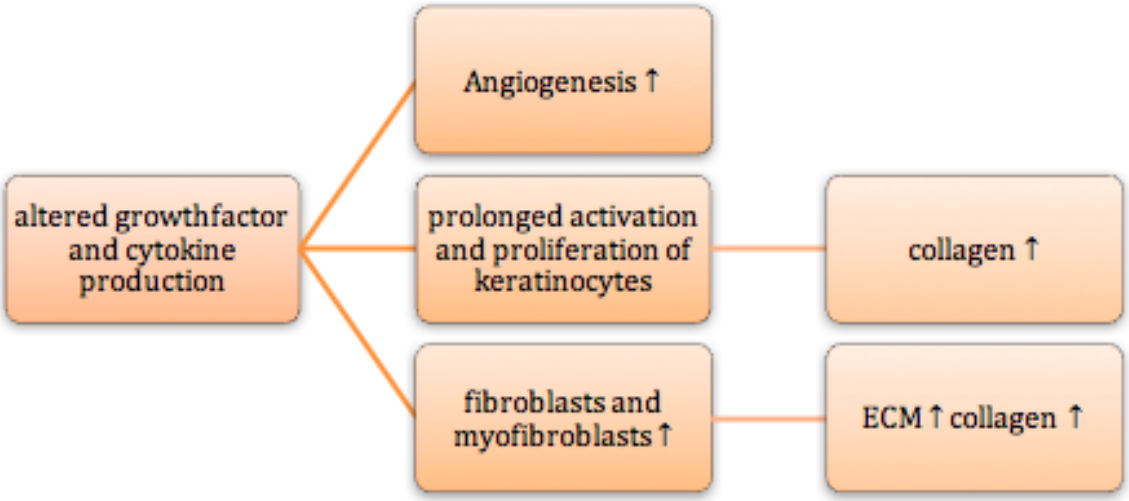

Figure 1: pathomechanisms for hypertrophic scarring

1.2.5.2.3 Atypical extracellular matrix remodeling

Hypertrophic scarring often becomes visible during the remodeling-phase, when the maturation of the ECM occurs. (Myo)fibroblasts replace the hyaluronic acid in the ECM with proteoglycans, like decorin. Decorin can bind and neutralize TGF-b1 and regulates the collagen fibrillogenesis. A Study has shown, that fibroblasts in hypertrophic scars produce less decorin than fibroblasts in normal tissue (34)(40). Since another study has shown, that decorin inhibits cell proliferation and downregulates the production of TGF-b1 and type 1 collagen, the reduced production of decorin may play a role in the development of hypertrophic scars (34)(41).

Enzymes called Matrix metalloproteinases (MMPs) play another important role in the remodeling-phase. While the concentration of these proteinases is typically low in normal tissue, many MMPs have shown to play a role in the remodeling of collagen during wound healing (2). Specifically MMP-2, which is involved in prolonged tissue remodeling, shows a persistent activity in the maturation phase of wound healing (42). MMP-2 is able to degrade many extracellular matrix proteins as well as denatured collagens (43). Another study showed, that MMP-2 activity was increased in hypertrophic scars and keloids (44).

Another interesting factor in hypertrophic scarring may be apoptosis. After contraction of the wound tissue and when the full epithelialization is completed, myofibroblasts usually enter apoptosis. Immature hypertrophic scar tissue is hypercellular, but as the scars mature the density reduces. In normal scar formation apoptosis of the myofibroblasts takes place 12 days after wounding and reaches its maximum at day 20 (45). A clinical trial showed, that in severely burned patients, maximal apoptosis in hypertrophic burn scars took place 19-30 months after injury and that the percentage of myofibroblasts was higher than in normal scars or in normal skin (39). Possible mechanisms behind that findings may be decreased death receptor ligand FAS in hypertrophic scars and the increased expression of the proto-oncogene bcl-2, which protects cells from apoptosis (45)(46)(47).

1.3 Scar-Rating-Scales

To quantify scar appearance and to properly assess the outcome of a scar treatment, scar rating scales have been designed. Currently there are various standardized rating scales for the assessment of scars. The rating scales consider several factors such as scar height or thickness, pliability, surface area, texture, pigmentation, and vascularity. (48)

1.3.1 The Vancouver Scar Scale (VSS)

The VSS was first describes by Sullivan in 1990. It is one of the most used scar assessment scores in Literature and research and assesses 4 different characteristics of the scar, which are vascularity, height/thickness, pliability, and pigmentation. The maximum score reachable is 13 points. Since the VSS is described by an observer, subjective description of the scar by the patient is missing in this evaluation. (48)

Vascularity	Height/thickness	Pliability	Pigmentation
0 normal	0 normal, flat	0 normal	0 normal
1 pink	1 <2mm	1 supple	1 hypopigmentation
2 red	2 2mm-5mm	2 yielding	2 hyperpigmentation
3 purple	3 >5mm	3 firm	
		4 banding	
		5 contracture	

Table 1: Vancouver Scar Scale

1.3.2 Patient and Observer Scar Assessment Scale (POSAS)

Another broadly used scar scale is the Patient and Observer Scar Assessment Scale. The POSAS consists of two parts, a Patient Scale and an Observer Scale. The Observer scale contains the factors vascularity, pigmentation, thickness, relief, pliability, surface area as well as the overall opinion. Each factor can be rated from 1 to 10. Furthermore, category boxes are available to score nominal parameters (e.g. type of color). The Patient scale contains seven subjective questions for the patients, concerning the pain and the itchiness of the scar as well as the color, the thickness, the stiffness and the irregularity and the overall opinion of the scar compared to the normal skin. All answers are rated from 1 to 10. (49)

1.3.3 Visual Analog Scale (VAS)

The VAS was not originally designed for scar evaluation. It was designed to assess the subjective experience of a patient´s pain. The patient was asked to rate the pain intensity by placing a mark on a 100mm line ranging from no pain to worst pain imaginable. (50)

For scar evaluation, the VAS is typically used as a photograph-based scale, assessing pigmentation, vascularity, acceptability, observer comfort and contour. The single scores range from “excellent” to “poor” and are summed up to get an overall score of the scar. (48)

1.3.4 The Manchester Scar Scale (MSS)

This scar scale is hardly used in research, probably due to the widespread use of the VSS and POSAS. The MSS is similar to the POSAS and additionally contains an overall VAS added to the individual attribute scores. The 7 parameters

described in the MSS are color, mat vs. shiny, relationship to surrounding skin, texture, margins, size and single or multiple. The scores from the two scales were added together and give the overall score for the scar. (48)

VAS Excellent ⟷ Poor				
Colour	**Mat vs. Shiny**	**Contour**	**Distortion**	**Texture**
1 Perfect	1 Mat	1 Flush with surrounding skin	1 None	1 Normal
2 Slight mismatch	2 Shiny	2 Slightly proud/Indented	2 Mild	2 Palpable
3 Obvious mismatch		3 Hypertrophic	3 Moderate	3 Firm
4 Gross mismatch		4 Keloid	4 Severe	4 Hard

Table 2: Manchester Scar Scale (48)

1.3.5 The Stony Brook Scar Evaluation Scale (SBSES)

The SBSES was rather designed to measure short term wound outcomes. It is a scar scale evaluating 5 different parameters: With, height, color, hatch marks/suture marks and overall appearance. It is a binary assessment, rating each parameter either with 1 or 0 and therefore yielding a total score ranging from 0 (worst) to 5 (best). (48)(51)

There are many more Scar Scales slightly different from the ones mentioned above. The most frequently used ones in research are the VSS and the POSAS, which will also be used in our study, to assess the outcome of the applied treatment modalities for hypertrophic cesarean section scars.

1.4 Abdominal skin incisions used in Caesarean Section

Caesarean section can be performed either using a midline vertical or a suprapubic transverse abdominal incision. Transverse incisions follow Langer lines of skin tension, and therefore superior cosmetic results can be achieved. Decreased rates of postoperative pain, fascial wound dehiscence, and incisional hernia compared with vertical entry are further benefits of the transversal entry.

There are two types of transverse abdominal incisions, the so called Pfannenstiel and the Maylard incision. The Pfannenstiel incision is most frequently used for caesarean delivery. With the Pfannenstiel incision, the skin and subcutaneous tissue are incised using a low, transverse, slightly curvilinear incision. This is made at the level of the pubic hairline, which is typically 3 cm above the superior border of the symphysis pubis. The incision is extended beyond the lateral borders of the rectus abdominis muscles. The width is typically 12 to 15 cm. The skin incision of the Maylard incision is similar to the Pfannenstiel incision, although it is set slightly higher, approximately 5-6 cm above the symphysis pubis.

For the vertical entry, a infraumbilical midline vertical incision is performed. It begins 2 to 3 cm above the superior margin of the symphysis and should be of sufficient length to allow fetal delivery without difficulty. Therefore, its length should correspond with the estimated fetal size, and 12 to 15 cm is typical. Sharp or electrosurgical dissection is performed to the level of the anterior rectus sheath. Skin closure is usually performed with a running subcuticular stitch using 4-0 delayed-absorbable suture or with staples. In comparison, final cosmetic results and infection rates appear similar. (52)

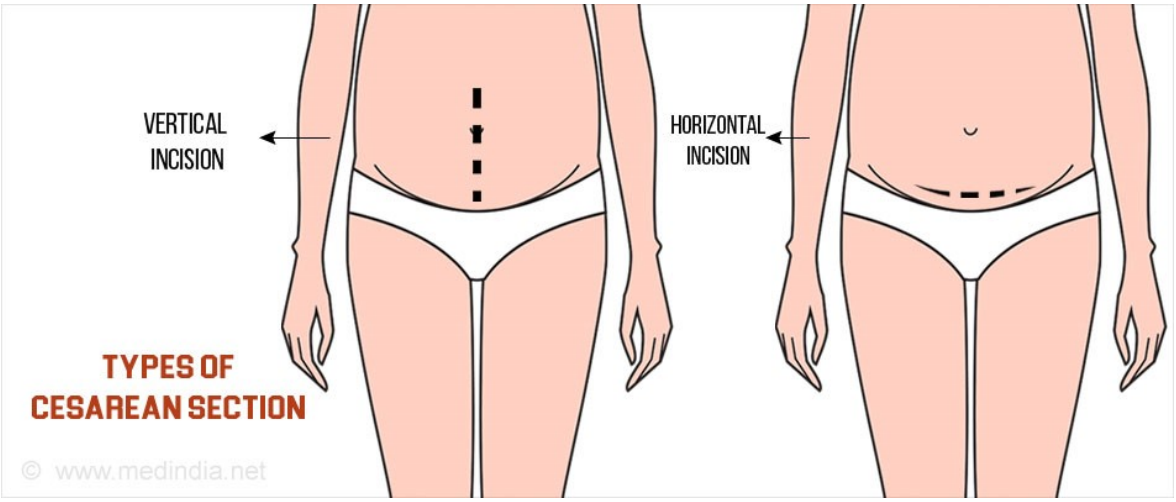

Figure 2: Types of cesarean section, web: http://www.medindia.net/surgicalprocedures/caesarean-section-types-and-indications.htm, 01.07.2017

