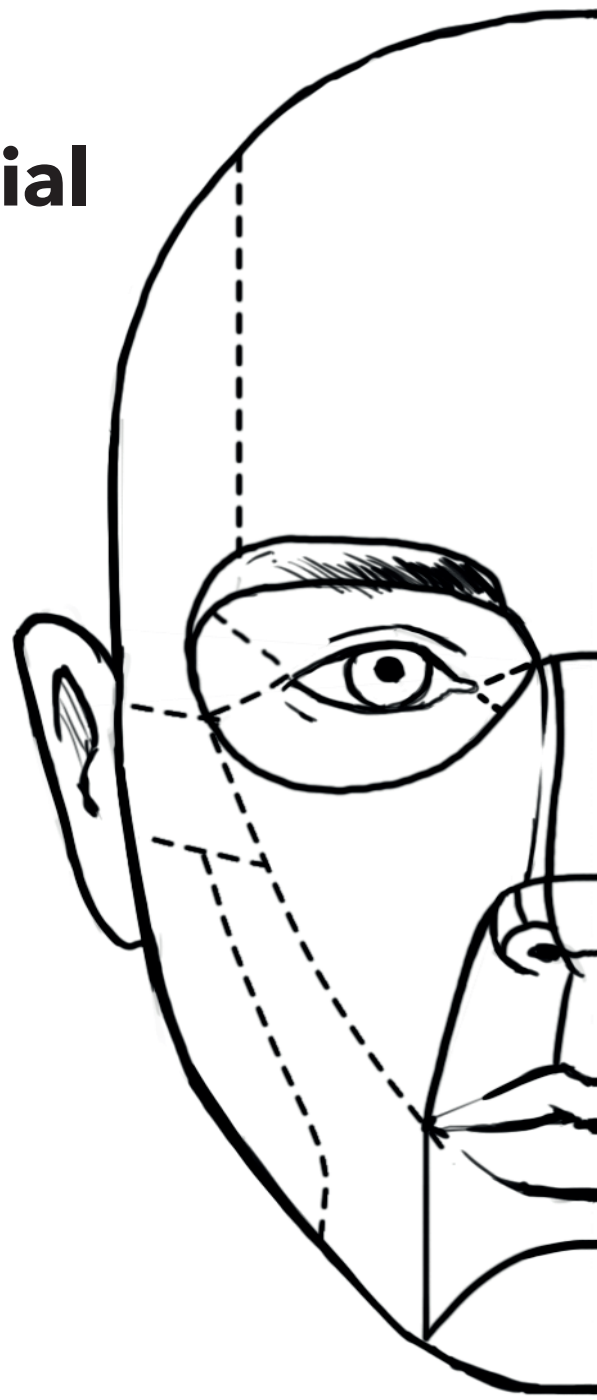
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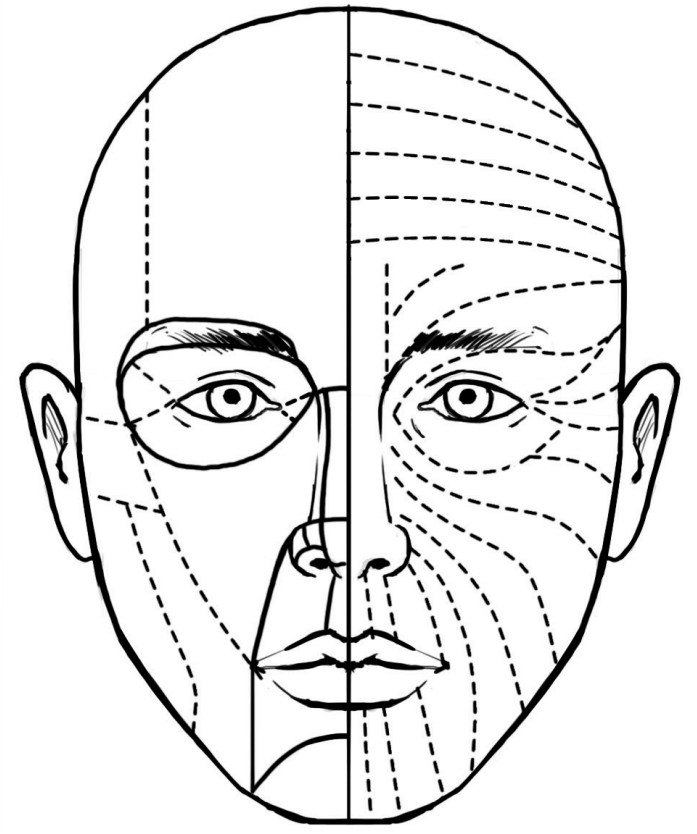
from scars to aesthetics



Sander B. Kant

Improving facial appearance

from scars to aesthetics



Sander B. Kant

Improving facial appearance: from scars to aesthetics
Sander B. Kant

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Improving facial appearance
from scars to aesthetics

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volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
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'There is no talent here, this is hard work. This is an obsession. You could be anyone if you put in the time. You will reach the top, and that's that. I am not talented, I am obsessed.'

Conor McGregor

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CHAPTER 1



Introduction of this thesis

An important pillar of plastic surgery is ensuring the restoration of function with specific attention to maintaining an acceptable aesthetic form. Plastic surgery differs from general surgery by its cutting-edge character concerning innovations related to the shifting and modulation of tissues. The Greek word from which plastic is derived, *plastikos* (which means shaping or modeling), applies perfectly to this profession. An obvious consequence of the nature of plastic surgery, however, is the development of scars.

Wound healing and scars

Almost every person develops scars during his or her life. Scars consist of fibrous tissue that replaces normal skin after damage and are a consequence of cutaneous wound healing. During this physiological process, known as the *wound healing cascade*, there are three consecutive processes that also overlap: the inflammation phase (4 to 6 days), the proliferation phase (4 to 24 days), and the remodeling phase (21 days to 1, 2, or more years).[1-3] When trauma causes interruption of the skin, this process begins: the coagulation cascade starts; inflammatory reactions take place; neovascularization, cell proliferation, and apoptosis occur; and the extracellular matrix is formed and remodeled.[4] An estimated 100 million people worldwide develop a scar every year.[5] Only embryos are known to be able to heal without scarring.[6,7]

Culture

A scar will not be perceived a priori by everyone as "bad." Scars are a part of life, and they can also remind people of something beautiful, such as a birth by Caesarean section. In some cultures, scars are even signs of beauty and attractiveness, such as in the Karo tribe in Ethiopia, where scars are self-inflicted to form distinct patterns and relief on the skin.

Consequences and impact of scars

Nevertheless, scars play a significant role in the practice of plastic surgery. Excessive scar tissue can have far-reaching consequences. For example, after burns, invalidating contractures may develop on the limbs or face. Also, scarring after tendon repair may reduce the mobility of joints, and excessive scar tissue in the breast capsule in women with breast implants may lead to capsular contracture with the presence of clinical symptoms.[8]

The impact of scars on quality of life can be extensive. Scars can cause functional, psychological, symptomatic, and cosmetic complaints.[9-11]

Types of scars

Abnormal and unwanted scars come in many types, including atrophic scars, scar contractures, hypertrophic scars, and keloidal scars.[12] Burn scars are known to be stigmatizing and to have a devastating impact on the quality of life.[11,13] Hypertrophic, atrophic, and keloidal scars can also be problematic and significantly impact life quality.[9,14-16]

These abnormal scars are often conspicuous and disfiguring and require tailored therapy. Since there are many types of scar treatment, finding tailor-made therapy is a challenging but an important part of plastic surgery.[17,18]

History of scar treatment

That scars are stigmatizing is evident by the fact that people have been treating scars for centuries. To promote wound healing, it appears that the ancient Egyptians and Greeks already used fat and honey more than 4,000 years ago.[19]

Scar therapy is considered to be most effective when scars are still active. Active scars are primarily characterized by the presence of erythema, thickening, and clinical symptoms such as itching and pain.[20-23] This active phase of scars is therefore clinically relevant. However, the estimates of the duration of the phase in which scars are still immature, and therefore treatable, vary. A better estimation of this period can be valuable in the treatment of scars and can provide a better understanding of the wound healing cascade overall. In **Chapter 2**, the duration of the immature phase of scars is investigated in a study analyzing 361 hypertrophic scars.

Current scar treatments

Currently available scar therapies can be roughly categorized into two options: surgical interventions (using a skin graft, z-plasty, or other skin flaps) and non-surgical interventions.

Non-surgical therapies

During the last few decades, experience with non-invasive treatments such as topicals (for example, imiquimod, mitomycin C, onion extract, hydrocortisone, silicone gels, green tea extract, aloe vera, and vitamin E), pressure therapy, and occlusive silicone sheets has been gained with varying degrees of success. This also applies to the more invasive techniques such as laser therapy (fractional and pulsed light lasers), intralesional injections, radiotherapy, and cryotherapy.[24-31] This abundance of treatments offers a wide range of possibilities, and even more so when therapies are used in combination. This has led to calls for the development of an algorithm for scar treatment.[32]

Nevertheless, patients are often dependent on the specific skills, knowledge, and experience of the therapist for the choice of therapy. Facial scar therapy, in particular, requires extra attention and customized treatment. For large facial scars, mechanical positive pressure therapy is the most studied non-invasive intervention.

Causes for disturbance of facial appearance

Facial pressure mask therapy, as used at the Maastricht University Medical Center (MUMC+), often follows facial surgery. The most common reason for facial surgery is the removal of skin cancer, of which basal cell carcinoma is the most common form.[33-35] Treatment

of facial skin cancer is mainly performed through standard surgical excision and Mohs' micrographic surgery. Thanks to these techniques, there are low recurrence rates of basal cell carcinomas.[36-38]

On the other hand, the aim is to preserve the aesthetic subunits of the face as much as possible so that any disturbance of the shape of the face is minimized. However, (complete) removal of facial skin cancer can lead to significant facial defects that may have a destructive impact on the general well-being and quality of life of the patient. **Chapter 3** investigates the impact of surgical facial skin cancer removal on the appreciation of patients' perceived facial appearance.

Facial pressure therapy

There have been fewer developments in the facial application of mechanical pressure in recent decades compared to the aforementioned (local) (non-surgical) interventions (such as creams, gels, laser therapy, and intralesional injections). In 1979, the transparent facial pressure mask was described as an effective therapy to treat hypertrophic scars caused by burns.[33-36] Another modality was elastic "hoods" that had to be placed over the entire head. They were replaced by transparent rigid masks because of their ease of use and better pressure distribution.[39]

This thesis primarily focuses on the possibilities of these transparent facial pressure masks to improve scars and deformities that persist after surgery. In **Chapters 4**, **5**, **6**, and **7**, the current literature on the clinical effects of transparent facial pressure masks is systematically summarized (**Chapter 4**), the manufacturing process of a pressure mask is described (**Chapter 5**), the effectiveness of pressure masks on scars and deformities after facial flap surgery is studied (**Chapter 6**), and insight is provided with regard to the change in the quality of life of patients after completion of treatment with a pressure mask (**Chapter 7**).

Treatment of keloids and hypertrophic scars

Specific forms of problematic scars are keloidal and hypertrophic scars. Keloids, in particular, are unsightly, usually itchy, painful, and conspicuous. Hypertrophic scars are raised, noticeable scars that can also cause clinical symptoms, although these symptoms are mostly less severe when compared to keloids. The main difference between keloids and hypertrophic scars is that unlike hypertrophic scars, keloids cross the original boundaries of the wound. In addition, spontaneous regression rarely occurs in keloid scars.[20,40-44] That is why adequate treatment of these types of scars is of particular importance for the patient, and it can significantly improve the quality of life. Cryotherapy and surgical excision have not proved to be unqualified successes for the treatment of keloids as recurrence rates, in particular, are problematic. A goal of this thesis is to test treatment with a new combination of two known drugs, triamcinolone and verapamil, by intralesional injections in hypertrophic and keloidal scars (see **Chapter 8**).

The assessment of scars

Assessing the severity of scars is something that has always been difficult for the practitioner. Differences in culture, gender, and age affect the severity of a scar experienced by a patient. One of the things that makes plastic surgery such a gratifying occupation is the ability to improve the quality of life of patients. With the development of patient-reported outcome measures (PROMs), quality of life can be measured more accurately than ever.[45] A questionnaire such as the Patient and Observer Scar Assessment Scale (POSAS, developed in 2004) has shown its added value in the assessment of scars when compared to the Vancouver Scar Scale (VSS) through its distinctive Patient Scale.[46-50] The POSAS contains results that are reported by a physician (Observer Scale) and a component that is only filled out by the patient (Patient Scale).

Another PROM that was more recently developed is the FACE-Q. This validated tool contains questionnaires developed to estimate the aesthetic assessment of the face.[51-53] The questionnaires are completed by the patient only, not by the practitioner. At a time when there is an increasing demand for testing, evaluation, and assessment of the effectiveness of treatments, this tool is highly beneficial and useful in plastic (aesthetic) surgery. The FACE-Q has the potential to play an important role in the field. For example, more than 20 FACE-Q subscales already exist to assess multiple parts of the face. In this thesis, all assessments of the effects of scar therapy were measured using the POSAS and FACE-Q. The assessment by the patient with regard to (the result of) the treatments is always central in this thesis.
The general aims of each chapter of this thesis are presented below.

Chapter 2: to develop a better understanding of the duration of the maturation time of hypertrophic scars to obtain added insight into the final part of the wound healing cascade;
Chapter 3: to obtain insight into the impact of the surgical removal of facial skin cancer from an aesthetic point of view;
Chapter 4: to review the clinical effects of transparent facial pressure masks in the treatment of facial scars;
Chapter 5: to describe the fabrication of a specialized facial pressure mask that aims to improve hypertrophic scars and facial deformities after surgery;
Chapter 6: to obtain insight into the clinical effectiveness of a transparent facial pressure mask on scars and facial deformities after facial flap surgery;
Chapter 7: to investigate whether patients who have undergone pressure mask therapy have experienced improvement in their quality of life after completing this therapy;
Chapter 8: to propose a new treatment for problematic scars—keloids and hypertrophic scars—with a combination of two well-known drugs: triamcinolone and verapamil; and
Chapter 9: to provide a general discussion.
Chapter 10: to provide a summary of this thesis.

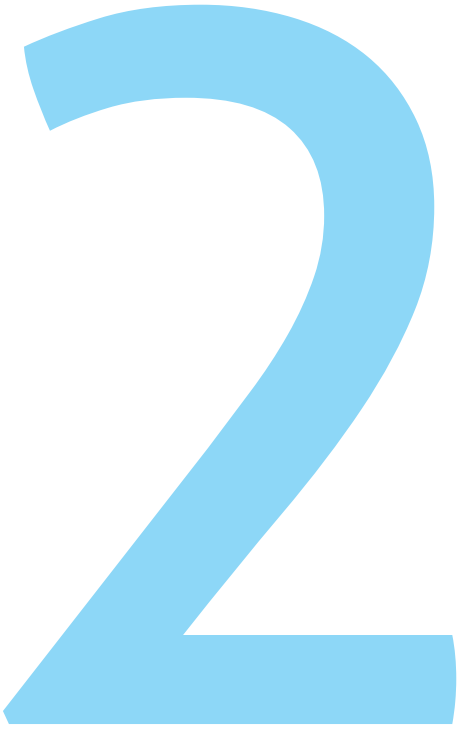
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CHAPTER 2



Duration of scar maturation: retrospective analyses of 361 hypertrophic scars over 5 years

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ABSTRACT

Objective: Maturation remains the least understood phase of wound healing; estimates of maturation time are broad and inaccurate. A more precise estimation of maturation time could influence scar therapy and give insight to the wound healing cascade. The objective of this study was to assess the mean time between onset and complete maturation of hypertrophic scars.

Methods: This retrospective study was performed in an outpatient clinic of the Maastricht University Medical Center exclusively focused on scar treatment; 361 patients with a hypertrophic scar were included between September 2010
and December 2015.

Main outcome measures: Date of onset and date of complete maturation were documented in patients' medical files. Patients were divided into 3 patient groups: <30 years, 30-55 years, and >55 years. Different scar causes and scar therapies were analyzed in relation to maturation time.

Main results: These results reveal statistically significant differences ($P < .05$) in mean maturation time between the <30 (35.76 months) and >55 patients (22.53 months) and between >55 and 30-55 year old patients (34.64 months). Significant differences in mean maturation time were also found between scars treated with pressure therapy (23.20 months) and combination therapy (30.59 months), silicone therapy (35.51 months), injection therapy (46.43 months), and other therapies (41.31 months).
No significant differences in maturation time were found relative to scar cause.

Conclusions: This study shows that hypertrophic scars take significantly more time to completely maturate than previously believed, and older patients show the fastest healing. Further, scars treated with pressure therapy maturate fastest.

Keywords: hypertrophic scars, maturation, pressure therapy, scar healing, scar maturation, scar therapy, wound healing

INTRODUCTION

The cellular changes that occur during scar maturation are increasingly understood. They are associated with remodeling of the extracellular matrix as well as normalization of type III and type I collagen ratio [1-3]. However, the process of scar maturation with regard to changes in the clinical appearance over time is the least understood phase of wound healing. Some studies state that maturation of scars takes place within one year [4-8]. However, most studies suggest a mean maturation period of 1, 2 or several years [1,9-15].

A more accurate estimation of the maturation time of hypertrophic scars is important, because it could enhance therapeutic efficacy and lead to prevention of surgical revision, by handling a more conservative approach. Scar therapy is believed to have an effect mainly during the immature phase of wound healing [16,17]. Since the length of the immature phase of wound healing differs so much in estimations, a more precise assessment of this phase is needed. This can lead to an improvement of therapeutic modalities as well as to the understanding of the complex wound healing cascade altogether. The purpose of this study was to retrospectively evaluate patients between onset of a hypertrophic scar and complete maturation.

METHODS

Study design

In this retrospective study, conducted at the Department of Plastic Surgery at the Maastricht University Medical Center (MUMC), 361 hypertrophic scars in 361 patients were examined for maturation duration between September 2010 and December 2015. Hypertrophic scars were defined as raised, thickened, red, and painful or pruritic active scars.[18-21]

Because all of the patients in this study suffered from hypertrophic scars, they were treated at a specialized clinic for scar treatment. Scars were located on the arms, legs, torso, neck, face, and ears. Patients were treated with silicone sheets, pressure garments, intralesional injections with triamcinolone and verapamil, combinations of these therapies, and alternative therapies such as cryotherapy and scar massage.

Participants

Records obtained between September 2010 and December 2015 were reviewed from all patients seen during MUMC outpatient clinic visits exclusively focused on scar treatment. A plastic surgeon, a plastic surgery resident, a physiotherapist specialized in scar treatment, and a prosthetist had examined all patients during their regular follow-up visits, which took place every 2 to 3 months. In this study, because of its retrospective nature, no distinction for ethnicity was made and no control group was formed. The study conformed to good clinical

practice guidelines and followed the recommendations of the Declaration of Helsinki. The protocol was approved by the local ethics committee.

All patients had a common start and end point: date of onset of the hypertrophic scar and complete maturation of the scar, respectively. Date of onset was the date a hypertrophic scar was formed (caused by trauma, surgery, or a burn). Only patients who had hypertrophic scars were included. Only patients for whom date of onset of the hypertrophic scar was known were included. The date of injury or disruption of the skin of these patients was collected as well.

Data collection

Assessed variables were patient age, scar therapy, date of skin injury, date of scar onset, and date of complete scar maturation.

For better understanding of scar maturation and to assess influences with respect to age (in accordance with Bond et al[10]), patients were divided into three groups: <30 years 30-55 years, and >55 years.

Patients were divided into five groups according to their scar therapy: pressure therapy, silicone therapy, injection therapy, combination therapy, and other therapy. The pressure therapy group consisted of patients who wore customized pressure garments. The silicone therapy group consisted of patients who were treated with topical silicone gel sheeting or silicone gel. The injection therapy group consisted of patients who received intralesional injections that consisted of a 1:1 mixture of triamcinolone acetonide and verapamil. The combination therapy group consisted of patients who were treated with more than one therapy during the period of active scarring. The other therapy group consisted of patients who received an alternative treatment to the aforementioned therapies such as cryotherapy, massage therapy, and radiotherapy.

In the literature, there is a clear association found between the persistence of scar erythema and hypertrophic burn scar formation.[22] Therefore, scar erythema combined with scar thickness was the most important parameter for assessment of a mature scar.[5,9,23-25] During each visit, scars were evaluated using the Patient and Observer Scar Assessment Scale (POSAS). The instrument uses both patient and observer data on vascularity, pigmentation, thickness, relief, pliability, pain, pruritis, and surface area. To enhance reliability, the POSAS data were re- corded by the same investigator on all patients.