1.5 Treatment options for hypertrophic scars

1.5.1 Silicones

Silicone is a widely-used treatment option for hypertrophic scarring. Silicone-based products are recommended as the gold standard option for both the prevention and treatment of hypertrophic scars. The mechanism of action of silicone products is not fully understood, but there are several theories proposed. (53)
The most accepted theory is that, the occlusion and hydration of the stratum corneum are responsible for the positive effect of silicone products on hypertrophic scarring. Silicone sheets, as well as silicone gel can reduce evaporation of water from the skin. The loss of water from the epidermis may lead to dehydration of keratinocytes, which may then release cytokines that increase collagen production (54). Therefore, the hydrating effect of silicone products may have a protecting effect on hypertrophic scarring. Also the occlusive effect of silicone products play a role in the mechanism of action of silicone products, since a study showed, that occlusive dressing had a beneficial effect in the treatment of scars with silicone cream (55).

1.5.1.1 Silicone sheets

Silicone sheets can be applied once the wound is closed and must be worn on the scar for 12–24 hours each day for three to six months. The sheets should be washed daily with mild soap and water to prevent side effects such as rashes and infections. Some silicone sheets are self-adhesive whilst others require taping to fix them to the skin. Silicone sheets are not suitable for use on large areas of skin and on mobile body parts such as the joints. (53)
Beginning treatment for hypertrophic scars is recommended when the scar is younger than three months, although a study showed, that treatment is effective for matured scars and keloids as well (56). Several studies confirmed the safety and efficacy of silicone sheeting for the prevention and treatment of hypertrophic scars (56)(8)(57)(58). A multi centered study with 224 patients and scar ages ranging from two weeks to 62 years showed significant improvement in color, thickness, and elasticity (56). Li-Tsang et al. showed that silicone gel sheeting (Cica-Care®) was effective to reduce thickness, pain, itchiness and pliability of posttraumatic hypertrophic scars among the Chinese population (8) while Momeni et al. showed a significant improvement of pigmentation, vascularity, pliability and

itchiness in hypertrophic burn scars, after silicone gel sheeting (57). The positive effect of silicone sheeting after surgery, was shown in a study of Sakuraba et al., that showed the prevention of keloid formation after median sternotomy, through silicone sheets (58). Summing up, a meta-amalysis of 20 studies involving 873 patients concluded, that there is a benefit of silicone gel sheeting, as it improves scar thickness and color, but also that most trials concerning this topic are of poor quality and highly susceptible to bias.

1.5.1.2 Silicone gel

Silicone gel should be applied twice a day as a thin layer. It dries to form an adherent, transparent, flexible silicone sheet that is impermeable to fluids. Such gels are suitable for use on visible areas such as the face and hands as well as on joints, where silicone sheets might have adhesive problems. (53)
There are several clinical trials supporting the beneficial effect of silicone gel on hypertrophic scarring. (6)(7)(59)(60)
In a 16-week controlled study with 29 completing patients with hypertrophic or keloid scars, 90% reported a marked improvement in their scar appearance. The study showed a noticeable decrease in the length of the scars, improvement in the color, and a high level of patient satisfaction after scar treatment with silicone gel (59). Medhi et al. examined the efficacy of silicone gel for the prevention of post-operative scars. 36 patients, who had undergone prior surgery and had recent post-surgical scars were asked to apply the gel twice daily to the affected areas for 3months. Treated scars showed a reduction of scar-height, hyperpigmentation, vascularity and pliability (7). Signorini et al. showed in their study, with a total of 160 patients, that the application of silicone gels to recent post-surgical scars was associated with significant improvements in clinical outcomes compared to placebo. Of the patients treated with silicone-gel, only 7% had hypertrophic scars or keloids after four months of treatment, compared to 26% of the placebo-treated patients. All patients considered the gel as easy to apply and none reported any side effects. (60)
Another randomized, placebo-controlled, double-blind clinical trial, evaluating the use of silicone gel on scars after median sternotomy, showed that silicone gel was effective in preventing the development of hypertrophic scars (6).
Other studies showed that silicone gel is more or as efficient as other topical treatments for hypertrophic scars. (61)

A study of 30 patients with surgical wounds, compared the efficacy and the convenience of use of silicone sheets and silicone gel. The study revealed, that there was no significant difference in the efficacy between the 2 products but also that patients found topical silicone gels more convenient to use. (61)(62)
Karagoz et al. examined the difference between the treatment of hypertrophic scars with silicone gel, silicone gel sheets, and Contractubex®, a topical onion extract including heparin and allantoin. The study contained 45 patients with hypertrophic post-burn scars. The difference between before and after treatment scores for each three groups was statistically significant. There was no difference in the efficacy between silicone sheets and silicone gel, but the study showed, that silicone products were superior to Contractubex® in the treatment of hypertrophic scars. (62)

1.5.2 Laser Therapy

Laser treatment for scars has developed over the past 30 years. During laser treatment, photothermal effects occur in the tissue. The aim of laser treatment is to create these photothermal effects in specific target chromophores in the skin while limiting damage to the adjacent tissue. (63)
For the treatment of hypertrophic scars many different lasers have been studied. Ablative lasers like the CO2-laser and the Er:YAG-laser have been proven to be effective in scar treatment as well as non-ablative lasers like the Pulsed Dye Laser (PDL). A common laser for hypertrophic scar treatment is the PDL with a wavelength of 585-595nm. The most common 585-nm PDL post-treatment side effect is post-treatment purpura, which can persist for several days to a week. Optimal treatment intervals are 6-8 weeks. For patients with darker skin phenotypes higher energy densities and longer treatment intervals are needed. (63)
The efficacy of PDL in the treatment of hypertrophic scars has been proven early in 1994, when a study of Alster showed clinical and textural improvement of 57% after the first treatment and 83% after the second treatment with PDL for hypertrophic surgical and traumatic scars. (64)
A systematic review, including eight randomized control trials, investigating the efficacy of PDL for the treatment of hypertrophic scars concluded that PDL was superior to conventional methods in improving overall scar appearance. (65)

Ablative lasers like the CO2 or Er:YAG laser are also an option for the treatment of hypertrophic scars and have especially shown improvement in acne, traumatic and surgical scars. Typical side-effects are erythema, dyspigmentation and acneiform eruptions. (63)

Poetschke et al. showed that fractional ablative CO2 lasers are effective in treating hypertrophic burn scars. After one treatment VSS and POSAS improved significantly, as well as the surface relief and firmness of the scar (66).

Another study of Azzam et al., investigating the effects of fractional CO2 laser treatment of hypertrophic scars also showed a significant improvement of the VSS after treatment with fractional CO2 laser. The scars especially improved in pliability and pigmentation. (67)

Choi et al. conducted a study, comparing fractional CO2 laser treatment with Er:YAG laser treatment for hypertrophic scars. Both treatment options showed an improvement in VSS, with an average percentage change of 28,2% in Er:YAG and 49,8% in CO2 laser treatment. Improvement was evident in terms of pliability, while insignificant in terms of vascularity and pigmentation. (68)

A meta-analysis of 28 studies, evaluating the effectiveness of various laser treatments showed an overall response rate for laser therapy of 71% for scar prevention and 68% for hypertrophic scar treatment. The meta-analysis showed that laser treatment of hypertrophic scars reduced VSS scores, scar height and scar erythema. The best results among all laser systems, according to the meta-analysis, were seen after treatment with 585/595-nm pulsed-dye laser and 532-nm laser subgroups. (69)

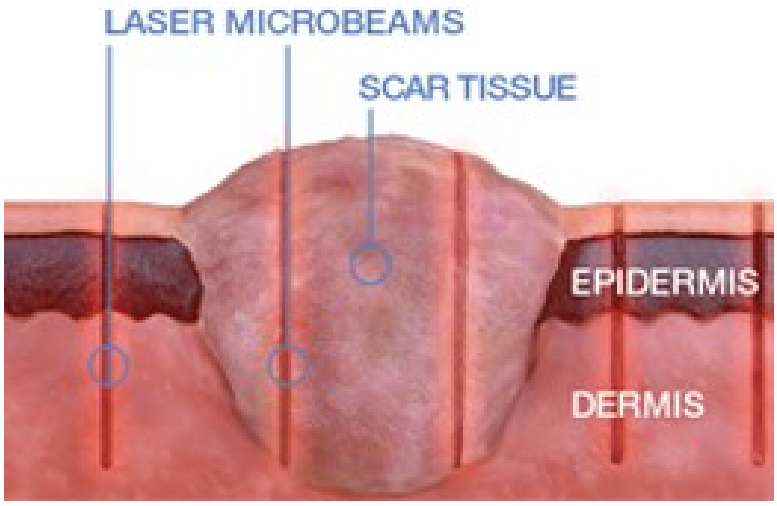

Figure 3: fractional CO2-Laser, Web: http://www.aesthetipedia.de/behandlungen/scaar-fx/, 01.07.2017

1.5.3 Needling

Another treatment investigated in our study is medical needling. The instrument used for needling is a drum-shaped cylinder studded with fine needles.

Figure 4: Needling device, Web: https://www.banggood.com/Wholesale-Derma-Needling-Roller-Skin-Care-For-Wrinkles-Acne-Scars-Anti-aging-p-48169.html, 01.07.2017

In microneedling, the length of the needles on the cylinder is typically 0,5-3mm long. Microneedling with a needle length of 0,5-1mm is usually recommended for skin rejuvenation whereas a needle length of 1,5-2mm is typically used for the treatment of acne scars. (70) For optimal results already after one treatment, 3mm needles can be used. The disadvantage of the treatment with 3mm needles is, that it has to be conducted under general anesthesia and side effects such as hematoma and strong swelling of the treated area are possible. (71)
The mechanism of action behind needling is to induce an inflammatory cascade by puncturing the skin with the needling device. The micropunctures lead to the release of various growth factors and lead to neovascularization, and neocollagenesis, and therefore leading to a rearrangement of the collagen network of the treated area. The procedure is typically performed under topical anesthesia. After disinfection, the skin is treated with the needling device, by rolling it horizontally and vertically over the area to treat. Multiple treatments should be performed at 3-8 week intervals.(70)

The use of needling for the treatment of hypertrophic scars has already been described in 1997 by Camirand and Doucet, who used a tattooing device without ink to treat various scars. (72) In 2010 Aust et al. examined the efficacy of the treatment of mature and hypertrophic burn scars with a 1mm needling device. In the study, subjective assessment of the scarring as well as the histological examinations revealed significant improvements. (5)
Kubiak and Lange examined medical needling as a treatment for scar formation following thermal injuries in children. In the study a 2,5mm needling device was used under general anesthesia and vitamin A and vitamin C oil was applied after treatment. All patients reported subjective improvement and overall VSS scores improved. After one treatment, scar vascularity, pliability and height improved, but there was no statistically significant effect on pigmentation. (73)

1.5.4 Pressure therapy

Today pressure garnets are mainly used for the prophylaxis of hypertrophic burn scar formation. Typically, elastic compression with elastic garnets are used for the prophylaxis of hypertrophic scaring if spontaneous wound closure takes longer than 10 to 14 days or if the wound requires grafting. The working mechanism of pressure therapy is not fully understood. However, there are several theories, trying to explain the mechanism of action. One theory is that pressure limits the supply of blood and oxygen to the scar tissue and therefore reduces collagen production, another theory suggests, that pressure therapy modulates the remodeling phase, by altering the release of cytokines during this phase.(74)(75)
It is suggested that pressure therapy reduces collagen production more rapidly than the natural maturation process and encourages the realignment of collagen bundles. Pressure garnets are normally used as soon as the wound is fully closed. Garnets must be worn continuously for at least 23 hours. Pressure must be applied until the scar is mature, which takes at least 6 months from wound closure. (76)
A big problem of pressure therapy in the treatment of hypertrophic scars, are the low compliance rates. In a study of Johnson et al. only 41% of all patients were compliant in wearing pressure garnets for burn rehabilitation. (77)
In fact, the effectiveness of pressure garnets on hypertrophic scarring remains controversial. While studies found no significant difference between treatments involving the use of high-pressure garments, lower-pressure garments, or no

pressure at all (76), others report success rates of 60% to 85% (78). A review about the effectiveness of pressure therapy (15 – 25 mmHg) for hypertrophic burn scars, including 12 randomized controlled trials, showed significant differences in Vancouver Scar Scale score, thickness, brightness, redness, pigmentation, and hardness, whereas no difference was shown in vascularity. (79)

1.5.5 Cryotherapy

Today there are different forms of cryotherapy for hypertrophic scarring, all of them leading to significant improvement or regression of the hypertrophic scar. Cryotherapy reduces the scar volume by inducing ischemic destruction and necrosis in the scar tissue. (74)

Contact or spray cryotherapy has shown to flatten keloids in 51% to 74% of patients after two or more sessions. Cryotherapy helps to soften the lesions and thereby makes it easier to the administrate intralesional medication. Contact cryotherapy should be applied for 15-30 seconds. Since Cryotherapy is quite painful it may demand infiltration of local anesthesia. In between the treatment sessions, several weeks are needed for postoperative healing. Common side effects are hypopigmentation, hyperpigmentation, moderate skin atrophy and pain. Another limiting factor is, that cryotherapy can only be used for the management of small scars. (80) (74) (81)

A prospective consecutive trial, that used contact cryotherapy for the treatment of hypertrophic scars and keloids, showed excellent responses in 32.3% and good responses 29.0% of all patients. Poor responses were seen in 29.0% and no response in 9.7% of all patients. In this trial, hypertrophic scars responded better to cryotherapy than keloids. Clinically responding lesions were examined histologically, there neovascularization and the loss of the anarchic arrangement of collagen bundles could be found. (82)

A study showed, that cryotherapy combined with intralesional triamcinolone injection lead to better results than cryotherapy or TAC-injection alone. (83)

Another cryotherapy method is the intralesional needle cryoprobe method. A cryoneedle is inserted into the long axis of the hypertrophic scar. For wider lesions, multiple needles can be inserted at right angles to the length of the lesion, although it is advised to rather use cryotherapy for smaller lesions. With the intralesional method, a bigger volume of scar tissue can be frozen and side effects as well as the time between treatment intervals can be reduced. On average a

reduction of 50% of the scar volume can be achieved after one session. (84) (74) (81)

1.5.6 Onion extract and heparin gel (Contractubex)

The topical gel consists of 10% aqueous onion extract, 50 U heparin per gram of gel, and 1% allantoin gel. This formulation has been used for many years to treat wounds. While onion extract reduces fibroproliferative activity and the production of ECM, heparin interacts with collagen molecules, by inducing the formation of thicker fibrils and promoting intermolecular bonding in collagen. Heparin and onion extract reduce hypertrophic scarring, by inhibiting inflammatory processes, fibroblast proliferation, and the synthesizing capacity of fibroblasts. (75)(85)
There are several studies, that indicate a positive effect of the topical preparation of onion extract and heparin gel on hypertrophic scarring. Wai et al. examined the effects of the use of Contractubex for the prevention of scarring after laser tattoo removal. 120 Chinese patients took part in the study. In the study the Contractubex group had a statistically significantly lower rate of scarring than the control group. In this study, Contractubex reduced the risk of scarring from 23.5% to 11.5% (85). Another study examined the effect Contractubex on fresh scars after thoracic surgery in children and adolescents. 45 young patients with fresh scars after thoracic surgery were randomly assigned either to the treatment-group or to a control group. Hypertrophic or keloidal scars were less frequent in the treated group (86). Chanprapaph et al. showed in their double blinded split-scar study, an improvement in height and scar symptoms after treatment with onion extract. There was no statistically significant difference in scar redness, scar pliability, and overall cosmetic appearance.

1.5.7 Intralesional corticosteroid injection

Intralesional steroid injections lead to HTS regression, by decreasing collagen and glycosaminoglycan synthesis, by reducing the inflammatory process and fibroblast proliferation and by increasing hypoxia. Adverse effects of intralesional corticosteroid injection are pain at injection, skin atrophy, hypopigmentation, telangiectasia, necrosis, ulceration and cushingoid features. Two or three injections of triamcinolone acetonide (TAC, 10 to 40 mg/mL) are usually sufficient. Response range from 50% to 100%, and recurrence rates from 9% to 50%. (2)(75)

Ina study of Muneuchi et al. one third of the patients treated with intralesional corticosteroid injection showed good or better results, but also one third withdrew from the study prematurely because of pain (87).
A study of Park et al. (88) and another study of Chowdri et al. (89) fund high recurrence-free rates, after intra- and/or postoperatively administered corticosteroid injections.

Figure 5: Corticosteroid Injection, Web:
http://www.medindia.net/patientinfo/keloids.htm, 01.07.2017

1.5.8 Bleomycin

Bleomycin is also administered as intralesional injections. The exact mechanism, by which bleomycin induces hypertrophic scar regression is not entirely clear, although Bleomycin was found to cause necrosis of keratinocytes. It also can also induce inflammatory infiltration and lead to the expression of various adhesion molecules. Further studies are needed to understand the complete work mechanism of Bleomycin in the treatment for hypertrophic scars. Occasional side effects are hyperpigmentation and dermal atrophy. Systemic toxic effects of intralesionally administered bleomycin are not common, because the concentration and dosage are not sufficient to incite systemic problems. (2)(75)
The treatment of hypertrophic scars and keloids with bleomycin showed promising results. Studies showed that the treatment of hypertrophic scars and keloids with bleomycin lead to flattening of the scar and relief of pruritus (90)(91).

1.5.9 Imiquimod 5% Cream

Imiquinod 5% cream is a topical immune-response modifier, that is used for the treatment of genital warts, basal cell carcinoma and actinic keratosis. The use of Imiquimod 5% cream for the prophylaxis and treatment of hypertrophic scars is questionable. Imiquimod stimulates proinflammatory cytokines, that lead to collagen breakdown and alters the expression of apoptosis-associated genes.(2) Studies about the efficacy of imiquimod for the treatment of hypertrophic scars and keloids are controversial. A double-blind, placebo-controlled study of Berman et al. showed no significant difference between the postoperative recurrence rates of keloids after the treatment with 5% Imiquimod Cream compared to the control group (92). Another small, randomized, prospective study though showed positive effects of postsurgical imiquimod therapy. In the study imiquimod was shown to significantly improve hypertrophic scar quality. (93)

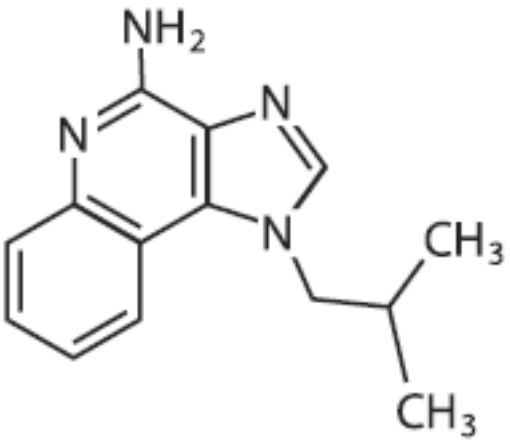

Figure 6: Imiquimod - structural formula, Web: http://www.rxlist.com/zyclara-drug.htm, 01.07.2017

1.5.10 5-Fluorouracil (5-FU)

5-FU is a pyrimidine analog which due to his antimetabolite activity is used is cancer chemotherapy. It has been shown to increase fibroblast apoptosis via inhibiting DNA synthesis. It also inhibits proliferation and myofibribroblast differentiation. 5-FU is administered intralesional and is found to be well tolerated for hypertrophic scar and keloid treatment. Side effects are local erythema, swelling, pain, molting, pigmentation, and occasional ulcers. To reduce side

effects, most current methods for the treatment of hypertrophic scars are low-dosed cocktail therapy. (2)(94)

In 1999, Fitzpatrick was the first to report the positive effects of 5-FU injections on hypertrophic scars and keloids. Patients received injections a mean of 5 to 10 times. The scar regression depended on the duration of exposure to the drug and the dose. (95)

A prospective study of Nanda et al. showed a 50% reduction in scar size in the majority of the patients, after weekly intralesional 5-FU treatment for 12 weeks (96). Gupta and Kalra showed a 50% flattening in half their patients, after weekly intralesional 5-FU therapy for a maximum of 16 injections (97).