When scar erythema no longer persisted, no clinical features (such as pain and pruritus) were observed, and scar thickness and height reduced and remained stable, scars were assessed to be mature.

Data analysis

Analyses were performed with mean values ± SD (in months), hazard ratios (HRs) with 95% confidence intervals (CIs), and percentages with SEs. Survival curves were formed by Kaplan-



Figure 1. A, an active hypertrophic scar on the left foot 7 months after burn injury. B, a mature hypertrophic scar on the left foot 48 months after burn injury

Meier graphs. The primary end point (maturation) was analyzed with a log-rank test without stratification. The HR and 95% CI were estimated with a Cox proportional hazards model with age (as continuous and categorical variables) and scar cause and scar therapy as the covariates. For analysis of differences in mean time between injury and hypertrophic scar formation, one-way analysis-of-variance tests with Tukey post hoc tests were used.

All patients were to be followed up until complete maturation of the scars occurred. The majority of patients (n=222) did not achieve scar maturation by the end of data recruitment.

An active and mature hypertrophic scar can be seen in Figure 1. All patients in this group were censored for analysis at the last known date of contact. Two-tailed values of $P<.05$ were accepted as statistically significant. All analyses were performed using the statistical software program SPSS 22.0 (IBM, Armonk, New York).

RESULTS

Participants

The study population consisted of 361 patients (166 males and 195 females) with a mean age of 37 years (1-87; Table 1). Most scars occurred on incisions (70.9%) or traumatic wounds (burns, 14.7%; other, 14.4%; Table 1).

Outcomes

The differences in resolution of hypertrophic scarring were examined by patient age, the type of injury, and the type of treatment (Table 1). Age was also assessed as continuous variable.

Follow-up information

Of the original cohort of 361 patients, 139 patients developed mature scars during a maximum follow-up period of 5 years and 131 days. The mean period of follow-up was 16.89 months (range, 1-64.3 months); 17.6% of the study population was followed up to more than 2 years, 31.4% had a follow-up between 12 and 24 months, 27.9% had a follow-up between 6 months and 1 year, and 17.6% were followed up to less than 6 months.

The mean period between hypertrophic scar onset and presentation on the outpatient clinic was 13.7 months (Table 2). During follow-up visits, the POSAS forms were filled out as an extra tool to assess scars. Because the POSAS forms were not filled out immediately after onset of a hypertrophic scar, mean POSAS scores were not used for statistical analysis.

Time between Injury of the Skin and Hypertrophic Scar Formation

For 337 of the 361 patients, the date of injury by burn (n=49), surgery (n=245), or trauma (n=43) was documented in their medical files. The mean time between injury of the skin and formation of a hypertrophic scar was shortest in scars caused by trauma (4.86 months; 95% CI, 3.41-6.32 months), followed by burns (5.83 months; 95% CI, 4.42-7.25 months) and surgery (7.64 months; 95% CI, 6.85-8.43 months; Table 3). Overall, the mean time between deep dermal disruption and formation of a hypertrophic scar was 7.02 months (95% CI, 6.38-7.67 months). Significant differences in mean time between injury and hypertrophic scar formation were found between trauma and surgery ($P<.013$; Table 4).

Table 1. Demographic and scar characteristics

Age, y	Range	1-87
	Mean (SD)	36.99 (23.37)
	Median	33
Age groups, n	<30 y	166
	30-55 y	94
	>55 y	101
Gender, n	Male	166
	Female	195
Scar cause, n	Burn	53
	Surgery	256
	Trauma	52
Scar therapy, n	Pressure	81
	Silicone	29
	Injection	39
	Combination	161
	Other	51

Table 2. Follow-up information

Length of follow-up, mo	Range	1-64.3
	Mean (SD)	18.89 (13.4)
	Median	13.21
Time between onset and first clinic visit, mo	Range	1-69.7
	Mean (SD)	13.7 (11.95)
	Median	10.6
Duration of follow-up, n	<6 mo	63
	6-12 mo	102
	12-24 mo	114
	>24 mo	82

When age groups were compared, no statistically significant differences in mean time between injury of the skin and hypertrophic scar formation among patients exist (Tables 3 and 4).

Age-specific maturation time

Based on these results, scars in patients <30 tend to resolve more slowly than in patients aged 30-55 years. This slower maturation rate in young patients occurs until 3 years after scar onset. These data also show that scars maturate most rapidly in older patients. In this specific group, all scars were completely mature at 4 years after onset.

Estimated Maturation Time. Kaplan-Meier estimates for mean maturation time can be seen in Table 5. Once more, this shows the difference in mean maturation time between the

Table 3. Mean time in months between injury and scar formation by cause and age

				95% Confidence Interval	
		Estimate	SE	Lower Bound	Upper Bound
Scar cause	Burns	5.83	0.40	4.42	7.25
	Surgery	7.64	0.71	6.85	8.43
	Trauma	4.86	0.72	3.41	6.32
	Overall	7.02	0.33	6.38	7.67
Age	<30 y	7.28	0.57	6.16	8.40
	30-55 y	7.08	0.69	5.72	8.45
	>55 y	6.65	0.43	5.80	7.50

Table 4. Cox regression with hazard ratios for mean time in months between injury and scar formation by cause and age

				95% Confidence Interval	
		P	Hazard Ratio	Lower Bound	Upper Bound
Scar cause	Burns vs surgery	0.126	0.93	0.37	1.69
	Burns vs trauma	0.712	1.24	0.40	1.89
	Trauma vs surgery	0.013	0.98	0.38	1.39
Age group	30-55 vs <30 y	0.968	0.81	0.55	1.13
	>55 vs <30 y	0.694	0.77	0.45	1.02
	>55 vs 30-55 y	0.876	0.85	0.57	1.37

<30 (35.76 months; 95% CI, 31.35-40.16 months) and >55 patients (22.53 months; 95% CI, 18.06-26.89 months), and between older and middle-aged patients (34.64 months; 95% CI, 28.52-40.76 months). In order to assess the statistically significant differences in maturation time among age groups, log-rank test was used (Table 6). Figure 2 shows the corresponding Kaplan-Meier curves.

Significant differences in Kaplan-Meier curves

Table 6 shows by log-rank test that significant differences exist in Kaplan-Meier curves (Figure 2) between <30 and >55 patients ($P<0.0001$) and between middle-aged and older patients ($P=0.001$). When middle-aged and young patients are compared, Kaplan-Meier curves are not significantly different ($P=0.548$).

Hypertrophic scars in patients over 55 maturated more than twice as fast than in patients <30 years during this 5-year follow-up period (HR, 2.37; 95% CI, 1.60-3.51; $P<.0001$). Between the 30-55 and >55 groups, significant differences in maturation time also occurred in this 5-year period (HR, 2.08; 95% CI, 1.32-3.25; $P=.001$) in favor of the patients >55 years.

When age is taken into account as a continuous variable, development of a mature scar occurs significantly faster as patients grow older (HR, 1.01; 95% CI, 1.00-1.01; $P<.0001$; Table 6).

Table 5. Mean time in months to scar maturation by age group, cause, and therapy

				95% Confidence Interval	
		Estimate	SE	Lower Bound	Upper Bound
Age group	<30 y	35.76	2.25	31.35	40.16
	<30-55 y	34.64	3.12	28.52	40.76
	>55 y	22.53	2.28	18.06	26.98
	Overall	32.22	1.58	29.14	35.31
Scar cause	Burns	29.69	4.10	21.65	37.73
	Surgery	31.95	1.72	28.57	35.33
	Trauma	33.56	3.99	25.75	41.37
	Overall	32.22	1.58	29.14	35.31
Therapy	Pressure	23.20	2.23	18.83	27.57
	Silicone	35.51	5.42	24.90	46.13
	Injection	46.42	3.61	39.36	53.49
	Combination	30.59	2.20	26.28	34.90
	Other	41.31	4.19	33.10	49.51

Table 6. Cox regression with hazard ratios for mean time in months between scar onset and maturation by scar cause, age, and therapy

				95% Confidence Interval	
		P	Hazard Ratio	Lower Bound	Upper Bound
Scar cause	Burns vs surgery	0.126	0.93	0.37	1.69
	Burns vs trauma	0.712	1.24	0.40	1.89
	Trauma vs surgery	0.013	0.98	0.38	1.39
Age group	30-55 vs <30 y	0.968	0.81	0.55	1.13
	>55 vs <30 y	0.694	0.77	0.45	1.02
	>55 vs 30-55 y	0.876	0.85	0.57	1.37

Cause-specific maturation time

According to the maturation percentages found in this study, all hypertrophic scars caused by burns are mature 5 years after onset. Scars caused by trauma have the lowest percentage of maturation after 5 years.

Estimated Maturation Time. Table 5 displays Kaplan-Meier estimates for mean scar maturation. According to 95% CI, no differences in maturation time exist based on scar cause. All causes have overlapping CI. The Kaplan-Meier curves log-rank tests (Table 6) support this observation; no significant differences in maturation time based on scar cause were seen. Corresponding Kaplan-Meier curves for scar cause can be seen in Figure 3. The overall Kaplan-Meier curve unspecified for age or scar cause can be seen in Figure 4.

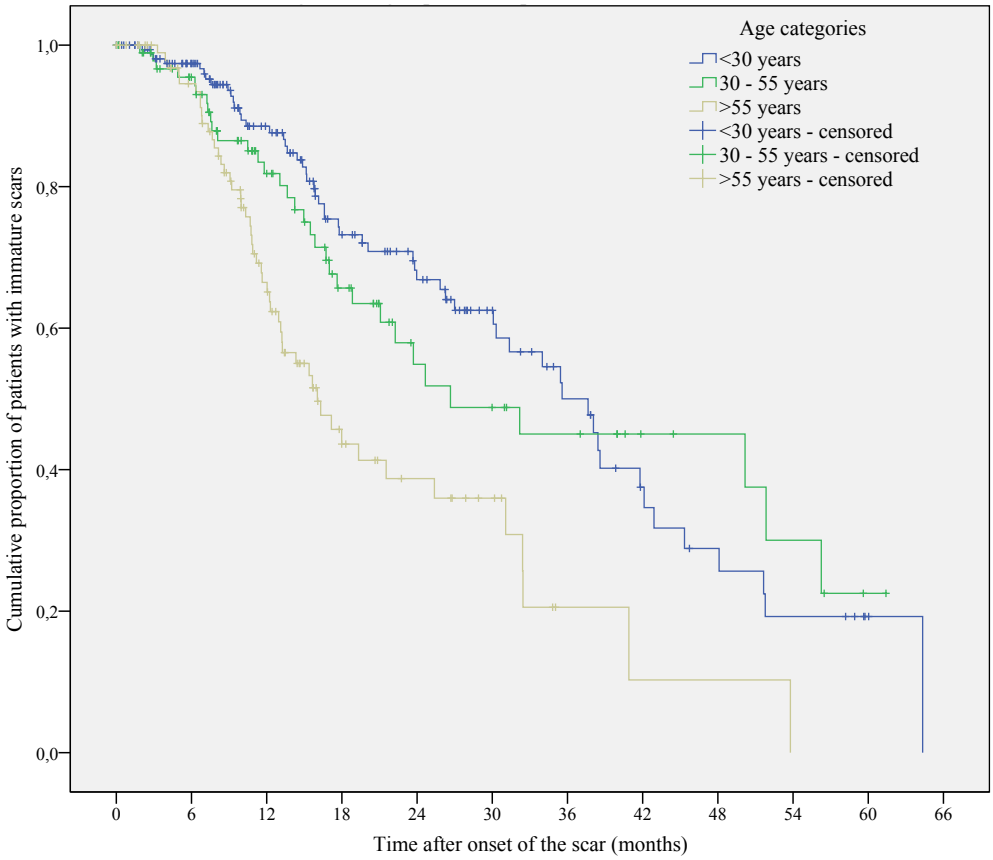


Figure 2. Kaplan-Meier curves for hypertrophic scar maturation by age groups

Therapy-specific maturation time

Scars treated with pressure therapy tend to show more rapid maturation than scars treated with silicones, injection therapy, combination therapy, or other therapy. Injection therapy shows the lowest maturation rate up to 2.5 years after onset of the scar and the lowest maturation percentage after 5 years.

Estimated Maturation Time. Kaplan-Meier estimates for mean maturation time are displayed in Table 5. This shows the shortest mean maturation time is reached when patients are treated with pressure therapy (23.20 months; 95% CI, 18.83-27.57 months), followed by combination therapy (30.59 months; 95% CI, 26.28-34.90 months), silicone therapy (35.51 months; 95% CI, 24.90-46.13 months), other therapies (41.31 months; 95% CI, 33.10-49.51 months), and injection therapy (46.43 months; 95% CI, 39.36-53.49 months).

Significant Differences in Kaplan-Meier Curves. Table 6 displays by log-rank test that significant differences in survival curves exist between pressure therapy and injections (*P*<

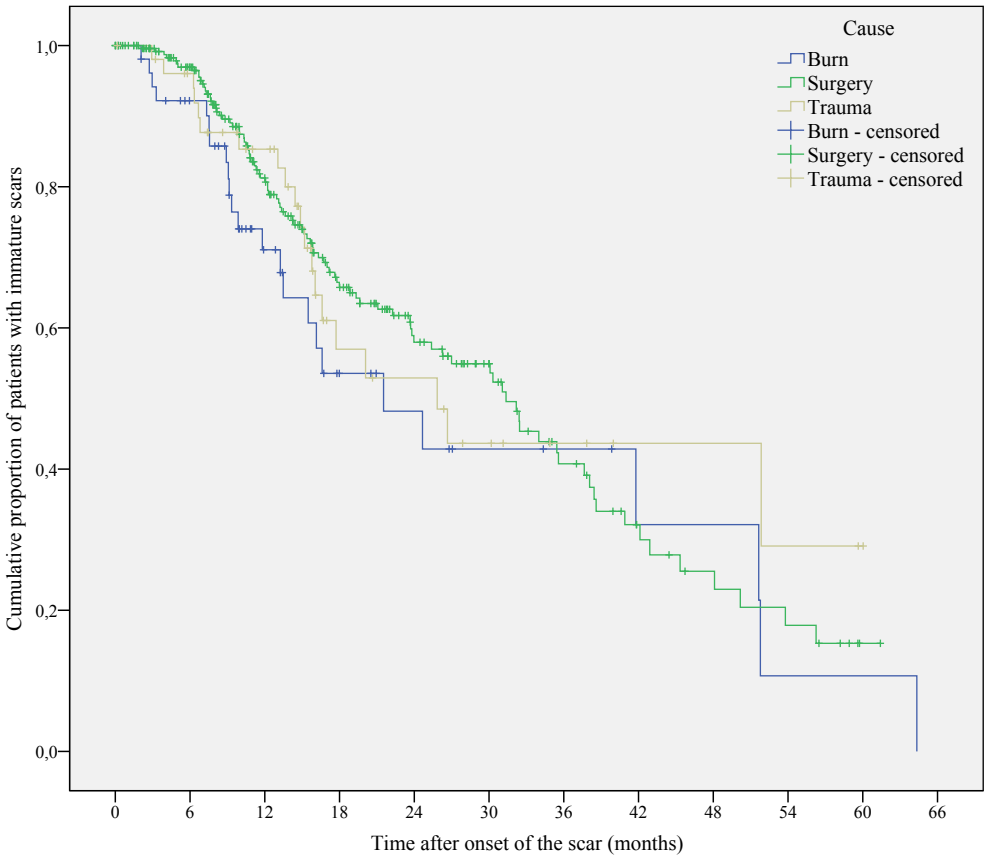


Figure 3. Kaplan-Meier curves for hypertrophic scar maturation by age groups

.001; HR, 5.18), silicones (*P*<.039; HR, 2.08), combination therapy (*P*<.023; HR, 1.57), and other therapies (*P*<.016; HR, 2.55; Figure 5). Further, significant differences were found between silicone therapy and injection therapy (*P*<.042; HR, 2.64) and between combination therapy and injection therapy (*P*<.001; HR, 3.38).

Time between injury of the skin and maturation of a hypertrophic scar

The mean time between injury of the skin and maturation of a hypertrophic scar includes the sum of the time between injury of the skin, formation of a hypertrophic scar, and complete maturation. This period is shortest for hypertrophic scars caused by burns (35.52 months; 95% CI, 27.36-43.69 months), followed by trauma (38.42 months; 95% CI, 25.75-41.37 months), and then surgery (39.59 months; 95% CI, 36.12-43.06 months; Table 7). No significant differences in mean time between injury and maturation were found in scars caused by trauma, burns, or surgery (Table 8).

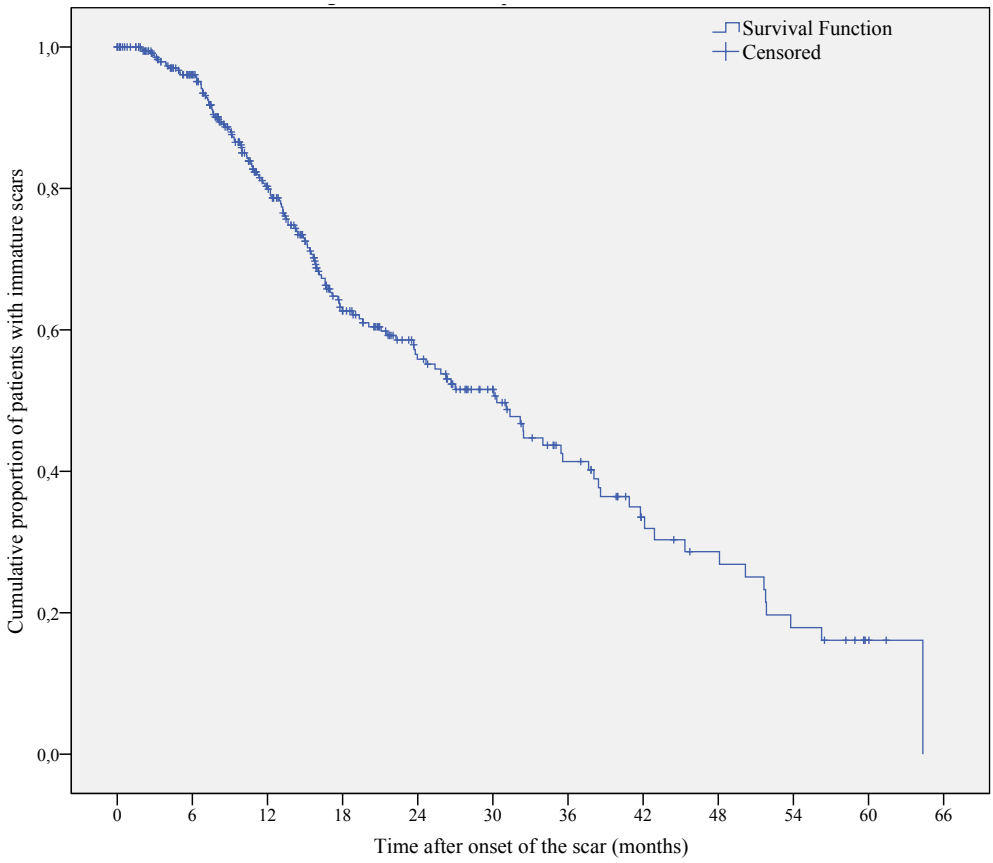


Figure 4. Overall Kaplan-Meier survival curve for hypertrophic scar maturation

Table 7. Mean time in months between injury and scar maturation by cause and age

				95% Confidence Interval	
		Estimate	SE	Lower Bound	Upper Bound
Scar cause	Burns	35.52	3.33	27.36	43.69
	Surgery	39.59	1.52	36.12	43.06
	Trauma	38.42	3.48	30.48	46.37
	Overall	39.24	1.33	36.09	42.40
Age	<30 y	43.04	1.98	34.53	51.55
	30-55 y	41.72	2.66	32.36	51.09
	>55 y	29.18	1.82	21.16	37.18
	Overall	43.04	1.98	34.53	51.55

Concerning age groups, the mean time between injury and maturation of the hypertrophic scar is shortest in patients >55 years (29.18 months; 95% CI, 21.16-37.18 months), followed by patients between 30-55 years patients (41.72 months; 95% CI, 32.36-51.09

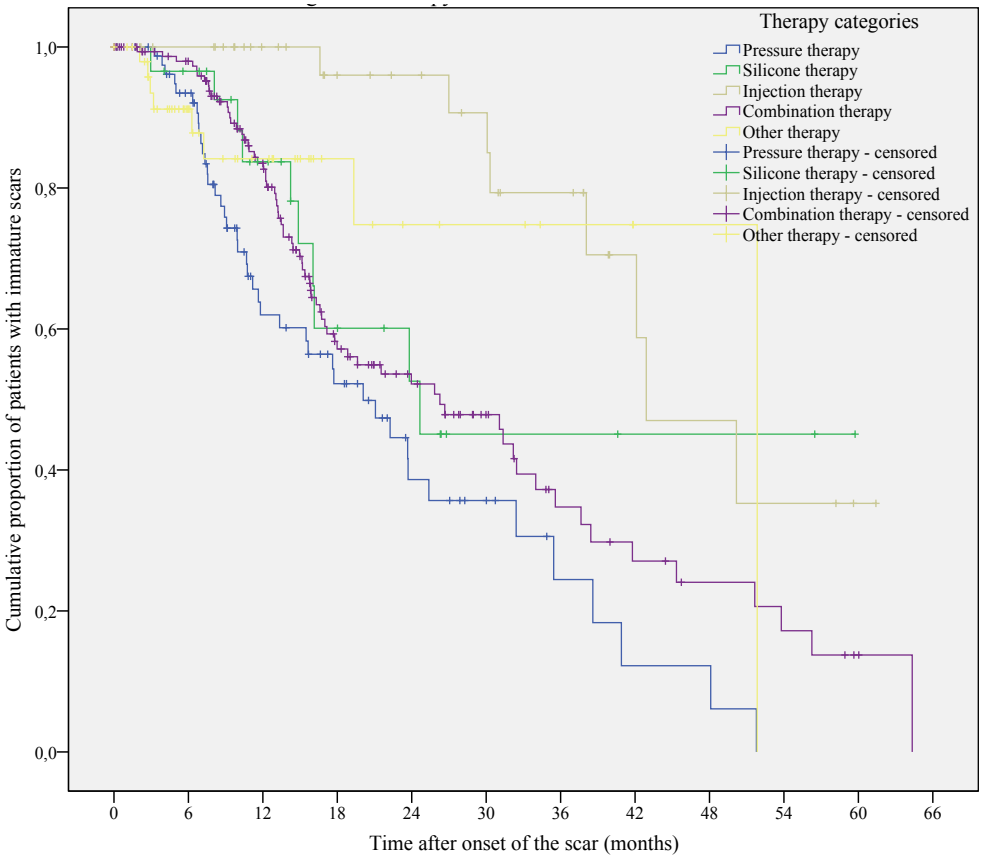


Figure 5. Kaplan-Meier survival curve for hypertrophic scar maturation by scar therapy

Table 8. Cox regression with hazard ratios for mean time in months between injury and scar maturation by cause and age

				95% Confidence Interval	
		P	Hazard Ratio	Lower Bound	Upper Bound
Scar cause	Burns vs surgery	0.96	1.48	0.94	2.34
	Burns vs trauma	0.449	1.26	0.69	2.31
	Trauma vs surgery	0.523	1.17	0.72	1.90
Age group	30-55 vs <30 y	0.478	1.17	0.76	1.81
	>55 vs <30 y	<0.0001	2.37	1.59	3.51
	>55 vs 30-55 y	0.002	2.02	1.29	3.16

months), and patients <30 (43.04 months; 95% CI, 34.53-51.55 months; Table 7). Significant differences were found between the 30-55 and >55 groups (HR, 2.02; 95% CI, 1.29-3.16) and between patients >55 and patients <30 years (HR, 2.37; 95% CI, 1.59-3.51; Table 8).

DISCUSSION

The major finding of this study is that the average length of maturation is longer than most providers realize. Maturation of hypertrophic scars is widely believed to occur in a period of 1 to 2 years.[8,11] According to these results, complete maturation of hypertrophic scars is often not achieved in a time frame of more than 5 years. Even at 3 years after onset, 34% of all hypertrophic scars were not deemed mature (Figure 4). The process of maturation of hypertrophic scars occurs more gradually than previously assumed.

Scar therapy is believed to be useful especially when scars are immature and not yet in a steady state. According to these results, it should be assumed that the immature phase of hypertrophic scars takes significantly more time than previously believed. Consequently, these authors advocate the use of scar therapy in many cases even after 5 years after scar onset.

Jones[26] stated scar correction by means of surgery should be delayed for at least 1 year. Based on these results, these authors advocate a delay in surgical intervention for hypertrophic scars until the scar is mature, which can take up to 3 years.

Judging scar maturation by age, those older than 55 years have a significant advantage in maturation time over other patients (Table 1, Figure 2). This finding was already suggested by Ashcroft et al[27] and Marcus et al;[28] older subjects tend to have a better clinical quality of scarring. A possible explanation is based on proliferation levels; younger people receive more proliferative stimuli than older adults, and so they pass into the maturation stage later.[28]

No significant differences were found when evaluating the mean maturation time by the three scar causes. Some research indicates that scars related to burn injuries tend to regress at a slow rate.[29] In this study, hypertrophic burn scars did not mat- urate significantly more slowly than traumatic hypertrophic scars. This could be because the patients with hypertrophic burn scars were patients with minor burns and scalds (and were not treated in a specialized burn center).

Another reason for the long maturation time found in this study could be the fact that patients referred to the MUMC scar clinic are patients with problematic scars that already had a history of scar therapy to which they did not respond. This potential source of bias is supported by the fact patient intake occurred at a late onset of scarring (mean, >13 months after wound closure, Table 2).

Only patients for whom the date of scar onset was known were included in the study. In general, the date of onset of hypertrophic scars was known because most of the patients had frequent outpatient clinic visits at the MUMC or affiliated hospitals. However, the exact dates scars became hypertrophic are not certain because of the retrospective nature of the study. To define the exact time between dermal injury and onset of a hypertrophic scar more precisely, extensive prospective studies would be needed.

Silicone therapy is considered a first-line treatment option for hypertrophic scars. Its clinical efficacy and scar-enhancing properties are well known.[30-32] Further, pressure garment therapy is also a reputable and effective method for reducing thickness and erythema in hypertrophic scars.[22] In this study, scars treated with pressure garments had a statistically significant advantage in maturation time compared with silicone therapy (HR, 2.08), injection therapy (HR, 5.18), combination therapy (HR, 1.57), and other therapy (HR, 2.55; Table 6). A reason for the faster maturation at scars treated with pressure therapy is that in many cases a step-up therapy scheme was used. Combination therapy was used mainly for hypertrophic scars that were more severe and required addition of silicone sheets next to pressure therapy. This could explain the prolonged maturation time for scars treated with combination therapy.

The use of intralesional injections is predominantly recommended when hypertrophic scars are more severe and topical noninvasive therapies fall short.[20] This can explain the prolonged maturation period for the injection therapy group, because this group presumably included more severe hypertrophic scars.

The clinical effects of pressure therapy, silicone therapy, and more invasive scar therapies have been thoroughly investigated since the 1980s. However, the effects of these therapies on the maturation time of hypertrophic scars are less studied and fairly unknown. Further well-controlled clinical trials to examine the effect of different therapies on scar maturation time are needed.

Strengths and weaknesses

Many noninvasive and invasive therapies have been described for the management of hypertrophic scars.[2,33,34] Although differences are found among the different treatment strategies, this does not necessarily mean that one of these therapies is going to be less effective than another. Because of the retrospective nature of this study, attribution error from the choices for one therapy or another could have been made.

During follow-up visits, scars were assessed by means of the POSAS and by the same investigators. The maturation assessment of each hypertrophic was made by this group of investigators, supported by low POSAS scores. All scars showed a clear reduction in the POSAS score between the first visit to the outpatient clinic and complete maturation. However, no formal cutoff point exists for a mature scar for any of the parameters of the POSAS. Therefore, the expert assessment of hypertrophic scars maturation was crucial, but not objective.

CONCLUSIONS

In summary, the present study suggests that hypertrophic scars take significantly more time to completely maturate than previously believed. This knowledge might promote scar treatment for multiple years after onset, as well as prevent premature surgical revision of hypertrophic scars. Additional prospective studies considering macroscopic changes of hypertrophic scars over a course of several years might help to understand the exact macroscopic changes that occur during maturation of hypertrophic scars. Further prospective randomized trials are needed to evaluate the effectiveness of the different scar therapies available at the moment.

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CHAPTER 3



Measuring aesthetic results after facial skin cancer by means of the FACE-Q

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ABSTRACT

Background: Skin cancer is the most commonly occurring type of cancer. However, the influence of facial skin cancer surgery on patients' perceived aesthetic appearance is poorly understood.

Objective: The objective of this study was to provide an insight into how patients perceive the aesthetic outcome of facial skin cancer surgery by means of a specialized Patient Reported Outcome Measure designed for the aesthetic evaluation of the face: the FACE-Q.

Methods and materials: A total of 47 patients with non-melanoma skin cancer who were scheduled for Mohs's micrographic surgery (MMS) or standard surgical excision (SE) were included. These patients filled out three different FACE-Q questionnaires: *satisfaction with facial appearance, social function,* and *satisfaction with outcome*. Follow-up was conducted after baseline at 1 month and 3 months post-surgery.

Results: No significant differences were detected between baseline and follow-up regarding social function and satisfaction with facial appearance. However, after 3 months patients were significantly more satisfied with the result of surgery when compared to the 1-month post-surgery follow-up.

Conclusion: The perceived aesthetic appreciation of patients does not seem to be significantly influenced by facial skin cancer SE or MMS surgery in this 3-month follow-up study.

INTRODUCTION

Skin cancer is the most commonly occurring type of cancer, of which basal cell carcinoma (BCC) is the most common form with an estimated incidence of more than four million cases in the U.S. alone.[1] In the Netherlands, the incidence of BCC is of almost thirty thousand cases each year.[2] The incidence of BCC is rising annually.[3]

Surgery is usually the first choice of treatment for non-melanoma skin cancer (NMSC). However, it can result in extensive facial defects with noticeable scars, negatively influencing the overall well-being of patients.[4]

Surgical treatment techniques for NMSC include standard surgical excision (SE) and Mohs' micrographic surgery (MMS). MMS has been developed to spare the healthy tissue by delivering a comprehensive assessment of resection margins.[5]

During the past decade, patient-reported outcome measures (PROMs) are becoming increasingly appreciated when evaluating different therapies in dermatology.[6,7]

To determine the health-related quality of life (QOL) after NMSC by means of PROMs, a number of studies have been conducted evaluating these types of tools. In patients with NMSC, promising PROMs with the most potential for clinical application include the Skin Cancer Index, Skindex, Skin Cancer Quality of Life Impact Tool, Skin Cancer Quality of Life questionnaire, and the Facial Skin Cancer Index.[8-11] These tools have proven to have a role in the assessment of the overall quality of life of patients with (facial) skin cancer. However, when skin cancer occurs in such a delicate area as the face, it can be insightful to be able to comprehend how the facial appearance perceived by patients is influenced by the surgical removal of skin cancer. For this purpose, the above mentioned QOL tools are not useful as they do not focus on the assessment of facial appearance by patients in detail after the removal of facial skin cancer.

In order to assess (facial) scars, some specific tools have been applied. The Vancouver Scar Scale (VSS), developed to provide a more objective measurement of burn scars, has proven to be a reliable tool and has been widely used for the assessment of scars.[12] However, one of the major disadvantages of this tool is that it does not take patient scar perception into consideration; therefore, it does not evaluate the quality of life of patients. Since 2004, the Patient and Observer Scar Assessment Scale (POSAS) has been developed as a useful alternative tool for assessing scars.[13,14] The distinctive characteristic of this tool is that it includes about the opinion of patients regarding their scar. Nevertheless, this tool does not cover the influence that scars have on patients' quality of life.[15-17] Regarding scars after NMSC surgery, a few studies have shown acceptable results in patients perception.[18,19] However, these data about the aesthetic evaluation after NMSC surgery are primarily limited because no validated PROMs were employed in these studies.

Extensive and qualitative data with respect to the patients' perceived facial appearance after face reconstruction after NMSC is lacking in times where there is an increasing emphasis in conserving a decent facial appearance after surgery.

The FACE-Q, developed by Klassen et al. in 2010, is a validated PROM designed to evaluate patients' experience and outcomes after facial aesthetic procedures. In contrast to POSAS, for example, FACE-Q entirely consists of questionnaires that are exclusively filled out by patients. The FACE-Q is composed of more than 40 independently functioning scales in four distinct domains: satisfaction with facial appearance, health-related quality of life, adverse effects, and process of care. It has proven to be a useful tool for evaluating multiple units of the face with respect to aesthetics.[20-22] Therefore we consider this to be a helpful instrument in assessing patient satisfaction with facial appearance after the removal of facial skin cancer.

Aim

The aim of this study was to provide more insight in the perceived aesthetic outcome of patients after facial skin cancer surgery. The judgement of aesthetic outcome will take place by means of a specialized aesthetic PRO instrument, the FACE-Q.

MATERIALS AND METHODS

Study design

This prospective study was conducted at the Maastricht University Medical Center (MUMC+) between October 2017 and April 2018. Patients undergoing a surgical treatment for a histologically proven facial skin cancer were approached and informed about the study via mail at least 1 week before the surgery was arranged.

Data collection

For the assessment of their facial image, patients were asked to complete three different FACE-Q questionnaires in total, at baseline and at the two follow-ups. Patients who had no cognitive impairment and who were fluent in Dutch were included. The questionnaires were sent to the patients via mail.

Study population and follow-up

Patients with different types of skin cancer, including basal and squamous cell carcinomas, intra-epidermal melanomas, and basosquamous carcinomas were asked to participate. Only patients with malignancies located on the face were included. All patients were treated by a board certified or resident dermatologist by means of surgical excision or MMS. Reconstruction was performed either by the same dermatologist, or by a board certified or

resident plastic surgeon. Patients who already underwent facial surgery for a different lesion in a period shorter than 6 months prior to the start of this study were excluded. Additionally, patients requiring surgery for multiple skin cancer lesion simultaneously were excluded. Only one procedure per patient was performed. Evaluation took place at the baseline (1 to 2 weeks prior to surgery), 1 month, and 3 months post-surgery.

The study conformed to good clinical practice guidelines and followed the recommendations of the Declaration of Helsinki. The study protocol was approved by the local ethics board.

Assessment

For the assessment of patients' satisfaction with their facial appearance in general and in social situations, FACE-Q questionnaires were used (Appendix 1-3). This tool was chosen because FACE-Q is one of the few tools that meets the current recommendation for the development and validations of PROMs.[23] Although the FACE-Q consists of over 40 scales in four domains, it is designed in a way that a subset of FACE-Q scales can be used, as each scale is scored independently. Therefore, it is not necessary to complete all scales.

Scales that were utilized in this study were *satisfaction with facial appearance* (for the assessment of patients' facial appearance in general), *social function* (to assess facial appearance in social situations), and *satisfaction with result*. The three scales were administered at baseline (except for the *satisfaction with result* questionnaire), 1 month, and 3 months follow-up. These questionnaires are part of the satisfaction with the facial appearance domain, the health-related quality of life domain, and the process of care domain of the FACE-Q, respectively.

Collected baseline characteristics were age, sex, the location of the skin cancer, and the maximum diameter of the skin cancer lesion in millimeters.

Data analysis

Responses to the FACE-Q questions were scored based on a Likert scale ranging from 1 to 4. FACE-Q questionnaires contain a table that transforms the sum of each FACE-Q questionnaire to a standardized Rasch transformed score from 0 to 100. A higher Rasch scores indicates a greater satisfaction or quality of life. Mean overall transformed Rasch scores were compared using paired t-tests when data was normally distributed and by means of Wilcoxon signed rank test when data was not normally distributed. Subgroup analyses were performed based on the location on the face and size of the defect. Power analysis indicated that at least 35 patients were necessary to detect a one-point difference in answers (according to the Likert scale) for FACE-Q questionnaires between the different follow-up moments. A one-point difference includes a change from very or somewhat (dis)satisfied to somewhat or very (dis)satisfied or from somewhat or definitely (dis)agree to definitely or somewhat (dis)agree (See Appendix 1-3).

RESULTS

A total of 138 patients were approached, of whom 47 (23 men and 24 women) participated in the study for an overall response rate of 34%. From the initial 47 included patients, 35 filled out the 1-month questionnaires and 42 filled out the final 3-month questionnaires. The main reason for loss to follow-up is that patients who were lost to follow up returned the 1-month and 3-month questionnaires too late. A delay of no more than 1 week was considered acceptable by the researchers. Patients who were scheduled for surgery were recruited via mail. Patients who did not return the consent forms were not contacted again for non-participation.

The mean age of the patients was 71 years (ranging from 43 to 85). Forty patients had a basal cell carcinoma, 4 suffered from a squamous cell carcinoma, 2 were diagnosed with intra-epidermal melanoma, and 1 patient had a basosquamous carcinoma. Skin cancer was located on the nose (30%), eyelids (17%), frontal or temporal (32%), and the nasolabial folds (21%).

Lesion diameters were between 2 mm and 17 mm, with a mean diameter of 7.9 mm. Surgery was performed on 41 occasions by a (resident) dermatologist and six times by a (resident) plastic surgeon. In 27 cases Mohs' surgery was used. The rest of the patients were treated by means of surgical excision. In 44 cases, the wounds were primarily closed. In two cases, full-thickness skin grafts were used and one time a Hughes flap was used for the closure of a defect at the lower eyelid. All patient characteristics are presented in Table 1.

Social function

Mean transformed Rasch scores regarding patients' satisfaction with their facial appearance in social situations are shown in Figure 1. No significant differences were found in social function between baseline (78.02, SD:19.41), 1 month (77.42, SD:22.79), and 3 months (80.78, SD:20.25) after surgery.

Satisfaction with facial appearance

When patients' satisfaction with their facial appearance in general was assessed, again no statistically significant differences were identified between start of the study and the two follow-up moments (Figure 1). Rasch scores were 70.27 (SD:17.98) at baseline, 68.53 (SD:17.34) 1 month post-surgery, and 73.05 (SD:22.32) at 3 months post-surgery.

Result satisfaction

Statistically significant differences in the mean Rasch scores were noticed when patients' satisfaction with the result of surgery was observed at the 1-month and 3-month follow-up. Mean Rasch scores rose from 59.48 (SD:30.05) at 1 month post-surgery to 71.63 (SD:24.11) at 3 months post-surgery, displayed by a *P* value of 0.041. When standard surgical excision (n=20) was compared to Mohs' surgery (n=27), no statistically significant differences in satisfaction with the end result were observed (Table 2).

Table 1. Patient characteristics

Mean age (years)	*71*
Min	43
Max	85
Sex	
Male	23
Female	24
Location	
Frontal/temporal	15
Nose	14
Eyelids	8
Nasolabial	10
Type of skin cancer	
*BCC**	40
*SCC**	4
Intra-epidermal melanoma	2
Basosquamous carcinoma	1
Lesion diameter	
Min (mm)	2
Max (mm)	17
Mean (mm)	7.9
< 5 mm	11
5 – 10 mm	14
> 10 mm	18

*BCC: Basal Cell Carcinoma, SCC: Squamous Cell Carcinoma

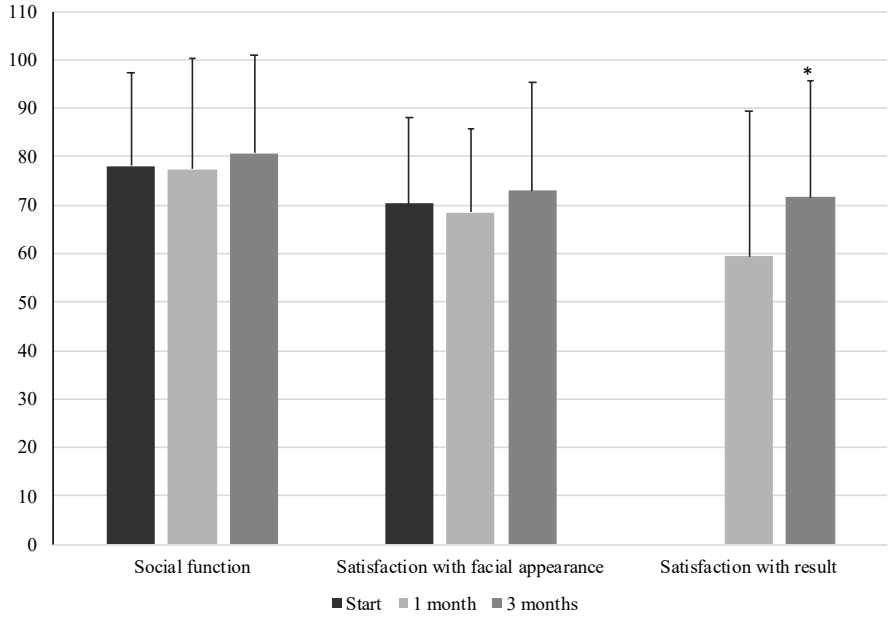


Figure 1. FACE-Q scores at the start of the study (1 to 2 weeks prior to surgery) and at the two follow-ups.