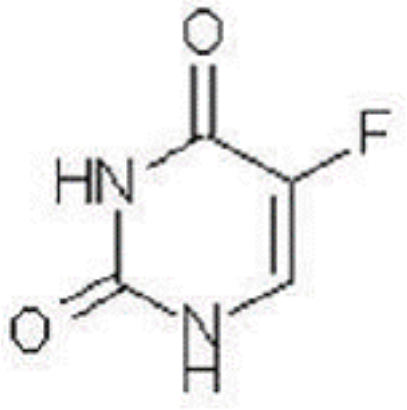

Figure 7: 5-Fluorouracil, Web: http://www.rxlist.com/fluorouracil-cream-drug.htm, 01.07.2017

1.5.11 Interferons (IFN)

IFNs decrease the overproduction of collagen and glycosaminoglycans by scar-forming fibroblasts and increase the level of collagenase activity. In particular, Interferon alpha and gamma inhibit the synthesis of collagen types I and III, acting on mRNA in the cell and reducing the levels of TGF-b. The treatment with INFs is quite expensive and adverse effects are common. These include flu-like symptoms and pain on injection. (2)(98)

Berman and Flores showed in their study, that injection of IFN-a2b into keloidal excision sites resulted in significantly lower recurrences compared with triamcinolone acetonide and excision alone (99).

In a study of Larrabee et al. five of 10 scars studied decreased at least 50% in linear dimensions, after intralesional INF gamma injection (100).

Findings from clinical trials reveal conflicting data, since other studies haven't shown a benefit of INF treatment in keloids and also showed high recurrence rates after intralesional INF therapy (98). Therefore, further clinical investigation is needed, to support the use of INFs as a treatment for hypertrophic scars and keloids.

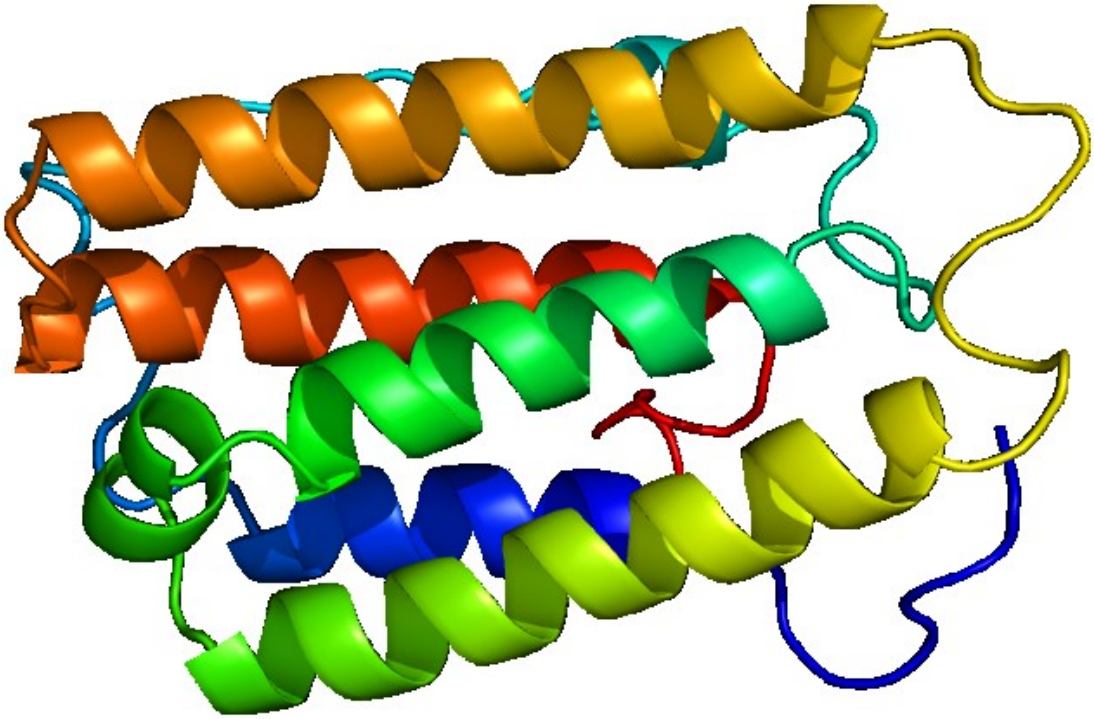

Figure 8: 3D-Structure of interferon alpha 2, Web: https://en.wikipedia.org/wiki/IFNA2

2 Methods

2.1 Primary Endpoints

- Scores of Vancouver scar Scale
- Scores of POSAS
- Porosity evaluated with 3D-Photography

2.2 Secondary Endpoints

- Best cost/outcome ratio
- 5-stage scale for scar improvement

2.3 Study Population

100 female subjects aged 18 – 65 years will be recruited. The subjects should feature hypertrophic scars after cesarean section. Exclusion criteria see 2.4.1.1.2.. Subjects will be recruited from the Graz area from gynecologic and pediatric clinics. Informed consent will be obtained prior to the study. The protocol will be approved by the Ethical Committee of the Medical University of Graz.

2.4 Study Procedures

Subjects will refer to Division of Plastic, Aesthetic and Reconstructive Surgery of the Medical University of Graz for the screening visit and will be randomly assigned to one of four treatment groups (by online randomizing IMI-MedUniGraz) or the control group. Screening visit will take place on the same day as Baseline.
Group 1: This group will be treated with a fractional CO_2 laser. The subjects of this group have to enter a series of study visits at the Center for Aesthetic Medicine.
Group 2: This group will be treated with a medical needling device. The subjects of this group have to enter a series of study visits at the Center for Aesthetic Medicine.
Group 3: This group will be treated with a silicone gel roller. The subjects of this group will have to perform study procedures at home according to a provided diary.

Group 4: This group will be treated with silicone sheets. The subjects of this group will have to perform study procedures at home according to a provided diary.
Group 5 – control group: This group will receive no treatment. This group functions as a control group for the groups 3 and 4. Patients have to refer to Division of Plastic, Aesthetic and Reconstructive Surgery of the Medical University of Graz only for screening-visit and follow-up visit.
For the follow-up visit, all subjects have to refer to the Division of Plastic, Aesthetic and Reconstructive Surgery - Center for Aesthetic Medicine.

Group assignment will be performed depending on the scar-age:
Group 1 and 2: Caesarean scars older than 1 year. The assignment to one of these two groups will be randomized.
Group 3, 4 and 5: Caesarean Scars younger than 1 year. The assignment to one of these three groups will be randomized.

2.4.1 Study days

2.4.1.1 Visit 1 – Screening - Baseline

The responsible physician will explain to the subject the nature, purpose and potential risks of the study and provide the subject with a copy of the study information sheet: Written informed consent must be obtained before a subject will be included in the study prior to any study related activities. If a subject is graded according to the scar age – less or more than one Year then it will be randomized into group 1 or 2 or into group 3, 4 or 5 respectively. A subject number will be assigned to the subject and the necessary data for inclusion/ exclusion will be obtained and recorded in the case report form (CRF) to check inclusion and exclusion criteria. 3D-Photographic documentation will take place for all subjects.

2.4.1.1.1 Inclusion Criteria

- 18 to 65 years of age, healthy volunteers
- Hypertrophic scars after caesarean section.

- Signed informed consent before any study-related activities

2.4.1.1.2 Exclusion Criteria

- Severe acute diseases
- Mental incapacity, unwillingness or language barriers precluding adequate understanding or co-operation
- Pregnancy, breastfeeding, intended pregnancy or not using adequate contraception.
- Any disease or condition which the investigator or treating physician feels would interfere with the trial or the safety of the subject
- Skin disease in scar area
- Concurrent participation in other study
- Orally administered cortisone medication

Group 1 and 2: first treatment with either CO_2 laser or needling with EMLA topical local-anesthesia.
At home patients will treat the scar with wound and healing ointment (e.g. Bepanthen) in week 1 and with baby oil form week 2 until week 6.
Group 3 and 4: study diary and silicone preparations will be handed to subjects
Group 5: no treatment.

2.4.1.2 Visit 2 – Week 6

Group 1 and 2: second treatment with either CO_2 laser or needling with EMLA topical local-anesthesia.
At home patients will treat the scar with wound and healing ointment (e.g. Bepanthen) in week 6 and with baby oil form week 7 until week 12.
Group 3 and 4: study diary and compliance will be checked and silicone preparations will be handed to subjects.
Group 5: no visit.

2.4.1.3 Visit 3 – Week 12

Group 1 and 2: third treatment with either CO2 laser or needling with EMLA topical local-anesthesia.
At home patients will treat the scar with wound and healing ointment (e.g. Bepanthen) in week 12 and with baby oil form week 13 until week 18.
Group 3 and 4: study diary and compliance will be checked and silicone preparations will be handed to subjects.
Group 5: no visit

2.4.1.4 Follow-up Visit – Week 24

all groups: Investigator assessment will be done according to a 5-step rating scale (severe improvement-moderate improvement-mild improvement- no change-impairment) 3D-Photographic documentation for all subjects.
Blinded evaluation of photographs by an independent board of physicians according to a 5-step rating scale (severe improvement-moderate improvement-mild improvement- no change- impairment) will take place.

2.4.2 Withdrawal and Replacement of Individual Subjects

In accordance with the Declaration of Helsinki (101), and other applicable regulations, a subject has the right to withdraw from the study at any time and for any reason without prejudice to her/his future medical care provided by the physician or the institution in question. It is, therefore, guaranteed that the subjects will receive the same level of medical care they received prior to their involvement in the study.