Table 2. Result satisfaction: standard surgical excision (SE) vs. Mohs' micrographic surgery

	SE	*SD*	*MMS*	*SD*	P
1 month	51.38	*28.45*	64.12	30.59	0.22
3 months	64.75	27.32	76.96	20.50	0.11

Figure 2 displays the satisfaction with the result surgery for the four different facial sites. The largest increase in satisfaction with the result between 1 and 3 months post-surgery was seen in skin cancer surgeries at the level of the nose (from 57.00, SD:39.12 to 84.92, SD:22.63), followed by skin cancer removal at the eyelids (from 58.67, SD:31.47 to 71.71, SD:22.02), nasolabial folds (from 46.00, SD:26.50 to 51.67, SD:26.49), and frontal/temporal (from 71.90, SD:17.50 to 73.15, SD:16.71). However, the improvement in satisfaction with the result for all facial sites was not considered statistically significant between the two follow-up moments. Also, no statistically significant differences were found between the four groups at the two follow-ups.

Regarding the size of skin cancer lesions, Figure 3 shows the satisfaction with the result of surgery. Lesion sizes were divided into smaller than 5 mm, 5 to 10 mm, and larger than 10 mm lesions. The Rasch scores from patients with lesions larger than 10 mm displayed a statistically significant increase between 1 month (62.79, SD:21.79) and 3 months (79.60, SD:20.64) post-surgery, displayed by a *P* value of 0.038. Lesions smaller than 5 mm (51.00, SD:39.11 at 1 month and 63.18, SD:31.12 at 3 months) and lesions between 5 and 10 mm (62.17, SD:32.74 at 1 month and 69.89, SD:22.04 at 3 months) did not show a statistically significant increase in the mean Rasch scores between 1 and 3 months post-surgery (*P* values of 0.378 and 0.795, respectively). Furthermore, no statistically significant differences in result satisfaction were found between all lesion sizes at the two follow-ups.

DISCUSSION

The major result of this study is that patients are significantly more satisfied with the aesthetic result of facial skin cancer surgery (by means of MMS or SE) at 3 months after the surgery when compared to 1-month post-surgery.

Our results also show that skin cancer surgery does not induce a significant decrease in the patients' perceived overall facial appearance between baseline, 1 month, and 3 months after surgery. These results have been, for the first time, measured by a PROM designed for the aesthetic evaluation of the face.

The increase in the patients' satisfaction with their facial appearance over the course of 2 months post-surgery could be explained by the hypothesis that in the first 3 months scars are erythematous and therefore more noticeable, as observed in a study by Bond and colleagues.[27] Furthermore, there is an increase in the net production of collagen until

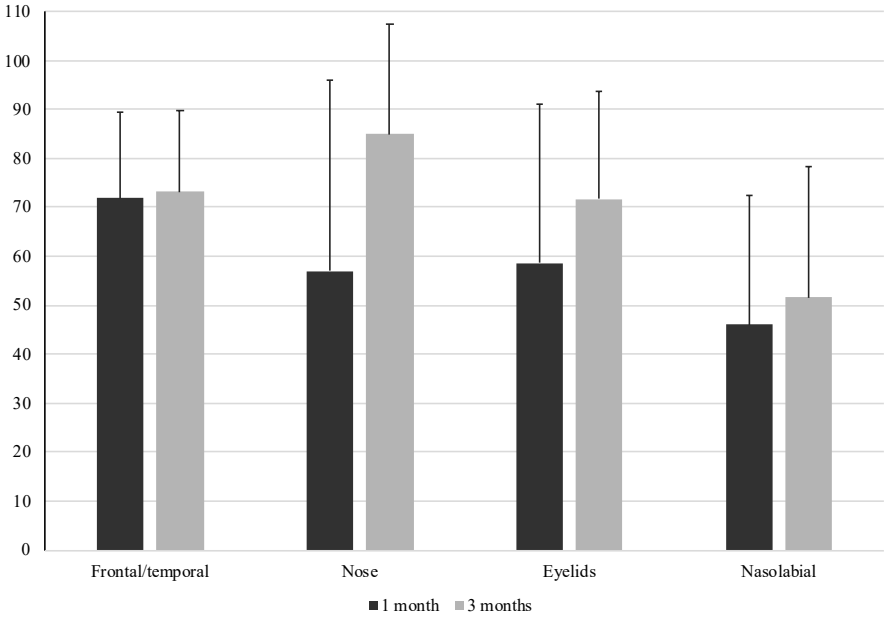


Figure 2. FACE-Q: satisfaction with outcome scores for four different facial sites at two follow-up moments.

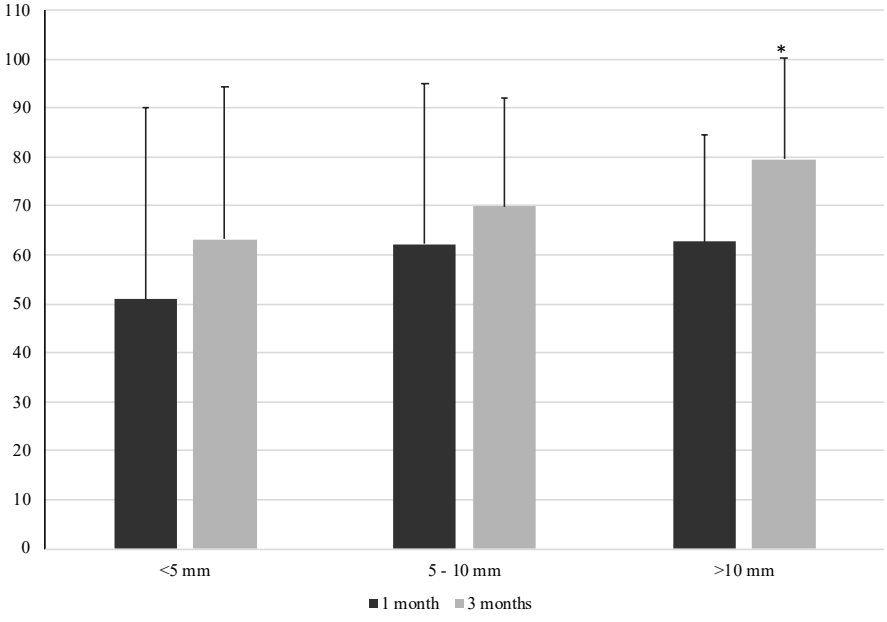


Figure 3. FACE-Q: satisfaction with outcome scores for the size of the skin cancer at two follow-up moments.

approximately 21 days after the skin injury takes place, giving scars a more thickened appearance. After this the collagen synthesis rate decreases. Subsequently, capillary redness density decreases as the regression of the inflammatory process occurs and scars pass into the maturation phase, becoming less prominent.[24]

The results also show that patients' satisfaction with the outcome of surgery significantly improves in larger defects on the face (>10mm) between 1 and 3 months post-surgery. The effect on patients' satisfaction with the surgery outcome over the course of 2 months for smaller defects (<10mm) appears to be less noticeable in this study, as no significant differences in patients' satisfaction with the outcome were observed between the two follow-up moments. We hypothesize that patients' expectations about the outcome of the surgery could be influenced by the information about the expected aesthetic result that was expressed by the physician before surgery. Because the selection of patients took place by different physicians, observer bias could have occurred. For a better understanding of the correlation between the size of facial skin cancer and patients' satisfaction with the outcome of the surgery, larger study populations with unambiguous instructions from doctors in future studies are needed.

The study also revealed that no significant differences in patients' satisfaction with the result of therapy were observed between MMS and SE at the two follow-ups. However, this study was not designed to compare SE and MMS with respect to the aesthetic outcome. Considering MMS does not belong to the standard treatment modalities in most hospitals in Europe yet, the results of this study can also be applicable in practices were the only therapeutic option is SE.

No significant differences were seen with respect to patients' outcome satisfaction when comparing different facial zones. However, in order to assess facial zones or better, the aesthetic subunits of the face where skin cancer surgery has the highest impact on the perceived aesthetic outcome, larger study populations are needed. Also, despite most patients' appreciation with their facial appearance in general and in social situations returns to baseline after three months follow-up, a longer follow-up period is preferable to assess the aesthetic impact of NMSC facial surgery more thoroughly.

CONCLUSION

This study showed that facial skin cancer surgery by means of SE or MMS is able to conserve the patients' perceived aesthetic appreciation of their face in a 3-month follow-up study assessed by means of FACE-Q scales. It also showed that patients' satisfaction with the aesthetic outcome resulted in a significant improvement between the 1- and 3-months post-surgery timeline.

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APPENDICES 1-3. FACE-Q SCALES

Appendix 1. FACE-Q™ - SATISFACTION WITH FACIAL APPEARANCE

For each question, circle only one **answer. With your** entire face **in mind, in the past week, how** satisfied or dissatisfied **have you been with:**

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a. How symmetric your face looks?	**1**	**2**	**3**	**4**
b. How balanced your face looks?	**1**	**2**	**3**	**4**
c. How well-proportioned your face looks?	**1**	**2**	**3**	**4**
d. How your face looks at the end of your day?	**1**	**2**	**3**	**4**
e. How fresh your face looks?	**1**	**2**	**3**	**4**
f. How rested your face looks?	**1**	**2**	**3**	**4**
g. How your profile (side view) looks?	**1**	**2**	**3**	**4**
h. How your face looks in photos?	**1**	**2**	**3**	**4**
i. How your face looks when you first wake-up?	**1**	**2**	**3**	**4**
j. How your face looks under bright lights?	**1**	**2**	**3**	**4**

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Appendix 2. FACE-Q™ – SOCIAL FUNCTION

For each statement, circle only one **answer. These are statements people might use to describe themselves. With your** facial appearance in mind**, in the past week, how much would you** agree or disagree **with the each statement:**

	Definitely disagree	Somewhat disagree	Somewhat agree	Definitely agree
a. I make a good first impression.	**1**	**2**	**3**	**4**
b. I feel confident when I meet a new person.	**1**	**2**	**3**	**4**
c. I am comfortable meeting new people.	**1**	**2**	**3**	**4**
d. It is easy for me to make new friends.	**1**	**2**	**3**	**4**
e. I feel confident when I participate in group situations (e.g. meetings).	**1**	**2**	**3**	**4**
f. I feel confident in new social situations (e.g. parties).	**1**	**2**	**3**	**4**
g. I am relaxed around people that I don't know well.	**1**	**2**	**3**	**4**
h. I feel confident when I walk into a room full of people I don't know.	**1**	**2**	**3**	**4**

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Appendix 3. FACE-Q™ – SATISFACTION WITH OUTCOME

For each statement, circle only one **answer. We would like to know how you feel about your** most recent **procedure. Please indicate how much you** agree or disagree **with each statement.**

	Definitely disagree	**Somewhat disagree**	**Somewhat agree**	**Definitely agree**
a. I am pleased with the result.	**1**	**2**	**3**	**4**
b. The result turned out great.	**1**	**2**	**3**	**4**
c. The result was just as I expected.	**1**	**2**	**3**	**4**
d. I am surprised at how good I look in the mirror.	**1**	**2**	**3**	**4**
e. The result is fantastic.	**1**	**2**	**3**	**4**
f. The result is miraculous.	**1**	**2**	**3**	**4**

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CHAPTER 4



Clinical effects of transparent facial pressure masks: a literature review

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ABSTRACT

Background*:* Severe facial hypertrophic scars are known to severely impact emotional well-being. Pressure therapy by means of transparent face masks has been used for almost 40 years, but evidence about the clinical effects remains sparse.

Objectives*:* To provide a summary on the efficacy of transparent face masks in the treatment of facial hypertrophic scars.

Methods*:* A literature search was conducted in PubMed, MEDLINE, and Cochrane databases through 1 January 2018. Articles describing the clinical effects of facial pressure therapy for remodeling the face after trauma or surgery with a validated tool were included. This review included studies of participants treated with facial hypertrophic scars, both minors and adults.

Results*:* Three articles involving 33 patients were selected for inclusion. Two studies described statistically significant improvement in facial scars measured by durometer, ultrasound, and the Patient and Observer Scar Assessment Scale (POSAS).

Conclusions*:* Facial pressure masks have been shown to deliver significant improvement in facial scars, measured by both subjective and objective tools. However, only three studies could be included in this literature review. Also, because of considerable limitations of the studies, it remains difficult to draw substantial conclusions about the efficacy of transparent face masks.

Clinical relevance

This literature review provides a summary of the current evidence on the subjectively and objectively measured clinical effects of transparent face masks in the treatment of facial scars, highlighting the need for further research on this topic.

Keywords: Orthotics, face masks, pressure therapy, facial scars.

INTRODUCTION

Hypertrophic scars caused by facial burns can have a detrimental effect on patient's mental well-being. The cornerstone in treating hypertrophic scars in the face consists of exerting mechanical pressure. Early treatment options consisted of hoods that were made of elastic fiber. However, due to the irregular shape of the face, the amount of pressure they delivered was often insufficient, especially over concave sites of the face. In the 1980s, rigid transparent plastic face masks were introduced and they have become a widely accepted treatment method for hypertrophic facial scars.[1–4] Although pressure therapy is widely used and accepted as the standard conservative therapy for treating hypertrophic facial scars, the exact working mechanism is not yet elucidated.

Meanwhile, varying fabrication methods and different types of facial orthoses' have been described.[5,6]

The conventional method of fabricating a custom transparent facemask requires an experienced orthotist/prosthetist. The fabrication process includes the formation of a negative and positive plaster mold, respectively, after which a transparent thermoplastic sheet is heated and molded over the positive plaster mold.[2,7]

In recent years, however, non-contact scanning of the face and three-dimensional (3D) printing of the mask have been developed and have become more attractive, as it is, in particular, more convenient and less burdensome for children.[5,8–10] With the help of specialized software, the model obtained by 3D scanning can be adjusted, and a mask can be printed by a 3D printing machine.

Although fabrication methods for face masks are still developing, robust evidence about their clinical effects is limited. Wearing a full-face pressure mask for a prolonged period may have a negative impact on emotional well-being as it can be demanding and uncomfortable. However, the psychological impact of wearing a face mask is not well-documented. In addition, there is doubt about the intervention as an evidence-based strategy.

A literature review addressing clinical and adverse effects of pressure therapy by means of facial pressure mask therapy may be helpful. Hence, the aim of this literature review was to provide an overview of the effectiveness of facial pressure therapy by means of transparent face masks in the treatment of facial hypertrophic scars as well as the side effects of this therapy.

METHODS

A computerized search was conducted in PubMed, MEDLINE, and Cochrane databases through 1 January 2018. The search query used in PubMed was (((“facial pressure mask” OR

"face mask" OR "face mask" OR "facial orthoses") AND ("scars" OR "hypertrophic scars" OR "burns"))). In addition, references were screened for other relevant articles.

Eligibility criteria

Inclusion criteria required articles to assess the clinical effects of facial pressure therapy for remodeling the face after trauma or surgery with a validated tool. This review included studies of both minors and adults treated for facial hypertrophic scars and protruding facial flaps after facial flap surgery.

Studies lacking actual data on the treatment outcome of the therapy were excluded, as well as studies that only described the formation process of a face mask and studies that were written in a language other than English. Primary outcome measurements were data obtained from tools for evaluating facial scars and adverse effects such as pain, pruritus, and psychological distress.

Randomized controlled trials, controlled trials, and in absence of these designs, observational studies (cohort studies, case-control studies, and case series) were also eligible for inclusion.

Data extraction

One researcher was involved in selection of articles matching the inclusion criteria and also in data extraction. A second researcher evaluated outcome measures and performed quality assessment of the included studies according to Oxford Centre for Evidence-Based Medicine guidelines.[11] Both researchers reviewed each article separately. Eleven study characteristics were extracted: lead author name (and publication year); study design; study population (age, nationality, scar type, and cause for mask therapy); mask materials; fabrication method; therapy details (daily hours of wearing, mean applied pressure, and time between injury and start of therapy); outcome measures (validated subjective and objective assessment tools); follow-up details; control groups; results; and adverse effects.

RESULTS

The literature search identified 102 articles, of which 3 articles met the inclusion criteria (Figure 1: PRISMA flow chart). Articles included were studies based on the clinical effects of a transparent face mask on facial scars or on facial scars after facial flap surgery with protruding flaps, measured by a validated tool. Excluded articles consisted of articles that described other types of masks (such as laryngeal masks and respiratory masks). Furthermore, 25 articles that described the use of a face mask were excluded because they did not use any validated measurement tool or because they solely described the fabrication process. Study characteristics are summarized in Table 1.

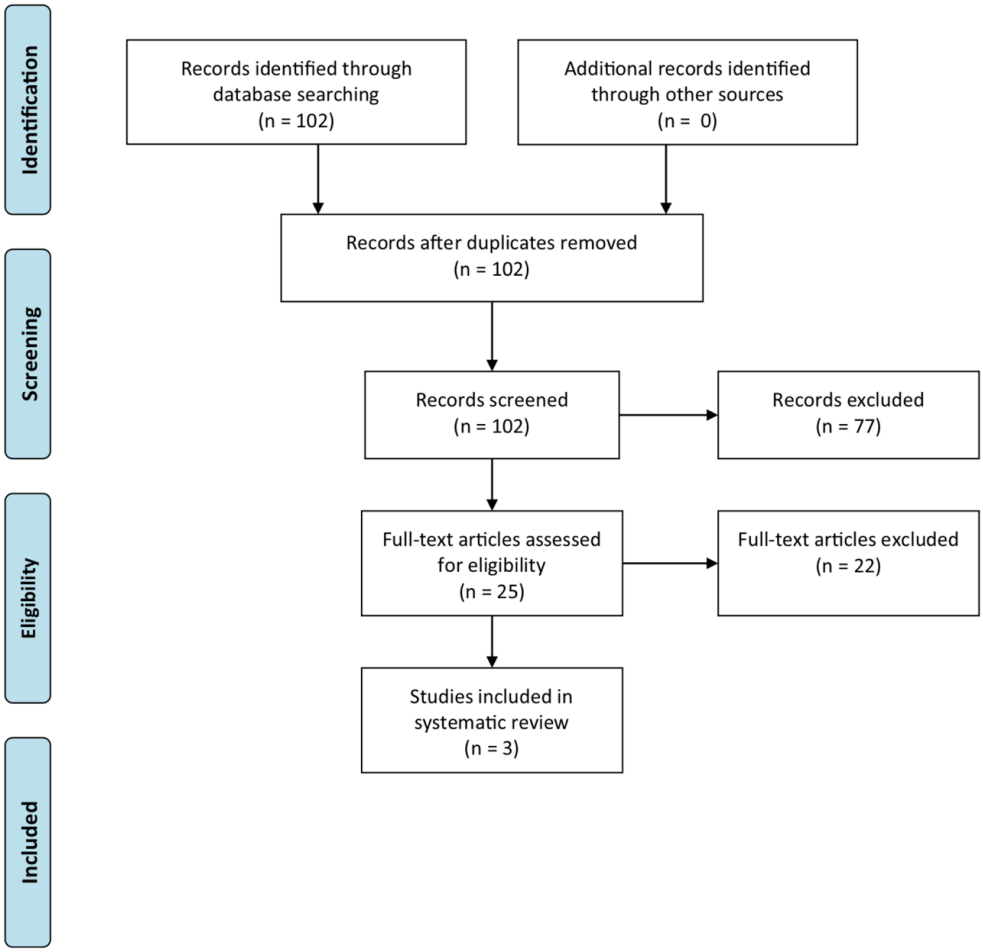


Figure 1. PRISMA 2009 flow diagram

All studies were performed in vivo. In total, 33 patients (both children and adults, age ranging from 1 to 80 years old) with hypertrophic scars or unsatisfying results after facial flap surgery (patients with facial hypertrophic scars and protruding skin flaps) were treated with transparent facial pressure masks. Study populations size ranged from 2 to 21 patients. All of the studies were observational studies and evidence was rated as Level 4 according to the Oxford Centre for Evidence-Based Medicine guidelines. No controlled trials were identified. The included articles originated from China (two) and the Netherlands (one) and were published in 2016 and 2017. Two articles described patients with hypertrophic scars caused by thermal or chemical burns[12,13] and one study[14] included patients with hypertrophic scars and protruding skin flaps after facial flap surgery.