2.4.2.1 Specific Criteria for Withdrawal

Subjects may be withdrawn from the study in the following case:

- Significant protocol violation or non-compliance
- A decision made by the investigator that the exclusion is in the subject's best medical interest
- Allergic reaction to the applied study material
- Onset of pregnancy during the study period
- Onset of illness during the study period

2.4.2.2 Replacement of Individual Subjects after Withdrawal

Subjects who drop out will be replaced.

2.5 Study Materials

The following medical devices will be applied in the study:

- EXELO$_2$ Scanned CO2 Laser System for Dermatology, Quantel SA, 2 bis, avenue du Pacifique, BP23, 91941 LES ULIS CEDEX, FRANCE
- Dermaroller® MC915, Dermaroller GmbH, Am Rehmanger 9, 38304 Wolfenbüttel, Germany
- Bepanthen® Narben-Gel mit Massageroller, Bayer Consumer Care AG, Peter Merian Strasse 84, 4052 Basel, Schweiz
- Dermatix® Silicon-Sheets, MEDA AB, Pipers väg 2, 170 73 Solna, Schweden

2.6 Data Management

2.6.1 Data Collection

Case Report Forms (CRFs) will be prepared and used for data collection during the study. The collected data will be transferred by hand from the source documents to a computer and submitted for review and analysis. A different person than the person transferring the data will perform this review. Furthermore, the persons performing the review and analysis are blinded. Thus, he or she does not know which data belongs to which group. The subject number and trial identification number will identify the subjects, as well as any biological material obtained from the subjects. Finally, to protect the identity of the subjects in all presentations and publications, appropriate measures such as data encryption or deletion will be enforced according to the local/regional ethics committee rules. In case of screening failures, no data will be entered to the database.

2.6.2 Handling and Storage of Data and Documents

Subject identification details will be coded according to professional standards of confidentiality and protected by strict security measures as well as restricted accessibility. The study related data will be locally stored. The study will be registered in a public registry of clinical trials.

2.6.3 Public Disclosure and Publication Policy

The study results will be submitted for publication in a medical journal.

2.7 Data Analysis

2.7.1 Null Hypotheses

There is no difference in improvement of hypertrophic scars, regardless which method is used.

2.7.2 Alternative Hypotheses

There is a difference in improvement of hypertrophic scars, depending on which method is used.

2.7.3 Statistical Methods

For statistical analysis, the software SPSS® 22 will be used.
Differences in the average 3D photography parameters and questionnaires will be examined for statistical significance either by ANOVA test or by Kruskal-Wallis-test, if data normality is not guaranteed.
For continuous data median, mean value, standard deviation, minimum and maximum will be calculated. For classed values the absolute and relative frequency will be calculated. Compared groups: Group 1 vs. Group 2
Group 3 vs. Group 4 vs. Group 5

3 Results

Recruiting was rather slow, therefore until now six patients participated in the study. Four patients finished the study, whereas two patients were lost to follow up. Two patients started in group 1 (fractional CO2 laser), one finished the study, one dropped out. Group two (needling) included two patients, both finished the study. There are no patients in group 3 (silicone gel) and one patient in group 4 (silicone sheet) that dropped out of the study. Group 5 (no treatment) included one patient, who finished the study.

3.1 Patient A1

Patient A1 was part of group 2 (needling). At the beginning of the trial, patient A1 had a VSS-score of 6/13 as well as at follow up. There were no changes in any criteria of the VSS. The total score of the POSAS at baseline was 78/140, the POSAS observer scale was 27/70 and the POSAS patient scale was 51/70. At follow up the total score of POSAS decreased to 48/140, the POSAS observer scale to 19/70 and the POSAS patient scale to 29/70. There was improvement in each criterion except itchiness, which showed no difference between baseline and follow up. The percentage change of the POSAS in this patient was -38,5%. 3D-photography evaluation, showed that the rugosity of the scar at follow up, improved 7,5% compared to baseline. Blinded evaluation of the photographs by an independent physician according to a 5-step-rating scale found mild improvement comparing the pictures of baseline to follow up.

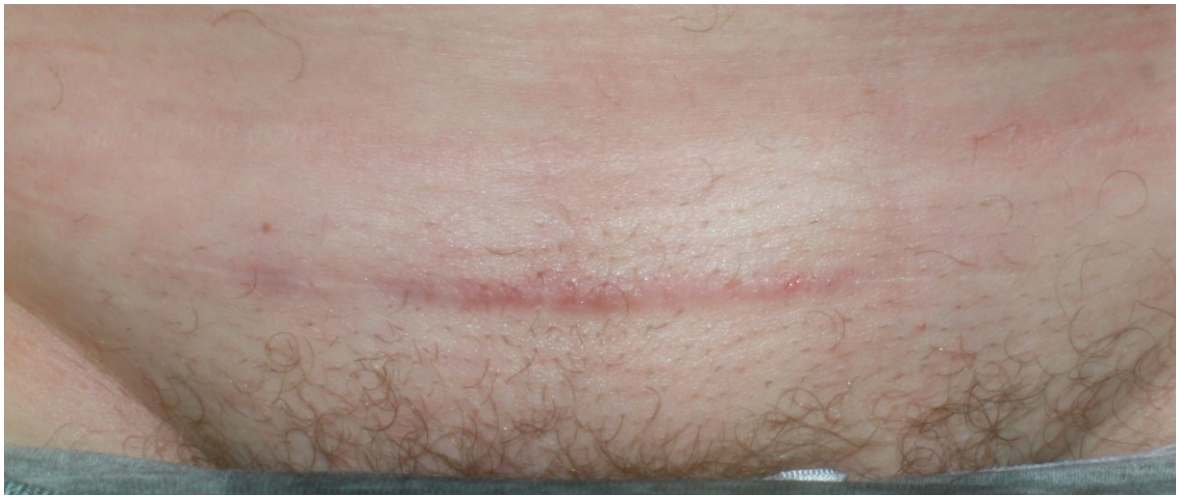

Figure 9: Patient A1 basline

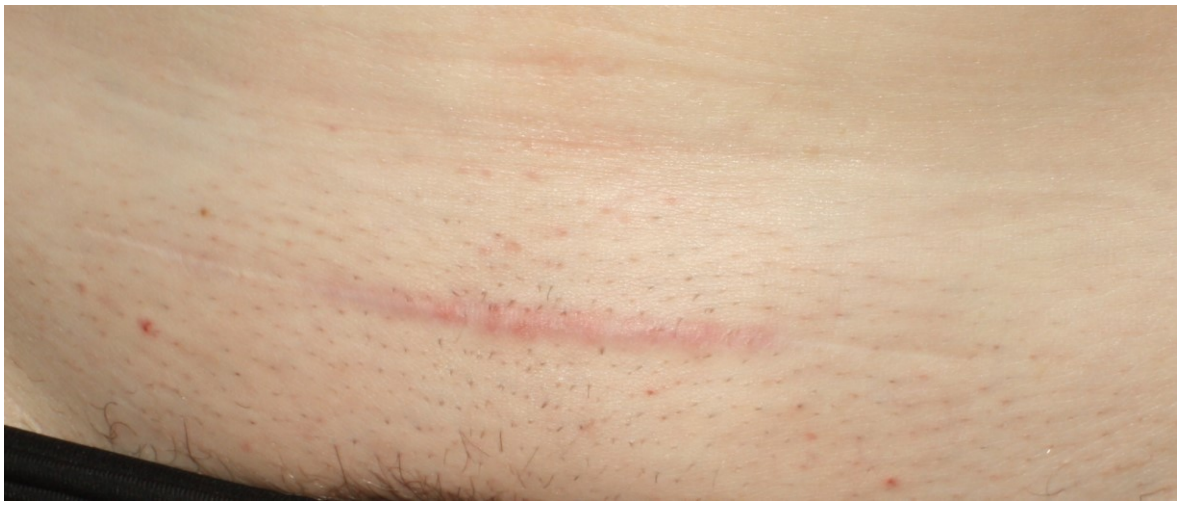

Figure 10: Patient A1 follow up

VSS	Vascularity	Pigmentation	Pliability	Height	Total
Score baseline	1	2	2	1	6
Score follow up	1	2	2	1	6

Table 3: Vancouver Scar Scale patient A1

POSAS Observer	Score baseline	Score follow up	POSAS Patient	Score baseline	Score follow up
Vascularity	4	3	Pain	4	2
Pigmentation	4	3	Itchiness	2	2
Thickness	4	3	Color	9	5
Relief	3	2	Stiffness	9	5
Pliability	4	3	Thickness	9	5
Surface Area	4	2	Irregularity	9	5
Overall opinion	4	3	Overall opinion	9	5
Total	27	19	Total	51	29

Table 4: POSAS patient A1

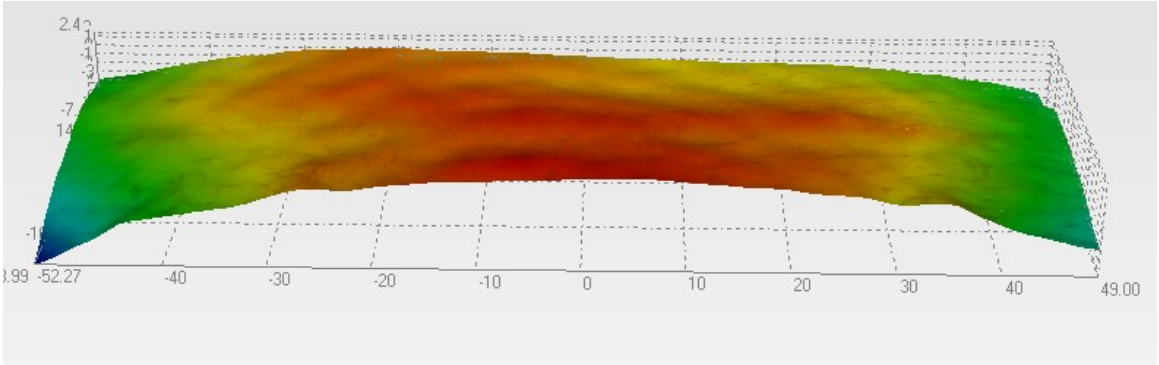

Figure 11: 3D-photo patient A1, baseline

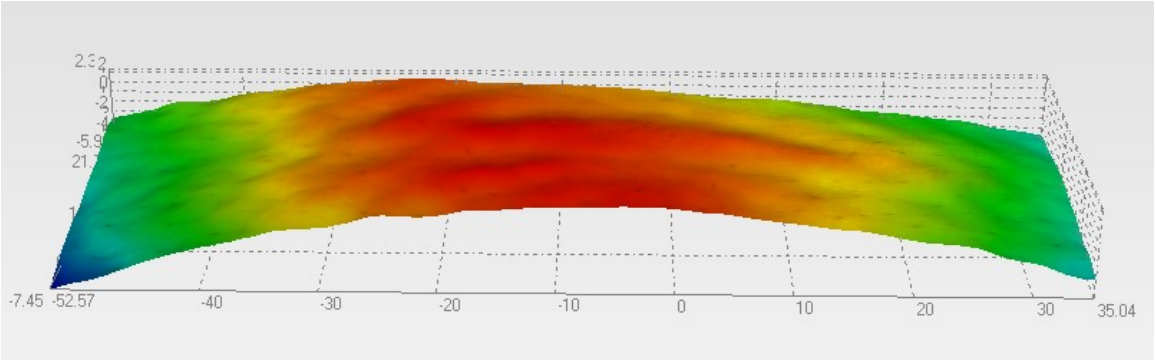

Figure 12: 3D-photo patient A1, follow up

3.2 Patient A2

Patient A2 was part of group 1 (laser). At the beginning of the trial, patient A2 had a VSS-score of 11/13, at follow up the VSS was 10/13. The only criteria of the VSS that improved in this patient was pliability (from 5/5 to 4/5). The total score of the POSAS at baseline was 86/140, the POSAS observer scale was 51/70 and the POSAS patient scale was 35/70. At follow up the total score of POSAS decreased to 80/140. The POSAS observer scale decreased to 44/70, whereas the POSAS patient scale increased to 36/70. There was improvement in each criterion of the POSAS observer scale except surface area, which increased from 8/10 to 9/10. The POSAS patient scale only showed improvement in itchiness, whereas the factors color and thickness of the scar worsened (both from 6/10 to 7/10). The percentage change of the VSS in this patient was -9,1% and -7% of the POSAS. 3D-photography evaluation, showed no significant change in rugosity of the scar (improvement of 0,7%) The blinded evaluation of the photographs by an independent physician according to a 5-step-rating scale found no change, comparing the pictures of baseline to follow up.

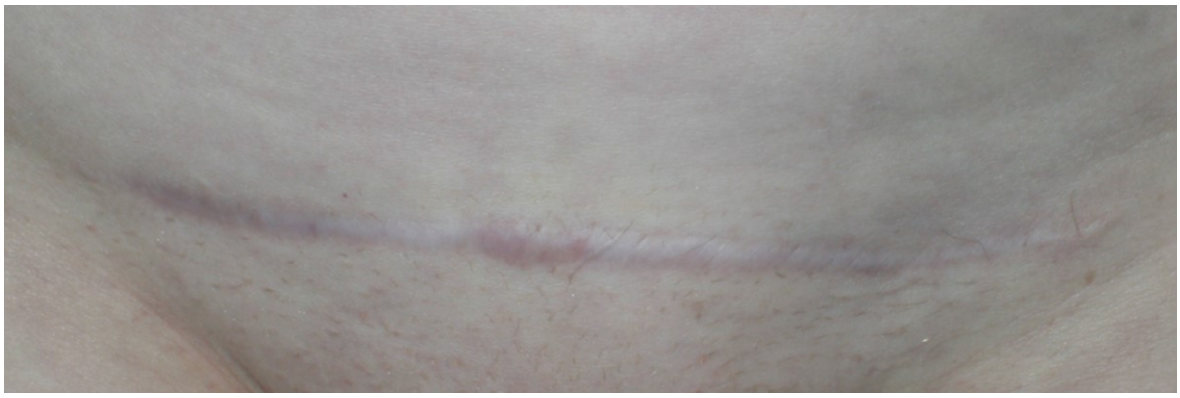

Figure 13: Patient A2 baseline

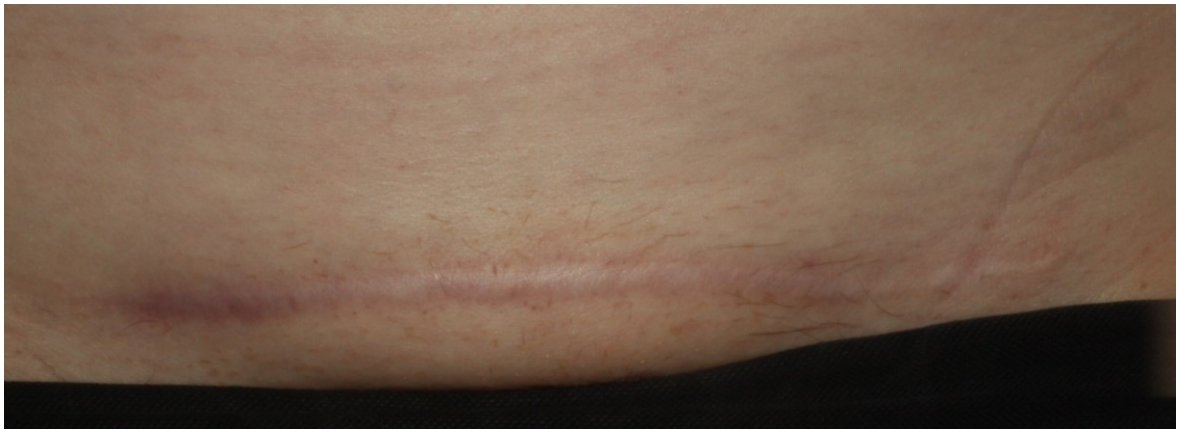

Figure 14: Patient A2 follow up

VSS	Vascularity	Pigmentation	Pliability	Height	Total
Score baseline	1	2	5	3	11
Score follow up	1	2	4	3	10

Table 5: Vancouver Scar Scale patient A2

POSAS Observer	Score baseline	Score follow up	POSAS Patient	Score baseline	Score follow up
Vascularity	3	2	Pain	1	1
Pigmentation	6	4	Itchiness	2	1
Thickness	9	7	Color	6	7
Relief	8	7	Stiffness	7	7
Pliability	9	8	Thickness	6	7
Surface Area	8	9	Irregularity	7	7
Overall opinion	8	7	Overall opinion	6	6
Total	51	44	Total	35	36

Table 6: POSAS patient A2

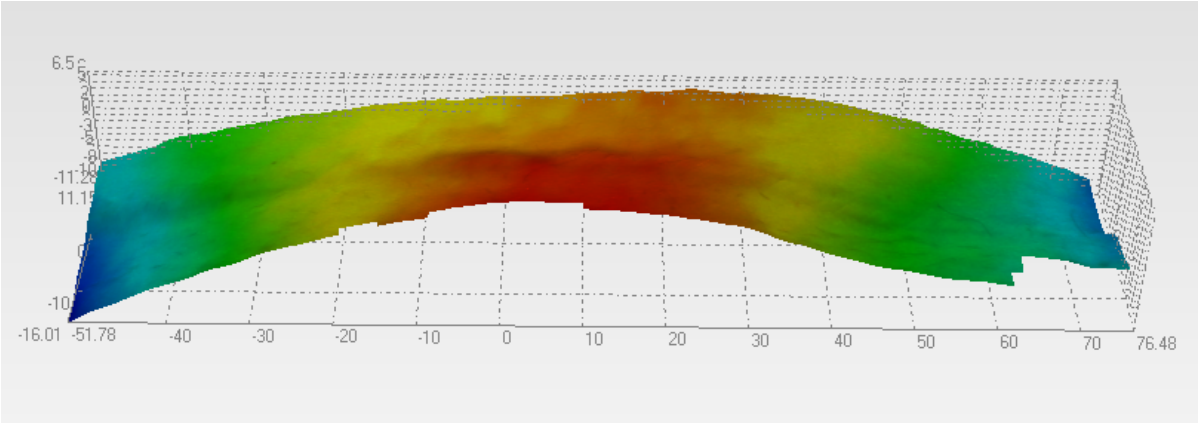

Figure 15: 3D-photo patient A2, baseline

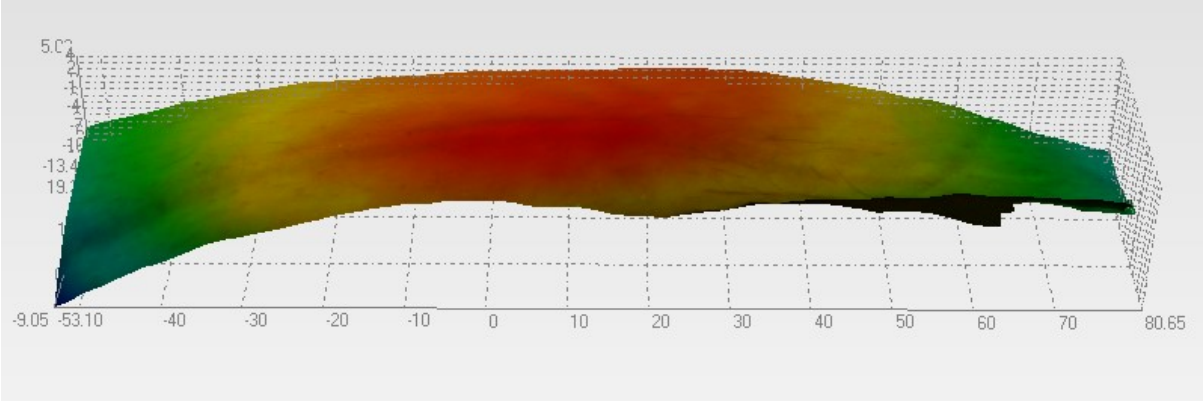

Figure 16: 3D-photo patient A2, follow up

3.3 Patient A3

Patient A3 was part of group 2 (needling). At the beginning of the trial, patient A3 had a VSS-score of 12/13, at follow up the VSS was 10/13. Improvement was seen in vascularity and pliability. The total score of the POSAS at baseline was 109/140, the POSAS observer scale was 59/70 and the POSAS patient scale was 50/70. At follow up the total score of POSAS decreased to 95/140. The POSAS observer scale decreased to 56/70 and the POSAS patient scale to 39/70.
The POSAS observer scale showed improvement in pigmentation, pliability and overall opinion. The POSAS patient scale showed improvement in each criterion, except itchiness. The percentage change of the VSS in this patient was -16,7% and -12,8% of the POSAS.
3D-photography evaluation, showed an impairment of 5,4% of rugosity of the scar at follow up, compared to baseline. The blinded evaluation of the photographs by

an independent physician according to a 5-step-rating scale found no change, comparing the pictures of baseline to follow up.