Fabrication process and materials used

All three studies varied concerning the process and materials used to fabricate the face masks. The two studies by Wei et al.[12,13] used non-contact scanning of the face followed by 3D printing for fabrication. In these studies, 3D scanning and adjusting took place by use of a computerized software model, after which masks were directly printed by means of biocompatible medical 3D printing materials.

In the study by Kant et al.,[14] the face mask was fully custom fabricated by an experienced prosthetist using a plaster imprint (negative model) and molding (positive model) technique. All masks were reported to have an adequate pressure distribution between the mask and the face, regardless of the fabrication technique.

In all studies, a silicone inner liner was added to the mask.

Exerted pressure underneath the mask was monitored in the two Chinese studies[12,13] by means of validated pressure sensors. The average pressure ranged from 9.34 mmHg to 22.62 mmHg. Mask therapy commenced between 3 weeks and 6months after injury or surgery. In one study, this period was not described.[13]

Follow-up information

Follow-up ranged from 1 to 25,7 months. Daily therapy duration was aimed between 10 and 20 hours. However, patient compliance to daily therapy wasn't objectively evaluated in any of the studies.

In one study consisting of 10 patients with active hypertrophic scars caused by extensive facial burns (>2,5% the total body surface area), a control group was formed.[12] The treatment group consisted of five patients who were immediately treated and the control group consisted of five patients who were observed for 1 month before commencement of the therapy.

Clinical effects

One study[14] reported outcomes solely by means of a validated scar assessment scale, the Patient and Observer Scar Assessment Scale (POSAS). This scale is designed for assessment of scars by both patient and clinician. It consists of two scales (the Patient and Observer Scale), each rating scars at six items and at an overall opinion from the clinician and patient between 1 and 10. The Total POSAS Score is the sum of the total Patient and Observer Scores. The study by Wei et al.[13] only used an objective measurement for measuring scar thickness by means of an ultrasound instrument. The article by Wei et al.[12] also reported scar thickness measurements by means of ultrasound, scar hardness by means of a durometer and the POSAS.

Concerning the two studies that used ultrasound for scar measurements, the study by Wei et al.[12] measured scar thickness in six facial zones (forehead, eyes, nose, mouth, cheek, and chin). This study contained a 1-month delayed treatment group. In the delayed treatment

group, scars thickness increased significantly during delay. After 1-month treatment, scar thickness decreased significantly in this group. Statistically significant improvement in scar thickness was found on the forehead, eyes, nose, and mouth after 1 month of treatment in both groups. The study also reported significant decrease in scar hardness after 1 month of follow-up in both groups.

In the study by Wei et al.,[12] one item of both the Patient and Observer Scale (the overall assessment of the scar) decreased significantly for all patients after 1 month of treatment. For the Observer Scale, the overall score decreased significantly in all patients. In the delayed treatment group, the overall scar assessment item and the total score of the Observer Scale significantly increased after delay and decreased after 1 month of treatment.

Finally, this study showed a positive linear relationship between changes for scar thickness and the pressure applied locally (Pearson correlation coefficient r=0.34).

Surface area demonstrated a statistically significant improvement between start and end of therapy in the Patient Scale of the POSAS in patients with hypertrophic scars and protruding flaps after facial flap surgery.[14] Furthermore, this study reported a statistically significant improvement in scar itchiness, pigmentation, pliability, and thickness. Concerning the Observer Scale, thickness, pliability, and surface area improved significantly. Furthermore, this study showed a significant decrease in the mean Patient Scale and Total POSAS Score between start and end of therapy. The mean Observer Scale did not show a statistically significant decrease.

The other study by Wei et al.[13] showed a decrease in average scar thickness after 1 month and after 3 months of treatment by ultrasound measurements compared to baseline in both patients. However, these differences in thickness were not reported as statistically significant.

Adverse effects and complications

Wei et al.[13] reported problems with scar flattening around the mouth, an area where the child moved a lot for speaking, which negatively affected the pressure around the mouth of the mask. No complications were reported in any study.

Table 1. Study characteristics

Reference		Study Population				Technical details		Therapy details		
Lead author name and publication year	*Study Design*	*Number of patients*	*Age*	*Nationality*	*Scar type*	*Mask Materials*	*Fabrication method*	*Wearing*	*Pressure*	*Timing*
Kant et al.[14]	Case series	21	34 – 80	Dutch patients	Protruding skin flaps and hypertrophic scars after facial flap surgery	Transparent polycarbonate material with a silicone inner liner	Conventional positive and negative molding	10-12 hours of daily wearing	Targeted pressure was 20 mmHg, not objectified in this study	Therapy started between 1 and 3 months after surgery took place
Wei et al.[12]	Case series	2	1 and 6 years	Chinese patients	Hypertrophic facial burn scars	Biocompatible and transparent 3D printing material with a double silicone inner liner	3D scanning and printing.	20 hours of daily wearing	Average pressure was 11,3 mmHg in one of the two patients measured. The type of measurement device is not described	It is not mentioned when therapy commenced
Wei et al.[13]	Cohort study	10	14 – 50	Chinese patients	Hypertrophic facial burn scars	Biocompatible and transparent 3D printing material with a silicone inner liner	3D scanning and printing	20 hours of daily wearing	Average pressure was 13,32 mmHg	Therapy started between 21 days and 6 months after injury

Reference	Outcome measures	Follow-up period	Control group	Main Results	Summarized clinical effects	Adverse effects	Level of Evidence
Kant et al.[14]	POSAS scores	46 weeks, range: 11 – 112	Absent	Components of the Patient, Observer and Total POSAS score decreased significantly. The mean Total POSAS score decreased from 48.87 (SD: 14.93) to 30.13 (SD: 9.82) (P<0.001) and the mean overall Patient Score decreased from 31.10 (SD: 9.76) to 16.29 (SD: 7.43) (P<0.001). The mean Observer score showed a reduction from 17.76 (SD: 7.38) to 13.86 (SD: 4.99) (P= 0.051). Furthermore, statistical significant (P<0.05) improvement in itchiness, pigmentation, pliability, thickness, and relief	Significant improvement in Total POSAS and Patient Score of the POSAS. Also, significant improvement in scar thickness, pliability, and surface area at both the Patient and Observer Scale of the POSAS. Additionally, significant improvement in scar itchiness and pigmentation at the Patient Scale	None reported	Level 4
Wei et al.[12]	Scar thickness, measured by ultrasound	3 months	Absent	Non-significant decrease in average scar thickness in both patients after 1 month and after 3 months compared to pre-treatment. No P-values were presented	No significant scar improvement	Problems with scar flattening around the mouth	Level 4
Wei et al.[13]	Scar thickness, measured by ultrasound, scar hardness by means of a durometer and POSAS scores	1 month	5 patients were immediately treated and 5 patients were treated 1 month later	Significant decrease in scar thickness at the forehead, eyes, nose and mouth in both groups (P<0,05). Positive correlation between applied pressure and reduction of scar thickness (R=0,34). Significant decrease in scar hardness in all patients (P<0,01). Reduction in items of the Patient and Observer POSAS scores: overall score (P<0,01) at the Patient Scale, overall score and total score at the Observer Scale (P<0,01) for all patients. Total and overall score of the Observer POSAS scale increased significantly after delay and decreased with 1-month of treatment (P<0,05)	Significant improvement in scar thickness and hardness measured by ultrasound and durometer. Also, significant improvement at the overall scar score of the Patient Scale and at the Observer scale of the POSAS. Furthermore, significant improvement at the Total Score of the Observer Scale	None reported	Level 4

DISCUSSION

This literature review aimed at outlining and critically evaluating the available evidence concerning the clinical effects of facial pressure masks in the treatment of hypertrophic scars.

With respect to these clinical effects, two of the three studies reported significant improvement on scars and facial flaps assessed by means of both subjective and objective measurements: ultrasound, durometer, and POSAS. The third study showed a reduction in scar thickness after 1 and 3 months; however, this difference was not statistically significant. No severe adverse effects were reported in the studies.

Evidence that was reviewed was limited to observational studies (one cohort study and two case series). Furthermore, patient populations were small, follow-up periods were short, and only study included a control group. Because of these limitations, it remains difficult to draw a substantial conclusion regarding clinical effective- ness of transparent facial masks.

Transparent facial pressure masks have been used for over three decades predominantly for the treatment of hypertrophic scars after burns.[1] Patients who are eligible for face mask therapy are required to be mentally stable enough to wear a face mask for several months and in some cases for over 2 years. Therefore, it is considered to be an extraordinarily demanding therapy and known to challenge patients' compliance.[15–17] Therefore, the scarcity of clinical evidence about the effects of face masks is understandable. However, a recent study about patients' satisfaction with their facial appearance after finishing face mask therapy described that aesthetic results to remain stable in a 5-year follow-up period with a study population of 87 patients.[18] However, this study did not describe the clinical effects of face masks.

Although the existing evidence about the clinical effects is limited, transparent facial pressure masks are the only modality for treating severe burn-related hypertrophic facial scars using mechanical pressure. Accordingly, face mask therapy is still the main treatment for severe facial scars. However, other modalities including microneedling, (sub)dermabrasion and fractioned laser therapy are also used for improving (less severe) hypertrophic facial scars in current clinical practice.[19–23]

In contrast, the use of mechanical pressure therapy on anatomic locations other than the face is well-documented.[24–27] It has been shown to be an effective modality, hypothesized to work by decreasing blood flow and reducing collagen synthesis as a result. Another suggested effect caused by pressure therapy is hypoxia, resulting in fibroblast degeneration and loosening of collagen fibrils.[28,29]

The suggested scar enhancing effects of facial pressure therapy are based on exerting a certain amount of pressure. There is no consensus about the exact amount of needed pressure. In an article by Candy et al.,[32] it is stated that applied pressure needs to be at least 24–25 mmHg to overcome capillary pressure in scar tissue. In other studies, lower pressure

dosages also seemed acceptable and effective.[24,31] Also, the suggested duration the mask should be worn daily varies in literature.[2,32,33]

In the studies included in this review, all face masks contained an inner layer of silicone gel. The rationale behind this was to add or optimize pressure in certain facial areas. Silicones are a well-known modality used in the treatment of scars.[30,34] Silicone gel sheet therapy has been suggested to be effective in reducing scar thickness and improving pliability by its proposed occlusive effects on scars, affecting skin hydration and decreasing capillary activity, and thereby reducing collagen deposition.[35–40]

However, available evidence about the combined effect of both pressure garments and silicones on hypertrophic scars is still inconclusive.[30,39,40]

CONCLUSION

This review provides an overview of the current evidence for the clinical effects of transparent facial pressure masks in the treatment of hypertrophic facial scars and protruding flaps. Two of the three studies described statistically significant improvement in facial scars and facial skin flaps, both subjectively and objectively measured. However, these studies had substantial limitations. Therefore, further clinical research with larger study populations and including control groups is necessary to confirm the suggested clinical beneficial effects of face masks on hypertrophic facial scars and protruding skin flaps.

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CHAPTER 5

5

Manual fabrication of a specialized transparent facial pressure mask: a technical note

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ABSTRACT

Background and aim*:* The objective of this study was to describe the manual fabrication of a transparent facial pressure mask for treating facial deformities. The mask combines the use of a silicone inner liner and mechanical pressure in the facial region.

Technique*:* A negative mold is formed by covering the face with plaster. Manipulation of soft tissue is a crucial part in this process. After hardening and removal of the negative mold, the positive mold is formed and dried. Next a rolled silicone sheet is placed over the positive mold in a vacuum environment. Subsequently, the silicones are vulcanized. Then the rigid outside of the mask is created. The silicone inner liner and outside shell are then affixed.

Discussion*:* This described technique results in accurate facemasks with precise fitting. During therapy, the mask is adjusted multiple times to keep excellent fit, as remodeling of scars and deformities takes place.

Clinical relevance*:* Facemasks are a reputable therapeutic modality to reduce excessive facial scarring. They require excellent fitting to give pleasing results. To provide a better understanding of facemask therapy, this study describes the manual fabrication technique.

Keywords: Facial deformities, facial pressure therapy, hypertrophic scars, orthotics, fabrication techniques

BACKGROUND

Facial burns are known to cause severe physical and emotional impairment. In many cases, rigid hypertrophic scars and contractions develop as a result. Until the 1980's, roughly the elastic 'Jobst hood' (Beiersdorf Jobst Inc. Charlotte, NC) was the norm in conservative treatment of these scars. Since then this technique has been replaced in many cases by the rigid transparent plastic face mask.[1-4] Multiple types of masks, differing in material and fixation methods are now used in daily practice.[5]

There are two basic principles that that have laid the ground stone for the development of this mask. The first principle is based on exerting mechanical pressure on the face. Mechanical pressure has proven that it can lead to flattening of scars.[6-9] The principal (hypothetical) effect of exerted pressure on the skin is hypoxia. Hypoxia can result in fibroblast degeneration and reduction of collagen synthesis.[10,11] Another suggested effect of pressure therapy is reduction of edema.[12,13] Furthermore, mechanical pressure may facilitate scar maturation and reduce pain and itchiness.[14,15]

The second principle is the use of silicones in scar therapy. Silicones have become standard practice in the treatment of scars. Silicone sheets and gels have demonstrated to have scar improving effects, primarily by smoothening and flattening of scars probably caused by an increase of hydration.[16-19] Although evidence is limited, combined use of both silicones and pressure therapy is suggested to deliver greater scar enhancing results than pressure therapy alone.[13,20]

A facemask combining silicones and pressure therapy has proven to deliver long-lasting results in a non-invasive way with limited adverse effects.[2,9,21] It is a reliable modality that is suggested to be effective in avoiding surgical revision of protruding hypertrophic scars. Furthermore, by means of accurate manual refinements of soft tissue parts during the molding process this mask provides an optimal fitting.

Aim

In our specialized scar outpatient clinic of the Maastricht University Medical Center (MUMC+) we presume a combined use of pressure and silicones applied in a facemask is the most effective way of treating hypertrophic facial scars and facial deformities. This therapy has recently proven to be effective as an adjuvant therapy for treating unaesthetic results after facial flap surgery.[22] In this article the fabrication process of this facial mask is put apart. The study was approved by the local ethics committee of the MUMC+.

TECHNIQUE

Part one: fabrication of the negative mold

Duration: approximately 50 minutes.

The patient is positioned in an upright seated position. Vaseline is now applied to the face to prevent plaster from sticking to the skin and facial hair. The area where the scar or deformity is located is marked on the face with a copying pencil (Faber-Castell®). In this way, this marking is mirrored in the negative mold. Sedation during fabrication is not necessary. However, for young children (generally under 6 years of age) sedation is desirable. When sedation is necessary, patients will be placed in High Fowler's position (a semi-upright position). Nasal intubation is preferred, although the mouth has to be closed when fabricating a full-face facemask. When these steps for sedation of young children are followed, fabrication of the negative mold is comparable to the normal situation when patients are awake. Relaxation of the facial tissue during general anesthesia will be less of a problem at young children because of the absence of skin laxity in general.

Plaster (Cellona®) is cut in strips varying in width and length to copy each facial contour and detail as precisely as possible. The plaster strips are now wetted and the orthotist now proceeds with covering the face in two layers of plaster strips. Covering the face starts cranially working the way down and laterally progressively. Nostrils and the oral cavity are kept free of plaster to ensure patients' air passage.

During the application of the plaster strips, the patient is advised not to move and to prevent facial expressions, in order to reduce irregularities in the negative mold. During this process the hardening plaster and underlying soft tissue parts are steered. The expected result of this shifting of the plaster and underlying tissue is to increase the pressure on the shifted facial area where additional pressure is desirable. This occurs when the orthotist manually shifts the soft plaster just before it hardens. Consequently, because of this manipulation the soft tissue under the plaster shifts. The orthotist holds this position for a few moments until the plaster hardens. When the plaster hardens, the plaster and shifted soft tissue underneath the plaster remain in the desired position the orthotist put it. Eventually, this position can be found in the positive mold and in the eventual Uvex outside of the mask.

Before removal of the negative mold the location of the buckle anchors that will be attached later on in the process will be marked. From these reference points the length of the elastic Velcro straps will be determined. The resulting negative mold is now carefully pulled from the face and the face is cleaned from plaster residues with water and soap (Image 1a).

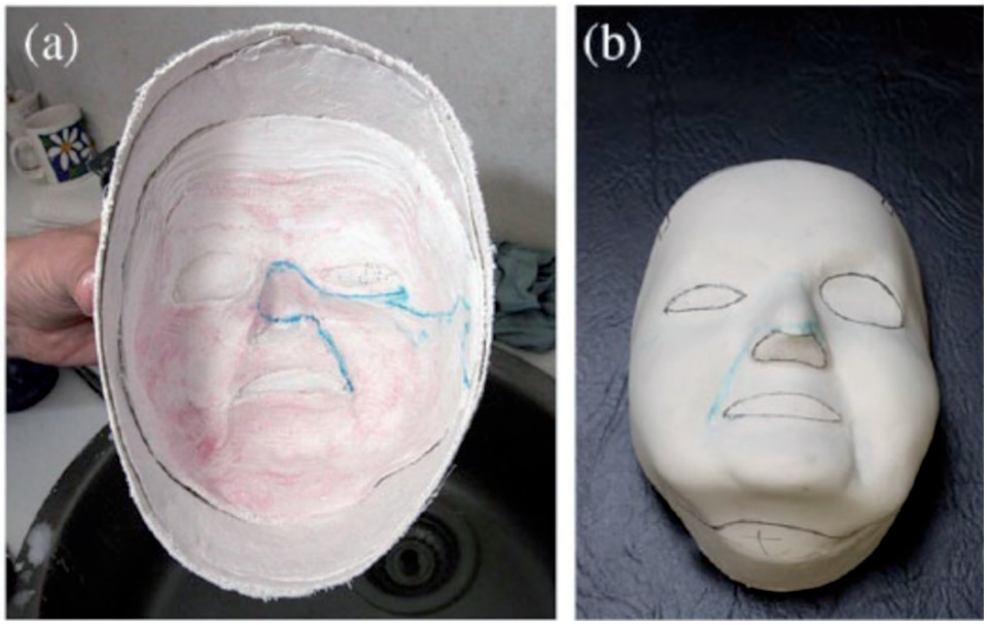


Image 1. (a) The negative mold obtained after part one of the fabrication process. (b) The positive mold after part two of the fabrication process.

Part two: fabrication of the positive mold.

Duration: approximately 2 hours.

The holes around the eyes, nostrils and mouth are sealed with plaster strips and the sides of the negative mold are raised with plaster strips, making it possible to fill it with liquid plaster later in the process. Then in a container with two liters of tap water approximately 400 grams of porous plaster (Otto Bock®) is mixed. The resulting mixture is still very liquid and contains a lot of air bubbles. Therefore, the container is placed on a vibration machine (Wasserman Dental-Maschinen GmbH KV-26) to remove air bubbles out of the mixture. After five minutes of vibration the mixture is now poured into the negative mold. A metal cylindrical bar fixed in a plastic cup is placed into the mixture in order to secure it in the vise. After approximately 20 minutes, the mixture has become solid.

The positive plaster mold is then carefully dismantled. This mold now contains all the contours and irregularities of the facial scars and deformities. Subsequently these irregularities and deformities are smoothened with a rasp, scrapers and mesh. In this way the orthotist corrects and reduces the thickness of the hypertrophic scars or facial reconstruction site out of the mold.

By means of sand paper with very fine grit the mold is wetly sanded. The positive mold is now finished and dried in an oven at 55 degrees Celsius for 2-3 h (Image 1b).



Image 2. The rolling process of the silicones

Part three: production of the Uvex mask

Duration: approximately 14 hours.

In this part the final mask is fabricated. This process consists of two parts. The first part is customization of the silicone inner liner. This material contains two components of medical silicones (OttobockÒ HTV (High Temperature Vulcanizing)-silicones, 35 Shore), which are merged and rolled together (while air bubbles are removed) until a thickness of 1mm is reached (Image 2). Then the silicones are applied to the positive plaster mold on a vacuum forming platform and air between the plaster model and the silicone liner is removed (Image 3). The silicone liner is now placed in an oven at 55 degrees Celsius during eight hours until the material is vulcanized.

The second part consists of fabrication of the rigid Uvex outside of the mask. An Uvex polycarbonate plate with a thickness of 4mm is heated in an oven at 120 to 160 degrees Celsius. The plate is fixated in a double sandwiched ring system. When the Uvex plate is sufficiently heated and becomes pliable it is applied to the positive mold and placed on the vacuum forming platform and air is removed). The outside of the mask is now formed.