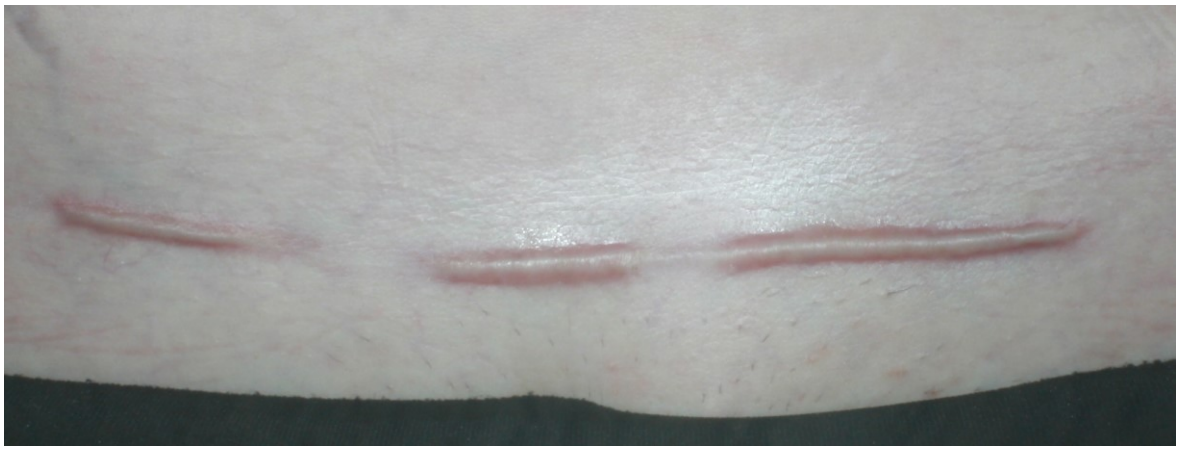

Figure 17: Patient A3 baseline

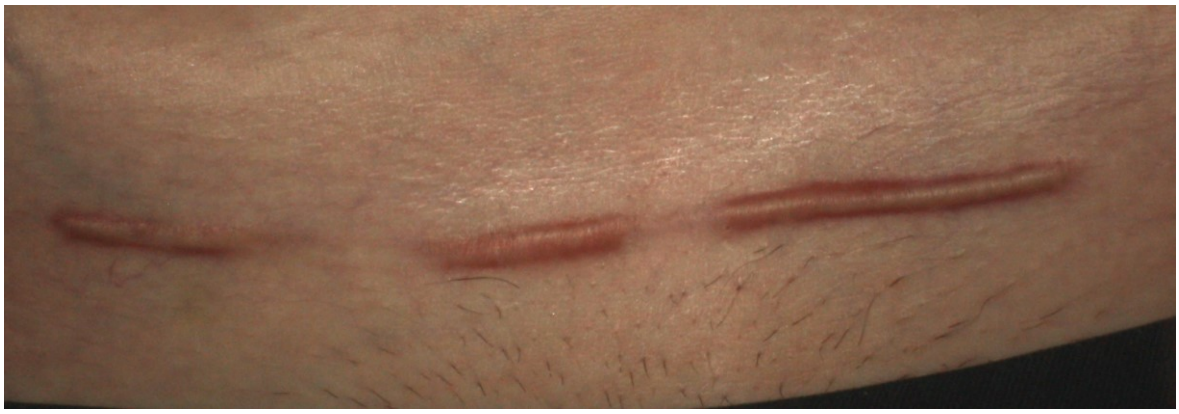

Figure 18: Patient A3 follow up

VSS	Vascularity	Pigmentation	Pliability	Height	Total
Score baseline	3	2	5	2	12
Score follow up	2	2	4	2	10

Table 7: Vancouver Scar Scale patient A3

POSAS Observer	Score baseline	Score follow up	POSAS Patient	Score baseline	Score follow up
Vascularity	7	7	Pain	5	2
Pigmentation	8	7	Itchiness	5	5
Thickness	7	7	Color	8	7
Relief	10	10	Stiffness	8	6
Pliability	10	9	Thickness	8	6
Surface Area	8	8	Irregularity	8	6
Overall opinion	9	8	Overall opinion	8	7
Total	59	56	Total	50	39

Table 8: POSAS patient A3

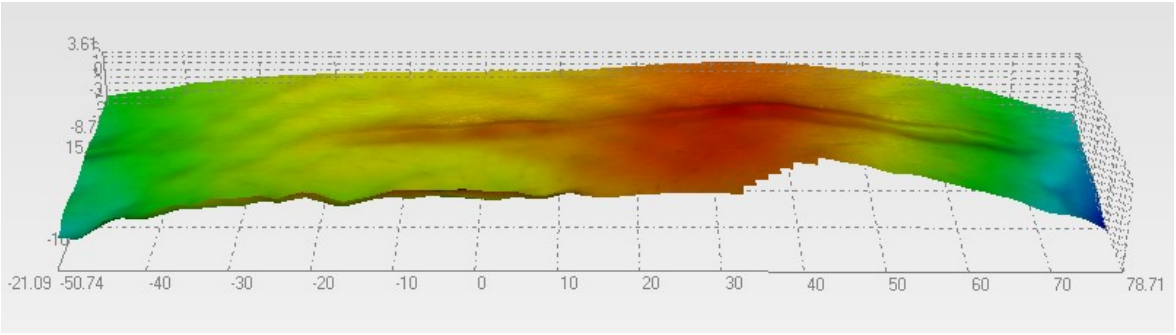

Figure 19: 3D-photo patient A3, baseline

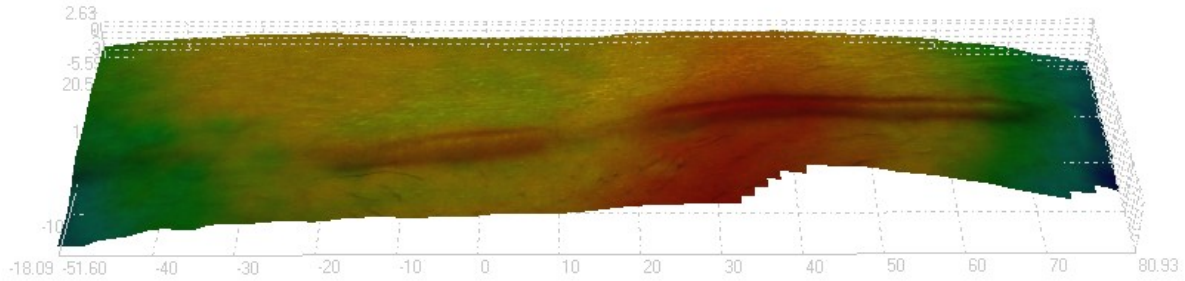

Figure 20: 3D-photo patient A3, follow up

3.4 Patient B1

Patient B1 was part of group 5, the control group (no treatment). At the beginning of the trial, patient B1 had a VSS-score of 13/13 as well as at follow up. The total score of the POSAS at baseline was 95/140, the POSAS observer scale was 70/70 and the POSAS patient scale was 25/70. At follow up the total score of POSAS increased to 111/140. The POSAS observer scale remained at 70/70 and the POSAS patient scale increased to 41/70. The POSAS patient scale showed worsening in color, stiffness, thickness, irregularity and overall opinion. The percentage change of the POSAS in this patient was 16,8%. 3D-photography evaluation, showed no significant change in rugosity of the scar (improvement of 0,3%). The blinded evaluation of the photographs by an independent physician according to a 5-step-rating scale found no change, comparing the pictures of baseline to follow up.