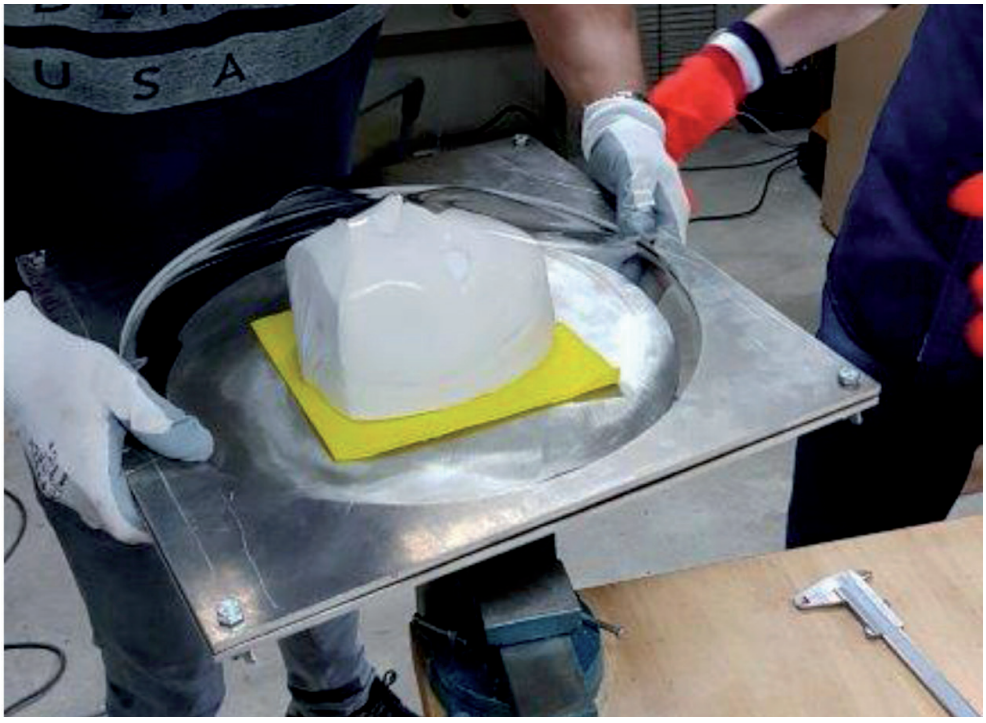


Image 3. Silicones are placed on the positive mold and air is removed.

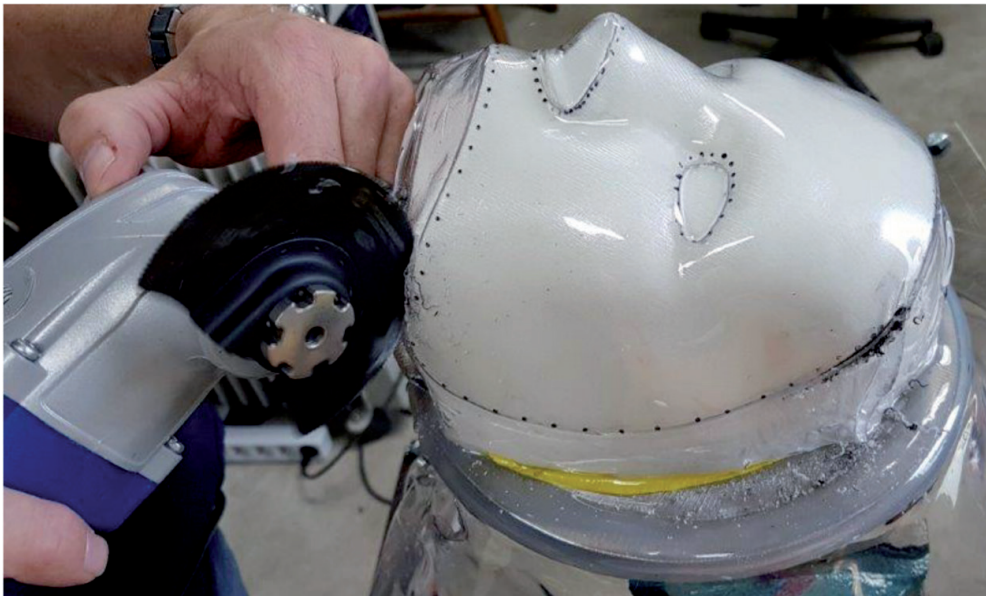


Image 4. Finalization of the fabrication of the rigid outside of the facemask.



Image 5. End product of the facial pressure mask. Note: the head bandage with its Velcro straps attached to the Uvex isn't shown on this image.

Next the edges of the silicone liner and the Uvex are trimmed with a hand-held circular saw and smoothened with sandpaper (Image 4). Then buckle anchors with nickel loops are attached to the Uvex outside. The Velcro straps on the silicone go through the loops on the Uvex outside. In this way the two parts are combined and the silicones are fixated to the transparent plastic shell (Image 5).

Part 4: fitting and delivery of the facemask

Duration: approximately 1,5 hours.

Now the facemask can be delivered and fitted onto the patient. In most cases a five-point design is chosen for an optimal and even pressure distribution.[6] Then the patient applies and fits the mask and pressure on the face is visually checked by looking for blanching of scars by adjusting the tightness of the bandages placed through the loops. Pressure exerted underneath the mask can also be measured by a means of a pressure sensor.[22] As remodeling of hypertrophic scars and deformities progresses during therapy, on average,

the mask is adjusted seven times in total in order to provide the most optimal pressure distribution at all times during therapy. As a result of remodeling of scars during therapy pressure underneath the mask decreases and fitting of the mask alters. Modification of the mask is aimed to keep fitting and pressure adequate. During follow-up visits, the treated areas are observed and the effect of the mask on the skin is assessed. An indication for facemask modification is when the height or thickness of the treated zone is significantly diminished since the last visit. This can be checked by means of the absence of blanching (as a result of decreased pressure) on the treated area when the mask is put on. When the thickness of the treated zone is significantly decreased, the technician uses sandpaper and other scraping tools to remove small parts of plaster on the positive mold at the same place the thickness decreased on the skin. Then, the outside Uvex of the mask is heated by means of a small blow dryer and placed on the altered positive mold. Next, the mask is put on after cooling of the Uvex and when blanching is observed, modification of the mask is completed. The main criterion for adjustment of the mask is maintaining adequate pressure underneath the mask (at least 20 mmHg).

DISCUSSION

In this technical note the fabrication process of a unique transparent facemask for treating facial hypertrophic scars and deformities is described. Pressure mask therapy is a very demanding therapy and therefore only highly motivated patients are selected for this therapy. Another limitation of this technique is that in some cases the silicones can cause skin irritation. Therefore, a steady build-up phase of therapy is advised (2 to 3 hours after 1 day, increased to at least 12 hours daily in the next 14 days). Also, patients should take apart and rinse the silicone inner liner by means of putting it in boiling water for 3 minutes once a day.

The mean total duration of facemask therapy mainly depends on the amount of hours of daily wearing, the severity and the extent of the treated zone, and the skin color type. The mean daily wearing is advised to be at least 12 hours. The mean total therapy duration is between 9 to 12 months for Caucasian patients with hypertrophic scars. Patients who have a dark skin type (Fitzpatrick 5 and 6) usually require 6 extra months of therapy. For patients who are treated after facial flap surgery, the mean wearing time is about 12 to 18 months because in general flap skin is more elevated than hypertrophic scars. The time between mask modifications is also dependent on the same parameters. However, in general the first modification is made 4 to 6 weeks after start of therapy. Then, once every 2-3 months modifications are done.

Although scanning of the face by means of 'computerized surface scanning' and 3D-printing has gained popularity recently, this technique hasn't become standard practice

in the Netherlands yet. Furthermore, manipulating and steering soft tissue parts manually during the molding process is crucial in fabricating a functional mask, which hasn't been described earlier. This manual process isn't comparable in efficacy yet to computerized surface scanning, as corrections aren't included in the manipulation and manufacturing process yet.[2,9] The process of tissue steering is able to result in superior pressure distribution of the mask on the face when compared to fabrication of a facemask by means of scanning of the face and 3D printing. However, to reproduce the technique of tissue steering it is helpful an orthotist/prosthetist who is familiar with the technique to show and teach it. For reproduction of this technique technicians need to understand the direction the hardening plaster needs to be moved during formation of the negative mold. For example, on areas with skin contractures that cause downward traction on the face, the solidifying plaster and tissue underneath must be shifted in the opposite direction in this specific area. Estimation of the extent of the manipulation is subject to a rather steep learning curve; there will be a quick increment of skill. The described fabrication technique allows manual modifications to take place with submillimeter precision because of the possibility of very precise and minimal removal of plaster on the positive mold. The described technique in this article can deliver very precise molds, is minimally invasive for patients and can be performed in smaller practices with no advanced 3D-printing machines. Also, pressure mask therapy has proven to be an effective therapy that can replace recurrent surgery of scars or surgical thinning of flaps in some cases.

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CHAPTER 6



A new treatment for reliable functional and aesthetic outcome after local facial flap reconstruction: a transparent polycarbonate facial mask with silicone sheeting

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ABSTRACT

Background: Facial flap surgery predominantly leads to good functional results. However, in some cases it can cause unsatisfactory aesthetic results. They include persistent erythema, pincushioning and development of hypertrophic scars. Conservative, reliable treatment for facial flaps is lacking. Pressure and silicone therapy have proven to result in significant improvement in scar erythema, pliability and thickness in post-burn hypertrophic scars. By combining these therapies in a facial mask, the aesthetic outcome of facial flaps could be improved.

Objective: In this retrospective study, the efficacy of a unique transparent face mask containing silicone sheets on the aesthetic outcome of postsurgical facial flaps, is assessed.

Methods and materials: 21 patients were assigned to facial pressure mask therapy after they underwent facial flap surgery between July 2012 and September 2015. Patients were treated for a mean duration of 46 weeks. The effects of pressure mask therapy were examined by means of the Patient and Observer Scar Assessment Scale (POSAS).

Results: All POSAS components showed a reduction between start and end of therapy, while itchiness, pigmentation, pliability, thickness and relief of the flap improved significantly ($P<$ 0,05). Mean Total and Patient Score showed significant reduction between start and end of therapy.

Conclusion: This study shows that a facial pressure mask layered with silicone results in noticeable flap improvement with a long lasting result.

Keywords: Facial flap surgery, pressure mask, silicones.

INTRODUCTION

Worldwide, the number of people that suffer from skin cancer is increasing every year. Surgical resection is the standard of care in facial plastic surgery.[1] One of the standard procedures to close facial defects are local or regional soft tissue flaps.[2]

In order to cover a defect and to restore facial anatomy as well as possible, many options for surgical flaps exist. Well-known and commonly used flaps include: Abbe, rhomboid, forehead, bilobed and glabella flap.[3, 4] All of these flaps are known to mostly give good aesthetic results. However, aesthetic outcome may not be satisfying in all cases. Most adverse effects after repair of defects in the face by flaps are mild. They include persistent scar erythema, pincushioning and development of hypertrophic and widened scars.[1,5-11]

Current therapies for flap revision after unsatisfactory aesthetic results include photothermolysis, laser resurfacing, liposuction, injections with corticosteroids and surgery.[1, 8,10,12] These treatment modalities are invasive, while studies evaluating long-term efficacy of these methods on flaps are lacking. Reliable conservative therapy with long-term stable result is the hiatus in current clinical practice.

Two non-surgical procedures that have been the cornerstone in treatment for hypertrophic and keloid scars for many years, are pressure garment therapy and therapy with silicones. [13-16]

We hypothesize that combination therapy of silicones and pressure could lead to reducing edema and rigidity as well as it could cause flattening of the facial flap, as an effect of applying mechanical pressure. Additionally, combination therapy could have scar enhancing and maturation accelerating properties, as effects of both silicones and pressure. In this way, silicone and pressure therapy could act in synergetic fashion to improve aesthetic outcome of thickened facial flaps with unsatisfying scars.

In order to incorporate pressure and silicone therapy, we believe a specialized pressure mask with a silicone layer as inner lining can improve pliability and color and reduce thickness, edema and irregularities of flaps exposing these qualities. In this study, the efficacy of a unique transparent face mask containing silicone sheets on the aesthetic outcome of postsurgical facial flaps is assessed.

MATERIALS AND METHODS

Design

In this retrospective study conducted between July 2012 and September 2015 twenty-one patients were assigned to facial pressure mask therapy with silicones after they underwent flap surgery. Patient characteristics and follow-up information can be seen in Table 1.

Table 1. Patient characteristics

Age at start therapy (years)	
<40	2
40 - 49	3
50 - 59	5
>60	11
Mean age (years)	57
Min	34
Max	80
Gender	
Male	9
Female	12
Follow-up time (weeks)	
10 - 20	5
20 - 40	6
40 - 60	3
60 - 80	3
80 - 100	3
> 100	1
Mean duration of treatment (weeks)	46
Min	11
Max	112

Table 2. Surgical flaps used

	No.
Abbe flap	1
Bilobed flap	3
Forehead flap	7
Glabella flap	2
Limberg flap	1
Transposition flap	3
Rotation flap	1
Z-plasty	3

Table 3. Reason for flap surgery

	No.
Reconstruction of the face after removal of:	
Basal cell carcinoma	13
Melanoma	2
Radical scar excision	3
Sarcoma	1
Squamous cell carcinoma	2

In order to improve the facial skin functionally and aesthetically at the autologous transplantation site (the flap) after surgery, treatment with a transparent polycarbonate facial pressure mask with a silicone layer as inner lining was applied. The different types of surgical flaps used, and the reason for surgery are documented in Table 2 and Table 3, respectively.

Patients

Eligible patients were men or women who had received facial flap surgery. Only patients in whom the flap clearly protruded from the normal skin, even after thinning of the flap, were included. Only patients that didn't receive any prior therapy for their facial flap were included. If these patients were physically and mentally able and motivated to wear a polycarbonate facial pressure mask for at least 12 hours a day, they were suitable and assigned for facial mask therapy. Therapy started when the operated skin passed into the maturation phase of wound healing. Therefore, therapy started between one month and three months after flap surgery took place. The study conformed to good clinical practice guidelines and followed the recommendations of the Declaration of Helsinki. The protocol was approved by the local ethics committee.

Procedures

From July 2012 to September 2015, 21 patients were assigned to therapy with a transparent polycarbonate facial mask with a silicone layer inside. The mask was fully custom fabricated by an experienced prosthetist.

In order to apply the required pressure to the flap underneath the mask, Velcro straps were attached to the polycarbonate outside of the mask. Targeted pressure was 20 mmHg. Pressure under the mask was measured by means of an aerial pressure sensor and pump.
Patients were advised and insisted to wear the mask as long as they possibly could endure, with the objective to wear the mask at least twelve hours every day. When an adequate and satisfying aesthetic result was reached, patient and doctor mutually decided to stop therapy. Compliance was evaluated and if patients were incompliant, mask therapy was stopped. Therapy was also stopped if patients reported a high level of discomfort. All included patients of the current study completed the therapy. The mean duration of the therapy was 46 (11 - 112) weeks. During this period, patients returned for follow-up every three to four months at the outpatient clinic. The flaps were assessed at the scar clinic by a team of experts in scar treatment and management including a senior plastic surgeon, a resident plastic surgeon, an prosthetist and a physiotherapist. At each visit, POSAS forms were filled out and photographs were taken. Facial mask pressure was monitored on each visit and when necessary, adjustments of the mask were performed by the prosthetist.

Assessment of flap

Because no objective and validated tool for assessment of thickened facial flaps exists, we used the previously validated Patient and Observer Scar Assessment Scale (POSAS) for evaluating facial skin and scars at the transposition site.[17] At most two weeks prior to fabrication of the mask the facial skin and scars were first assessed. The flap was rated numerically on a ten-step scale by both the patient and doctor on six items. The Observer Scale rates: vascularity, pigmentation, thickness, relief, pliability and surface area. The Patient Scale consists of pain, itchiness, color, pliability, thickness and relief. Patients were informed to assess the facial reconstruction as a whole (both flap and scar together) not solely the scar, on the six components of the Patient Scale.

One of the reasons POSAS was chosen for flap evaluation is because it is the only scar assessment tool to include a component for patients to fill out. Furthermore, we chose POSAS because of its distinctive feature of reflecting subjective symptoms like pain and itchiness and because of its usefulness for everyday practice.[18-20]

On each visit, an expert and the patient independently filled in a POSAS form in order to assess the transposition site.

Data analysis

POSAS scores are presented as means with standard deviations. Those scores were compared with the use of One-Way ANOVA for significance in means. Two-tailed values of $P< 0,05$ were accepted as statistically significant. All analyses were performed using the statistical software program SPSS 22.0.

RESULTS

Outcome Mean Patient, Observer and Total POSAS score

All flap sites were evaluated prior to or on the day the mask therapy started by means of POSAS scores. POSAS scores at baseline and at the end of therapy were compared by means of One-Way ANOVA.

Figure 1 and Table 4 show mean POSAS scores decreased significantly ($P< 0,05$) between baseline and end of therapy, with a total of 18,72 points.

Patient Scores also decreased significantly ($P< 0,05$) with a mean total of 14,81 points, between baseline and end of therapy (Table 5).

Observer Scores showed a mean reduction of 3,90 points between baseline and end of therapy. However, this reduction wasn't statistically significant (Table 6).

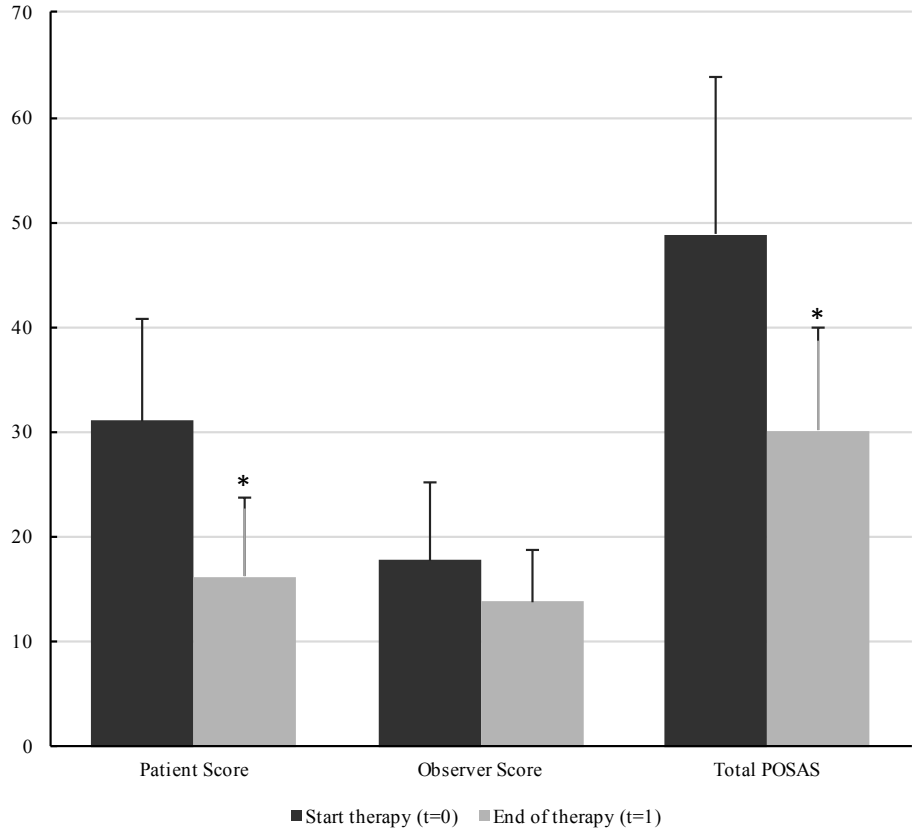


Figure 1. Mean patient,observer, and total POSAS scores are shown at baseline and end of therapy. Statistically significant differences (*P*< 0.05) between means are marked by an *asterisk*

Table 4. Mean total POSAS scores

	Start therapy	*SD*	*End of therapy*	*SD*	*P value*
Total POSAS	48,86	14,97	30,14	9,82	<0,001

Table 5. Mean patient scar scores

	Start therapy	*SD*	*End of therapy*	*SD*	*P value*
Pain	2,48	2,21	1,38	1,32	0,060
Itchiness	3,62	2,42	2,10	1,81	0,026
Pigmentation	5,67	2,99	3,67	1,74	0,012
Pliability	5,90	2,64	2,86	2,01	<0,001
Thickness	6,81	1,81	2,86	2,01	<0,001
Relief	6,67	2,13	3,43	2,04	<0,001
			Overall Patient Score		
	Start therapy	*SD*	End of therapy	*SD*	*P* value
Patient Score	31,10	9,76	16,29	7,43	<0,001

Table 6. Overall observer scar scores

	Start therapy	*SD*	*End of therapy*	*SD*	*P value*
Vascularization	3,62	1,88	3,00	1,55	0,252
Pigmentation	2,14	1,42	2,00	1,05	0,713
Thickness	3,38	1,40	2,19	1,08	0,004
Relief	3,48	1,20	2,67	1,16	0,035
Pliability	2,95	1,43	1,90	1,09	0,011
Surface Area	2,57	1,63	1,95	0,87	0,132
			Overall Observer Score		
	Start therapy	*SD*	End of therapy	*SD*	*P* value
Observer Score	17,76	7,38	13,86	4,99	0,051

Patient compliance

At every follow-up visit, patients were asked how long they wore the mask. In general, patients declared they wore the mask for a mean time of ten to twelve hours a day.

Patient Scores

Table 5 and Figure 2 show the six characteristics of the Patient Score (pain, itchiness, pigmentation, pliability, thickness and relief) at start and end of therapy. All Patient Score components showed a decrease after baseline. The largest decrease was observed in thickness, with a mean reduction of 3,95 points at the end of therapy. Itchiness, pigmentation, pliability, thickness and relief showed a statistically significant reduction ($P< 0,05$) between baseline and end of therapy.

Observer Scores

Table 6 and Figure 3 show the six characteristics of the Observer Score (vascularization, pigmentation, thickness, relief, pliability and surface area) at start and end of therapy. Corresponding to the Patient Scores, all components of the Observer Score decreased after start of therapy. The largest decrease in Observer Score was seen in flap thickness, with a

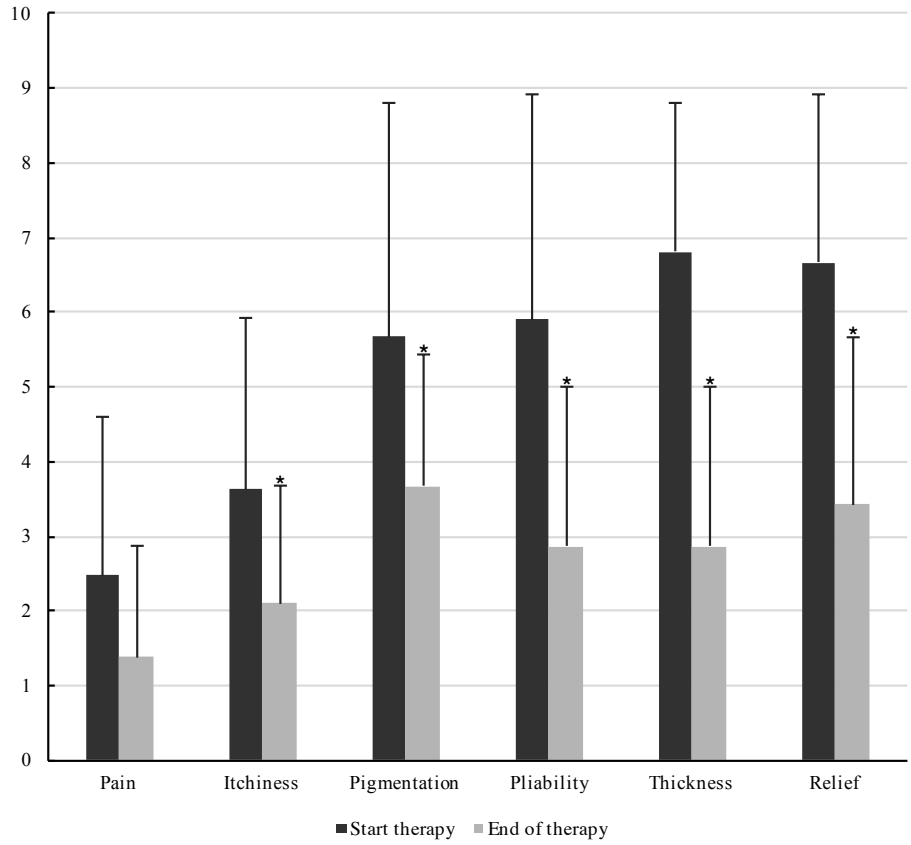


Figure 2. Components of the patient score as part of the total POSAS score are displayed at start and end of therapy. Statistically significant differences ($P < 0.05$) between means are marked by an *asterisk*

Table 6. Mean Observer scar scores

	Start therapy	*SD*	*End of therapy*	*SD*	*P value*
Vascularization	3,62	1,88	3,00	1,55	0,252
Pigmentation	2,14	1,42	2,00	1,05	0,713
Thickness	3,38	1,40	2,19	1,08	0,004
Relief	3,48	1,20	2,67	1,16	0,035
Pliability	2,95	1,43	1,90	1,09	0,011
Surface Area	2,57	1,63	1,95	0,87	0,132
			Overall Observer Score		
	Start therapy	*SD*	End of therapy	*SD*	*P* value
Observer Score	17,76	7,38	13,86	4,99	0,051

mean reduction of 1,19 points between baseline and end of therapy. Pliability, thickness and relief were the Observer Score components that showed statistically significant reduction ($P < 0,05$).

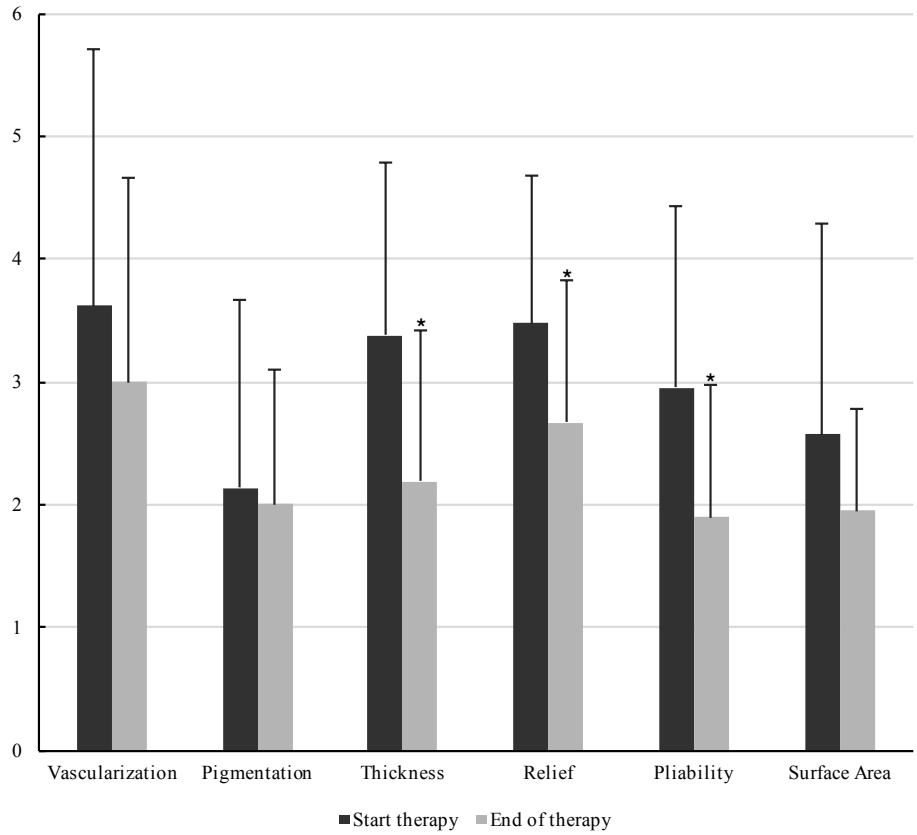


Figure 3. Components of the observer score as part of the total POSAS score are displayed at start and end of therapy. Statistically significant differences ($P < 0.05$) between means are marked by an *asterisk*

DISCUSSION

Pressure therapy

Mechanical compression by means of pressure garment therapy is a reputable modality to diminish collagen synthesis by reducing blood flow. Another hypothesis for the action of pressure therapy is a decrease in blood flow that causes hypoxia, resulting in fibroblast degeneration and loosening of collagen fibrils.[21, 22] Pressure garment therapy has also proven to result in significant improvement in scar erythema and thickness in post-burn hypertrophic scars.[23]

Since the 1980s roughly, various types of facial topical therapies have been described.[24,25] The transparent face mask or transparent face orthosis is a well-known and effective modality in the management of burn-related hypertrophic scars, as it has proven to reduce hypertrophic scars significantly.[26] For the fabrication process of the mask different techniques exist, among the formation of both manual and laser-generated molds.[24, 27]

When pressure therapy is applied to flaps in extremities, it reduces edema, and it helps to reconstruct and re-shape a defect after flap surgery.[28] Further evidence for pressure therapy in reshaping and correcting flaps can mainly be addressed as anecdotal.

Silicone therapy

Silicone therapy for scars has become standard practice among plastic surgeons, as there is good clinical evidence of the efficacy.[29, 30] One of the mechanisms to occur after application of silicones to the skin is an increase of hydration. As an effect of increased hydration capillary activity could decrease, thereby reducing local collagen deposition.[31] The clinical effects of increased hydration include improvement of pruritus, pain, pliability and decrease of edema.[32,33]

Combination therapy

However, the combined effect of pressure therapy and silicones is less studied. A randomized controlled trial (RCT) demonstrated silicones combined with pressure therapy were associated with significant improvement in pliability, thickness and vascularity of 38 hypertrophic burn scars.[34] A smaller pilot RCT showed inconclusive evidence on the potential beneficial effect of combination therapy on 30 hypertrophic burn scars.[35] A larger RCT demonstrated combined therapy to be effective in improving thickness of hypertrophic post-burn scars, compared to silicone and pressure therapy separately.[36]

In this study, we have shown that specialized facial mask therapy significantly improves aesthetic outcome after facial flap surgery. Mean Total POSAS scores showed a significant decrease between baseline and end of therapy (Table 4, Figure 1), with mean therapy duration of 46 weeks (Table 1).

Our results show patients' opinion about their facial reconstruction improved the most, with a significant improvement ($P< 0,05$) in itchiness, pliability, pigmentation, thickness, and relief (Table 5, Figure 2).

Overall observer POSAS scores didn't show significant reduction over time ($P= 0,051$). However, thickness, relief and pliability, as part of the Observer Score, did reduce significantly (Table 6).

To our knowledge, extensive and long-term studies about aesthetic outcome after facial flap surgery are lacking. Also, the effect of a facial pressure mask for improvement in aesthetic outcome for flaps hasn't been documented earlier. A limited amount of methods for aesthetic refinement after flap surgery is available in current clinical practice. Yet intraoperative intradermal injections of methylprednisolone can reduce flap edema, according to an animal study.[37] Other methods for aesthetic refinements after facial flap surgery include photothermolysis and laser resurfacing.

In accordance with our results, we believe our specialized pressure mask could be an effective modality to avoid surgical debulking or thinning of flaps, with small risk of complications and adverse effects in contrast to surgery.

Strengths and limitations

This is the first clinical cohort study to assess the usefulness of a facial pressure mask with silicones for enhancement after facial flap surgery. There were some limitations of this study. In absence of a flap assessment scale, the validated and well-known clinical scar assessment tool POSAS is the only instrument for flap assessment used in this study. Other qualitative methods for judging flaps are lacking in this study. Preferably, the current study would contain a larger study population and a control group. However, the vast majority of patients appear to have good aesthetic results after facial flap surgery, causing the remaining eligible patient group to be of small size. Additionally, the burden of wearing a pressure mask for at least twelve hours a day shouldn't be underestimated. The strength of this study is that it shows clearly that patients that wore a pressure mask had strong aesthetical improvement of the facial reconstruction site.

Further research

In order to assess aesthetic outcomes after flap reconstruction more extensive and precise, 3D digital flap volume measurements, as well as continuous pressure measurements underneath the mask would be of great value. Ideally, further studies would contain a control group, considering that information about the natural course of thickened, hypertrophic and unaesthetic facial flaps over time is lacking.

A major goal of this study was improvement in overall aesthetic outcome: restoration of flap skin close to normal skin. In this study patients showed a clinical significant result in aesthetic improvement of facial flaps.

CONCLUSION

In this study our aim was to assess the efficacy of a specialized facial pressure mask on the aesthetic outcome of facial flaps, since no other study examined the effect of facial pressure therapy with silicones on flap enhancement over a reasonable amount of time. Our retrospective study showed that a transparent facial pressure mask with silicones results in noticeable flap improvement with a long lasting result, particularly in our patients' view.

Acknowledgements

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None.

Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

For additional illustration images of two patients are displayed before, during and after mask therapy (Image 1-3, Image 4-8).

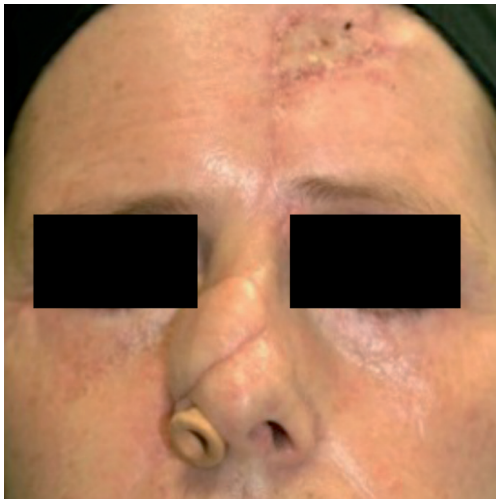


Image 1. A 50-year old female patient at the start of pressure mask therapy 4 months after surgery



Image 2. Same female patient with pressure mask applied during therapy



Image 3. Same female patient at the end of pressure mask therapy 9 months after surgery

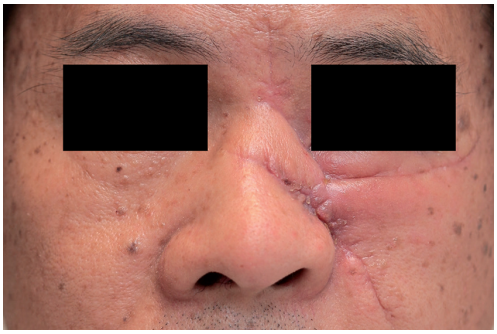


Image 4. A 48 year-old male patient at the start of pressure mask therapy 3 months after surgery (frontal view)



Image 5. A 48 year-old same male patient at the start of pressure mask therapy 3 months after surgery (oblique view)

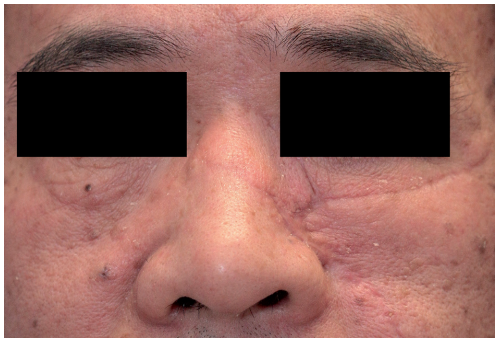


Image 6. Same male patient at the end of pressure mask therapy 15 months after surgery (frontal view).

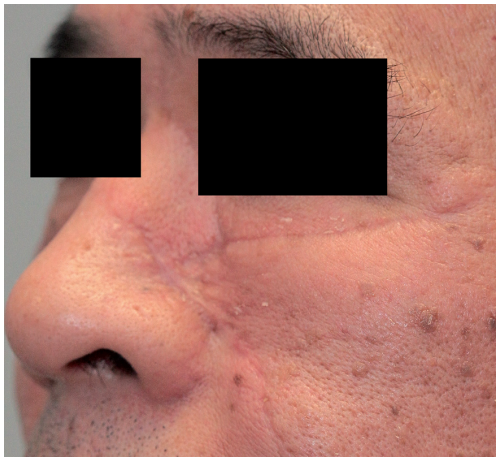


Image 7. Same male patient at the end of pressure mask therapy 15 months after surgery (oblique view).

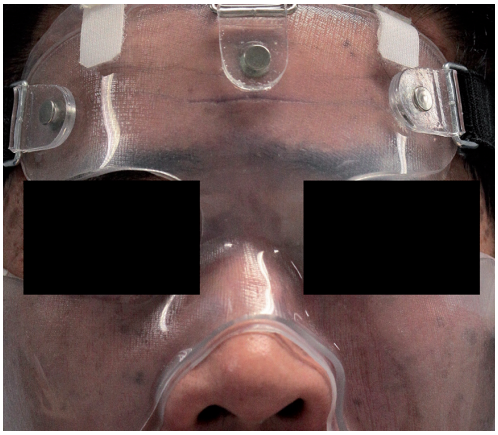


Image 8. Same patient with pressure mask applied during therapy.

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CHAPTER 7



Satisfaction with facial appearance and quality of life after treatment of face scars with a transparent facial pressure mask

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ABSTRACT

Background: Treatment of facial hypertrophic scars and deformities has developed from the use of elastic fabric hoods to transparent facemasks. The clinical effects of these masks have been described. However, the psychological impact of wearing such a mask is not well documented.

Aim: The aim of this study was to assess patients' satisfaction with their current facial appearance, to assess the end result of facemask therapy, and to assess the decision to have undergone facemask therapy by means of four different FACE-Q questionnaires.

Materals and methods: Out of the eligible 87 patients who completed the facemask therapy between January 2012 and November 2017, 42 filled out the questionnaires. These patients wore a custom-fabricated facemask because of facial hypertrophic scars and severe postsurgical facial irregularities.

Results: Patients who wore the mask 12 to 16 hours per day were significantly more satisfied with the end result compared with those who wore it 4 to 8 hours daily. Also, patients who wore the mask 8 to 12 and 12 to 16 hours each day were more satisfied to have undergone therapy compared with those who wore it 4 to 8 hours daily. Furthermore, patients who finished therapy 3 to 4 years and 4 to 5 years ago reported a significant higher satisfaction with facial appearance compared with those who completed therapy in a time period shorter than 1 year ago. Patients who finished therapy 3 to 4 years ago reported higher satisfaction with their facial appearance compared with those who finished therapy 2 to 3 years ago. Additionally, the Patient and Observer Scar Assessments Score (POSAS) showed a significant reduction between start and end of therapy.

Conclusion: This study shows facemask therapy to result in long-lasting stable results. It also shows a longer daily wearing of the facemask to result in the highest satisfaction according to patients.

Keywords**:** facemask, scars, quality of life

INTRODUCTION

Posttraumatic and postsurgical facial scars can cause a severe psychological, emotional, and social burden for patients.

Facial pressure mask therapy has proven to be an effective therapy for treating hypertrophic scars after burns since 1979, by exerting mechanical pressure with flattening of scars as a result.[1–4] Facial pressure therapy has evolved from the use of elastic fabric hoods to transparent rigid masks with different designs and manufacturing techniques.[5–7]

Furthermore, a facial pressure mask with a silicone inner layer has been reported to be effective when used as an adjuvant therapy in the case of unsatisfactory aesthetic results after facial flap surgery. Treatment with such a mask results in a reduction of flap thickness and scar erythema, improvement of skin irregularities, and pliability of the skin.[8]

However, from a psychological point of view, the impact of wearing a full-face pressure mask is not well documented.

Additionally, long-term follow-up data with respect to satisfaction with the clinical end-result and quality of life from patients after completing facial mask therapy is lacking, therefore making the decision of commencing a demanding therapy like a facial pressure mask remains difficult for patients.

The aim of this study was to interview patients who underwent therapy with a facial pressure mask and to assess their satisfaction with their current facial appearance in general and in social situations, to assess the result of the therapy, and to assess satisfaction with their decision to have undergone facial mask therapy.

We hypothesize that a facial pressure mask delivers longlasting results with respect to satisfaction with facial appearance in patients' perspective.

METHODS

Design

The Maastricht University Medical Center (MUMC+) offers patients with facial hypertrophic scars and severe postsurgical facial irregularities therapy with a custom-made pressure mask fabricated by an experienced orthotist/prosthetist. The transparent mask consists of a rigid polycarbonate outside with a soft silicone layer inside. Velcro straps are attached to the outside of the mask to deliver a targeted pressure of 20 mm Hg underneath the mask, therapeutically monitored by a pneumatic pressure sensor.[9]

In this prospective study conducted between July 2017 and November 2017 at the MUMC+, patients who were treated with a transparent facemask between July 2012 and July 2017 were interviewed. Patients assigned to mask therapy were patients with disfiguring facial scars after trauma and patients who had unsatisfactory aesthetic results after they

Table 1. Demographic data, reason for mask therapy and location of the defect

Sex		Cause						Location on the face				
Male	Female	BCC*	SCC*	Mela-noma	KA*	Trauma	Burns	Nose	Fore-head	Cheek	Eyelid	Multiple locations
15	27	24	1	4	1	9	3	24	3	10	2	3

** Basal Cell Carcinoma (BCC), Squamous Cell Carcinoma (SCC), Keratoacanthoma (KA).*

had undergone facial reconstructive surgery. These complaints included the presence of hypertrophic scars with persistent erythema and contractions and/or edema of the flap. Patient characteristics can be seen in Table 1.