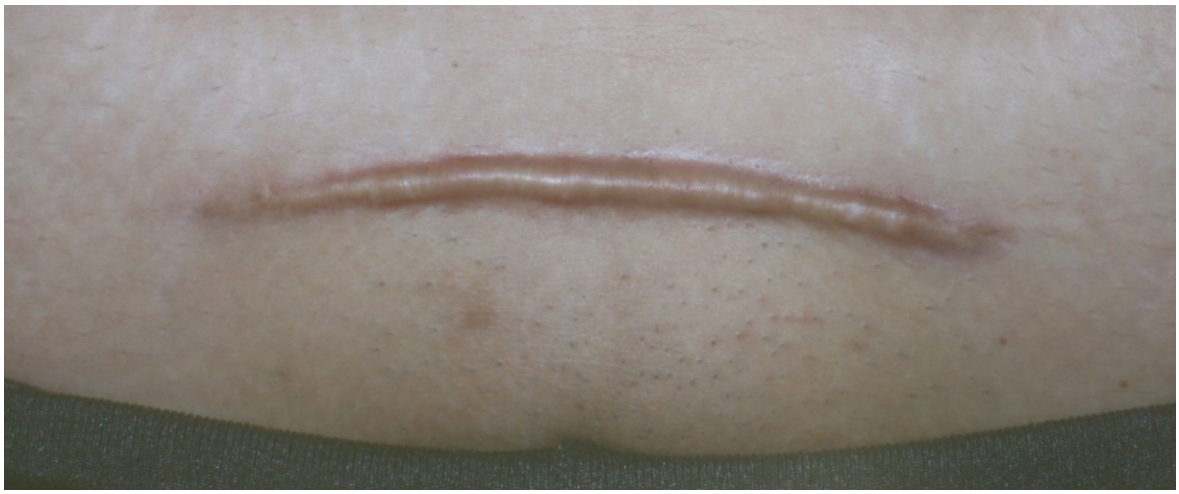

Figure 21: Patient B1 baseline

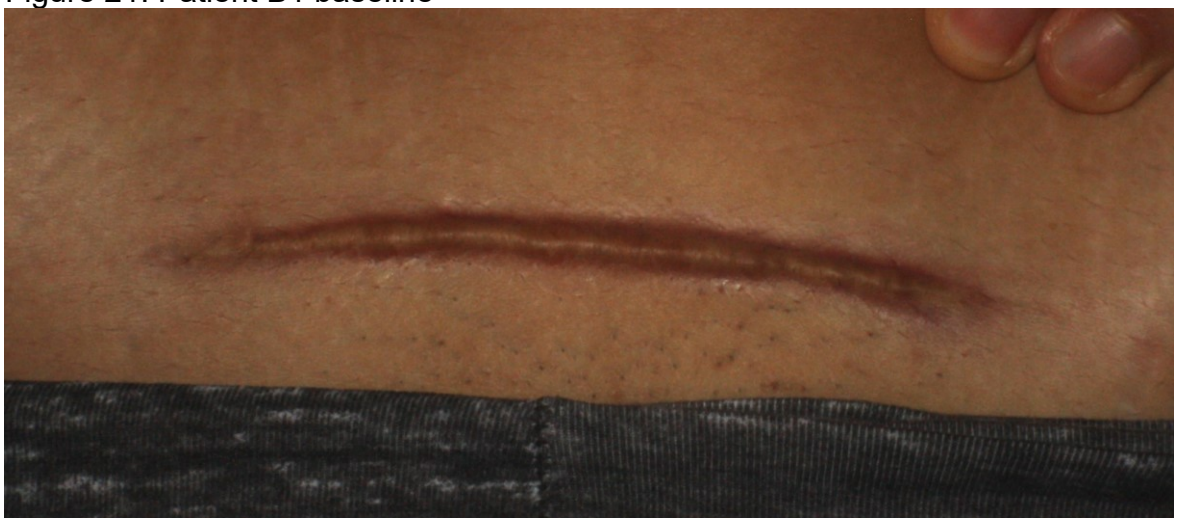

Figure 22: Patient B1 follow up

VSS	Vascularity	Pigmentation	Pliability	Height	Total
Score baseline	3	2	5	3	13
Score follow up	3	2	5	3	13

Table 9: Vancouver Scar Scale patient B1

POSAS Observer	Score baseline	Score follow up	POSAS Patient	Score baseline	Score follow up
Vascularity	10	10	Pain	1	1
Pigmentation	10	10	Itchiness	1	1
Thickness	10	10	Color	1	5
Relief	10	10	Stiffness	6	7
Pliability	10	10	Thickness	5	10
Surface Area	10	10	Irregularity	5	7
Overall opinion	10	10	Overall opinion	6	10
Total	70	70	Total	25	41

Table 10: POSAS patient B1

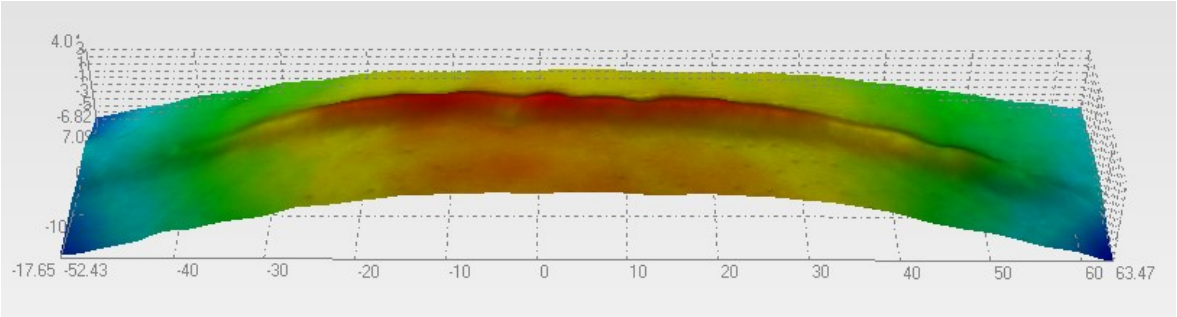

Figure 23: 3D-photo patient B1, baseline

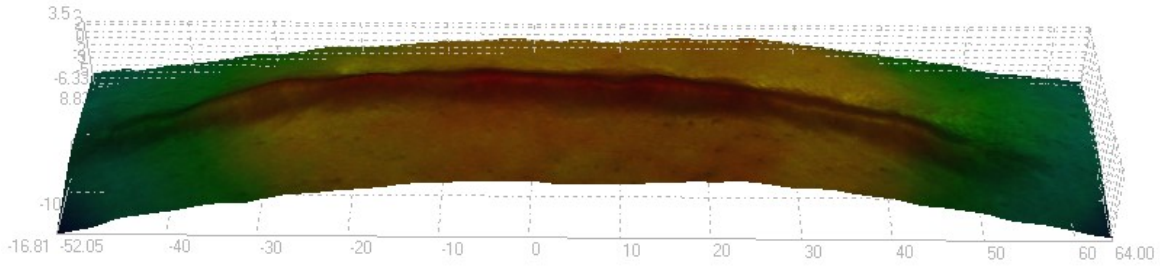

Figure 24: 3D-photo patient B1, follow up

4 Discussion

4.1 Recruitment

The recruitment of the patients for our study didn't work as fluent as expected. Up to now only 6 patients, fulfilled all inclusion criteria and participated in the study. Although information about the trial was sent to numerous gynecologic and pediatric clinics in Styria, with the request of forwarding this information to patients who fulfill the inclusion criteria, only a few patients contacted us. This leads to the conclusion, that not enough patients are reached by this form of recruitment. In order to recruit more patients for this ongoing trial, cooperation with a study about the epidemiology of hypertrophic scars after CS is planned.

4.2 Results

Due to the rather slow recruitment, we only achieved results for the treatment options needling and fractional CO2 laser. No results for the silicone products are available yet.

In literature needling treatment showed improvement according to the VSS, vascularity, pliability and height (5) (73). In our patients three treatments were

performed as recommended in literature in 6-week-intervals. While our first patient (A1) treated with needling showed no change in the VSS, the second patient (A3) treated with needling, showed results similar to the ones in literature. There was improvement in vascularity and pliability, although no change was seen in height. The evaluation of the POSAS on the other hand, showed improvement in both patients. Although the VSS showed no change in Patient A1, the POSAS observer scale, which evaluates similar parameters, showed an improvement of 29,7%. This shows, that due a wider range of possible points in the POSAS compared to the VSS (70 in observer scale compared to 13 in VSS), smaller changes in the scars appearance can be measured with the POSAS observer scale. In patient A3 small changes were seen in the VSS as well as in the POSAS observer scale (a total of two points in each scale). While this resulted in a percentage improvement of 16,7% in the VSS, the POSAS observer scale only improved 5,1%. This indicates, that small changes in the appearance of scars are quantified more accurate using the POSAS compared to the VSS. Bigger changes were found in the POSAS patient scale (improvement of 43,1% in A1 and 22% in A3), evaluating the subjective view of the patient. Both patients showed improvement in all parameters except itchiness. In both patients, the percentage improvement of the POSAS patient scale was higher than the percentage change of the POSAS observer scale, showing that the benefits measured by the observer do not equal the benefit experienced by the patient.

While fractional CO2-lasers show good results in literature for the treatment of hypertrophic scars, as Poetschke et al. showed improvement of the VSS, POSAS and surface relief in their study (66), the results of our patient are controversial. The VSS only improved in pliability, resulting in a total improvement of 9,1%. The POSAS observer scale improved in each criterion, except surface area, and showed a total improvement of 13,7%, the POSAS patient scale on the other hand showed very divers results. The POSAS patient scale only improved in itchiness and actually worsened in the factors color and thickness. The worsening of the factor thickness is interesting, since in the observer scale, the same factor was described as improved. This, as well as the total percentage change of the patient scale resulting in an impairment of 2,9%, shows once again, how divergent the evaluations of observer and patient can be.

As expected, no improvement was seen in our control-patient. The VSS with the maximum points of 13/13 did not change at follow up, as well as the POSAS observer scale with a total of 70/70 points at baseline as well as follow up. The POSAS patient scale, however worsened in the factors color, thickness, stiffness, irregularity, and overall opinion. The total percentage impairment of the patient scale was 64%, showing again that, even though no change was visible for the observer, the patient may feel very different about the change of the scar.

With 3D-photography, we evaluated the surface rugosity of the scars. For needling treatment, 3D-evaluation showed an improvement of 7,5% in patient A1 and an impairment of 5,4% in patient A3. The outcomes of the 3D evaluation also show similar results for the surface of the scar, as evaluated in the POSAS observer scale. The POSAS observer scale shows improvement in the factors relief and surface area in Patient A1 whereas it showes no change in the same factors in patient A3, indicating, that 3D-evaluation is a more accurate tool to measure small changes in surface appearance. The patient treated with the fractional CO2-laser showed no significant change in rugosity at follow up. Also in this patient, the factors relief and surface area did not change in total (while relief improved one point, surface area worsened one point), the same applies to the control-patient, no change was seen in 3D-evaluation and the factors relief and surface area.

Last, an evaluation of photographs of the scars according to a 5-step-rating scale (severe improvement - moderate improvement - mild improvement - no change - impairment), was performed by an independent physician. In this evaluation, “mild improvement” was seen in patient A1. The scars of the other patients showed “no change” comparing baseline to follow up. Patient A1 had the biggest percentage change in the score of the POSAS as well as in 3D-photography evaluation. The other patients had lower percentage changes in their POSAS scores and especially in 3D-photography evaluation, the scars showed no change or even impairment at follow up. It shows, that although small changes in the scar may be evaluable with scar scales, those changes may not result in an improvement, visible to independent observers. On the other hand, it showed that the changes seen in 3D-evaluation were comparable to the changes in our 5-step-rating scale,

indicating that 3D-evaluation is a good parameter to measure visible changes in the scars appearance.

4.3 Conclusion

Since there are only four patients, who completed the study yet, predictions on the most effective treatment option are hard to make. More patients are needed to achieve significant results for each treatment option. The examination of these four patients however, already showed that scar treatment as well as the evaluation of these are complex tasks. It also showed, that different types of scoring and evaluating, may lead to different results in one and the same patient. Also, the evaluation of the improvement of the scar performed by an observer does not necessarily match the self-evaluation by the patient. Still, the outcomes in this very small number of patients clearly display that self-evaluation is more subjective than the evaluation by a physician. Therefore, in clinical trials multiple different types of evaluation should be utilized.

It should be mentioned, that for the optimal evaluation of 3D-photography, standardized conditions should be held for each picture. Illumination and the angle of the camera should always be the same, clothes and hair should not be visible on the pictures. Sadly, this was not the case in all pictures taken up to now, but it is something that can be improved for further patients, that will participate in this study.

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