Data collection

Patients participating in this study were asked to complete four different FACE-Q questionnaires (Appendices 1–4) to assess satisfaction with facial appearance and satisfaction with their decision. Patients who had no cognitive impairment and spoke Dutch well enough to answer the questions were included. Patients who received adjuvant facial pressure therapy or silicone therapy after completion of the mask therapy were excluded. Furthermore, minors under the age of 16 were excluded.

Study population and follow-up

In total, 87 patients wore a facial pressure mask and completed therapy between January 2012 and November 2017. Nine of them were minors under the age of 16 and were therefore excluded from this study. Furthermore, eight patients did not complete the therapy because of experienced discomfort (2), switching to another hospital (2), or because of recurrence of skin cancer (4). From the remaining eligible 69 patients, 42 patients completed the questionnaires. The patient group consisted of 14 men and 27 women with a mean age of 61 years (18–83 years). Mean therapy duration was 12.34 months (3–30 months; SD: 6.50). During therapy, patients returned for follow-up every 3 to 4 months at the outpatient clinic of the MUMC+. At each visit at the outpatient clinic, the pressure underneath the mask was monitored and necessary extra adjustments were made by the orthotist/prosthetist resulting in a mean number of visits of seven controls per patient. Pressure mask therapy was stopped when a mutually satisfying aesthetic result was reached by both patient and doctor

Assessment

For assessing patients' satisfaction with their facial appearance and quality of life, FACE-Q questionnaires were chosen (Appendices 1–4).

The FACE-Q is a patient-reported outcome measure (PROM) developed to measure the experience and outcomes of aesthetic facial procedures from the patient's perspective.[10,11] FACE-Q scales measure four domains: satisfaction with facial appearance, health-related

quality of life, adverse effects, and process of care. The scales used in this study were: overall *satisfaction with facial appearance* (from the satisfaction with facial appearance domain), *social function* (from the health-related quality of life domain), *satisfaction with decision*, and *satisfaction with result* (from the process of care domain).

The questionnaires were based on patient's current appreciation about their facial appearance in general and in social situations, if the therapy was worth it and about their current satisfaction with the result of the therapy. Responses to the questions were scored based on a Likert scale ranging from 1 to 4. The sum of each questionnaire was standardized to a Rasch transformed score of 0 to 100, where higher scores resemble a greater satisfaction or quality of life.

Also, during follow-up visits the Patient and Observer Scar Assessments Score (POSAS) forms were filled out by both patient and doctor.[12,13] To also include a physician's assessment of the face instead of solely a patient's judgement, POSAS was chosen. Since the POSAS is developed for assessing scars and not flaps, patients who had undergone flap surgery were asked to assess the facial reconstruction as a whole (both flap and scar together). The scar or reconstruction site was scored on a patient and observer scale on six items on a 10-step scale. Then both scales are added up to form the total POSAS Score (with scores ranging from 12 to 120).

Other variables collected were: age, gender, location and cause of the facial defect or deformity, duration of the therapy and the mean amount of hours patients wore the mask daily (<8 hours, 8-12 hours or 12-16 hours). To compare differences in satisfaction with facial appearance, satisfaction with decision, satisfaction with the result and quality of life, groups were formed based on the time passed since completion of the therapy. Furthermore, analyses were performed based on the mean amount of hours patients wore the mask.

Data analysis

Mean overall Rasch transformed scores were compared using analysis of variance (ANOVA) tests. Subgroup analysis was performed for groups based on therapy duration and daily amount of hours the mask was worn. Data were normally distributed, according to Shapiro–Wilk tests, therefore ANOVA tests with post hoc t-test were used to perform subgroup analysis. Two-tailed values of $P < 0.05$ were accepted as statistically significant. All analyses were performed using the statistical software program SPSS 22.0.

RESULTS

Daily amount of hours the mask was worn

Patients were divided in three groups according their self-reported daily adherence during pressure mask therapy. Seven patients wore the mask 4 to 8 hours a day, 20 patients wore

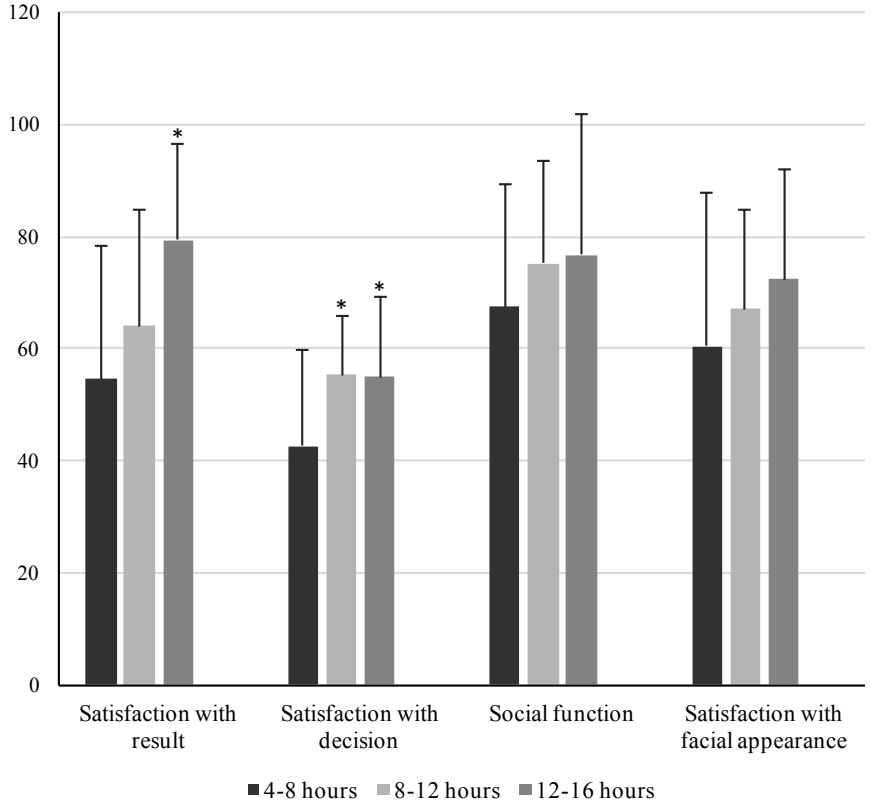


Figure 1. FACE-Q scores divided by the mean amount of daily hours the pressure mask was worn, according to patients. Statistical significant values are indicated by an asterisk (*).

the mask 8 to 12 hours each day, and 15 patients reported a therapy adherence of 12 to 16 hours each day.

Our results show that a longer daily period of wearing the mask (12–16 hours) leads to a statistically significant higher satisfaction with the result compared with a shorter amount of hours daily (4–8 hours), displayed by higher mean Rasch scores (79.45, SD: 17.21 vs. 54.63, SD: 23.83, *P*= 0.013) (Figure 1). Patients who wore the mask for 8 to 12 hours (55.39, SD: 20.79) and 12 to 16 hours (55.00, SD: 14.43) were significantly more satisfied with the decision to have undergone mask therapy compared with patients who wore the mask for 4 to 8 hours daily (42.75, SD: 21.79), displayed by *P*-values of 0.032 and 0.048, respectively.

A longer daily adherence to therapy also tends to lead to a better satisfaction with facial appearance and to a better social function compared with a shorter daily period, displayed by higher Rasch scores. However, these differences are not statistically significant.

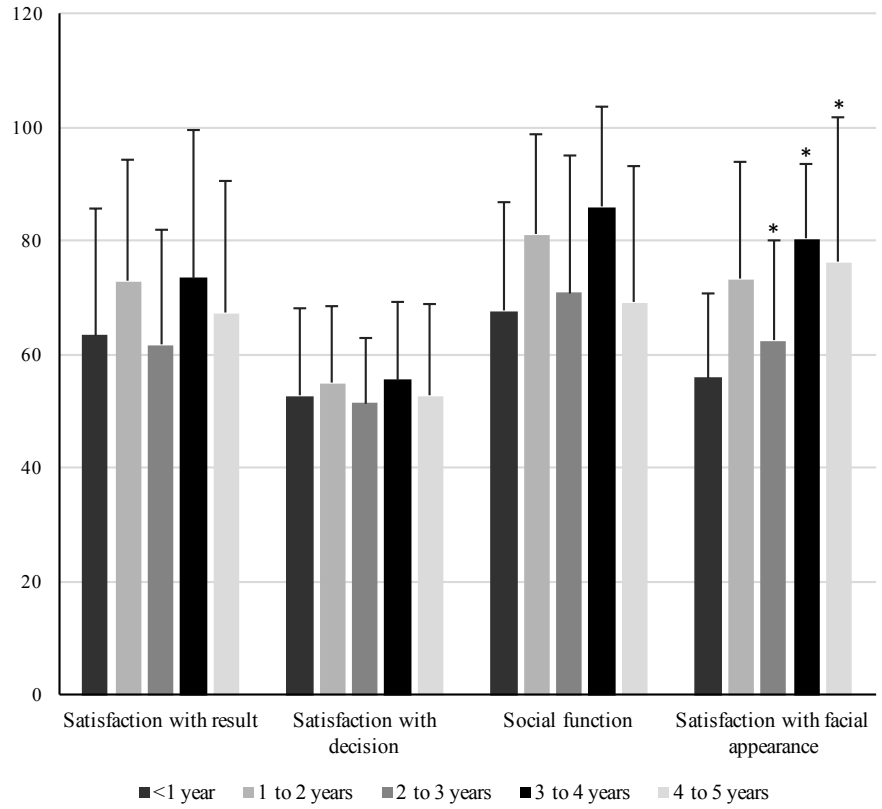


Figure 2. FACE-Q scores divided by the years passed after completion of the mask therapy at the start of the study. Statistical significant values are indicated by an asterisk (*).

Comparison of 5 follow-up groups

Based on the time passed after completion of the mask therapy (within 1 year (n=8), 1 to 2 years (n=7), 2 to 3 years (n=11), 3 to 4 years (n=8) and 4 to 5 years (n=8) at the start of this study), five follow-up groups were formed.

No statistically significant differences were found in satisfaction with the decision to have undergone mask therapy, in social function, and in satisfaction with the end result (Figure 2). Patients who finished therapy 3 to 4 years (80,38, SD: 13,21) and 4 to 5 years (76,29, SD: 25,73) ago reported a significant higher satisfaction with facial appearance compared to those who completed therapy in a time period shorter than 1 year ago (55,89, SD: 15,12), displayed by *P*-values of 0,010 and 0,036 respectively. Furthermore, patients who finished therapy 3 to 4 years ago reported higher satisfaction with their facial appearance compared to those who finished therapy 2 to 3 years ago (62,55, SD: 17,65, *P*=0,046).

Table 2. Mean POSAS scores at start and end of therapy

	Start therapy	*SD*	*End of therapy*	*SD*	P *value*
Patient Score	30,19	13,17	19,92	10,07	<0,001
Observer Score	19,00	6,97	14,31	4,45	0,002
Total POSAS	49,19	17,49	34,23	14,52	<0,001

Patient and Observer Scar Assessments Scores

At follow-up visits during therapy, both patient and doctor filled out a POSAS form. The mean patient score decreased significantly from 30.19 (SD: 13.17) to 19.92 (SD: 10.07, $P< 0.001$) between start and end of therapy. Mean observer scores also showed a significant decrease between start and end of therapy (19.00, SD: 6.97 vs. 14.31, SD: 4.45, $P=0.002$) (Table 2).

Strengths and limitations

Patients were instructed to wear the mask as long as they could endure, with the advice to wear the mask at least 8 to 12 hours each day. As the data about therapy compliance is reported by patients and could not be objectified, these data are susceptible for bias. Furthermore, a major limitation of this study is the absence of a control group. In this study, 42 of the 69 eligible patients replied and completed the questionnaires. Although this response rate was deemed acceptable, it could be that the most unsatisfied patients did not reply, which could have biased our data.

Because of several patients that had finished therapy almost 5 years ago, questions with respect to satisfaction about the decision to have undergone mask therapy are susceptible to recall bias. Nevertheless, no significant differences in satisfaction with decision were found between follow-up groups. All other questionnaires were focused on patients' current opinions about their facial appearance and results.

DISCUSSION

Data from these questionnaires confirm pressure mask therapy results in stable aesthetic results over a period of 5 years, as there are no significant differences in satisfaction with the result over time based on five follow-up groups (Figure 2). Furthermore, appreciation of facial appearance in social situations is also stable at patients finishing therapy within 1 to 5 years ago.

However, patients who finished therapy 3 to 5 years ago reported a higher satisfaction with facial appearance compared with patients who finished therapy within 1 year ago.

This could be due to the possibility that it might take several years for patients to accept facial disturbances or irregularities, improving their opinion about their facial appearance over time as a result.

Another explanation could be due to a possibly prolonged remodeling period of scar tissue which is reported to take up to 2 or several years, improving patients' perceived aesthetic outcome over time.[14,15] Nevertheless, the maturation phase of wound healing remains the least elucidated part of wound healing, therefore statements about the scar remodeling duration cannot be backed by substantial evidence.

The burden to wear a full-face pressure mask should not be underestimated, as it is conspicuous and burdensome for patients. Accordingly, studies have shown therapy adherence can be a serious problem, displayed by a compliance for head and neck pressure garments of 44% in a study by Johnson et al.[16,17]

Although clinical evidence is lacking, recommendations about facial mask therapy for hypertrophic burn scars suggest a pressure mask should be worn 18 to 24 hours a day, with a targeted continuous pressure of at least 20 mm Hg for 6 to 18 months.[18–20]

In this study, patients were asked to wear the mask for a minimum of 8 to 12 hours a day, preferably during the night.[21] Primarily, this was decided for preventing social, emotional, and physical difficulties as much as possible. This recommendation is supported by a study by Stewart et al where patients' adherence to pressure garments was problematic, displayed by a daily wearing of no more than 10 to 14 hours at 30%, when 23 hours a day was instructed.[17]

It should be mentioned that this study only included patients with minor burns and predominantly patients with irregularities after facial surgery and therefore a shorter daily wearing period was acceptable. Patients with severe facial burns were treated in a specialized burn center.

Even though facial pressure therapy is predominantly advised to be used for a longer daily period, in this study no statistical differences in satisfaction with facial appearance in general and in social situations were found between the three groups with different amount of daily hours of facial pressure therapy. However, patients who wore the mask 12 to 16 hours a day seem to be most pleased with the result of the therapy compared with patients who wore the mask 4 to 8 hours daily. These results suggest that a longer daily use of a facial pressure mask could lead to better improvement in the aesthetic outcome compared with a shorter daily period of wearing the mask, yet this has to be investigated further clinically.

Additionally, patient, observer and total POSAS scores showed a significant reduction between start and end of therapy, indicating improvement of scars or the reconstruction site by both patient and doctor (Table 2). In addition to the results of the patient-reported outcomes in this study, this also shows a significant improvement of the face occurred as observed by a doctor.

CONCLUSION

A major goal of this study was to examine if results of facial pressure mask therapy are stable in the long run. This study showed that there were no significant differences in satisfaction with facial appearance in general and in social situations between patients who finished therapy within 1 until 5 years ago.

Furthermore, it showed that wearing the mask 12 to 16 hours daily results in the highest satisfaction.

Our results suggest that facemask therapy results in a long lasting stable result with respect to aesthetic outcome.

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APPENDICES 1-4: FACE-Q SCALES

Appendix 1. FACE-Q™ – SOCIAL FUNCTION

For each statement, circle only one **answer. These are statements people might use to describe themselves. With your** facial appearance in mind**, in the past week, how much would you** agree or disagree **with the each statement:**

	Definitely disagree	Somewhat disagree	Somewhat agree	Definitely agree
a. I make a good first impression.	1	2	3	4
b. I feel confident when I meet a new person.	1	2	3	4
c. I am comfortable meeting new people.	1	2	3	4
d. It is easy for me to make new friends.	1	2	3	4
e. I feel confident when I participate in group situations (e.g. meetings).	1	2	3	4
f. I feel confident in new social situations (e.g. parties).	1	2	3	4
g. I am relaxed around people that I don't know well.	1	2	3	4
h. I feel confident when I walk into a room full of people I don't know.	1	2	3	4

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Appendix 2. FACE-Q™ – SATISFACTION WITH OUTCOME

For each statement, circle only one **answer. We would like to know how you feel about your** most recent **procedure. Please indicate how much you** agree or disagree **with each statement.**

	Definitely disagree	Somewhat disagree	Somewhat agree	Definitely agree
a. I am pleased with the result.	1	2	3	4
b. The result turned out great.	1	2	3	4
c. The result was just as I expected.	1	2	3	4
d. I am surprised at how good I look in the mirror.	1	2	3	4
e. The result is fantastic.	1	2	3	4
f. The result is miraculous.	1	2	3	4

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Appendix 3. FACE-Q™ - SATISFACTION WITH DECISION

For each statement, circle only one **answer. We would like to know how you feel about your decision to have your** most recent **procedure. Please indicate how much you** agree or disagree **with each statement.**

	Definitely disagree	Somewhat disagree	Somewhat agree	Definitely agree
a. It was worth the time and effort.	1	2	3	4
b. It was money well spent.	1	2	3	4
c. It was just what I wanted.	1	2	3	4
d. It was just what I needed.	1	2	3	4
e. It made me look how I want to look.	1	2	3	4
f. It changed my life for the better.	1	2	3	4

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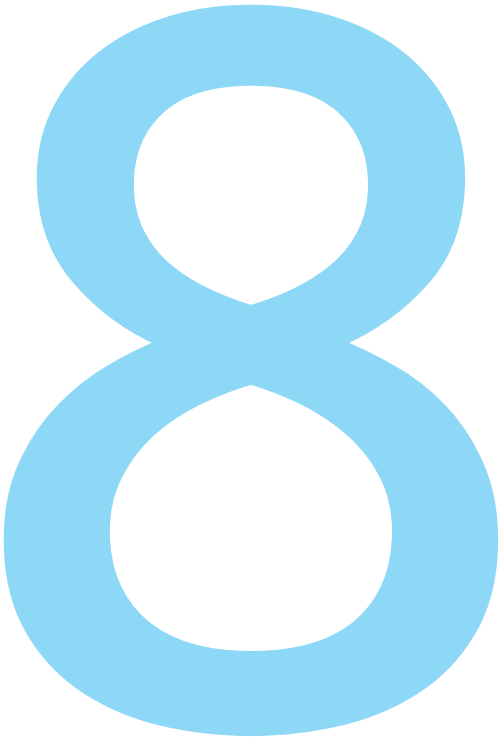
Appendix 4. FACE-Q™ - SATISFACTION WITH FACIAL APPEARANCE

For each question, circle only one **answer. With your** entire face **in mind, in the past week, how** satisfied or dissatisfied **have you been with:**

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a. How symmetric your face looks?	1	2	3	4
b. How balanced your face looks?	1	2	3	4
c. How well-proportioned your face looks?	1	2	3	4
d. How your face looks at the end of your day?	1	2	3	4
e. How fresh your face looks?	1	2	3	4
f. How rested your face looks?	1	2	3	4
g. How your profile (side view) looks?	1	2	3	4
h. How your face looks in photos?	1	2	3	4
i. How your face looks when you first wake-up?	1	2	3	4
j. How your face looks under bright lights?	1	2	3	4

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CHAPTER 8



A new treatment of hypertrophic and keloid scars with combined triamcinolone and verapamil: a retrospective study

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ABSTRACT

Background: Since the management of keloid and hypertrophic scars still remains a difficult clinical problem, there is need for adequate, effective therapy. In this study, we explored for the first time the efficacy and the potential synergetic effect of combined triamcinolone and verapamil for the treatment of hypertrophic and keloid scars. The objective was to assess the efficacy of combined intralesional triamcinolone and verapamil therapy for hypertrophic and keloid scars.

Methods: Fifty-eight patients with hypertrophic scars (*n*=31) and keloid scars (*n*=27) were included. A specific injection therapy scheme was applied. Five follow-up moments were chosen, with a maximum follow-up of nearly 2 years. The effects of combination therapy on scar pliability, thickness, relief, vascularization, surface area, pain, and pruritus were examined by means of the Patient and Observer Scar Assessment Scale (POSAS).

Results: Our results reveal a fast and abiding improvement of both keloid and hypertrophic scars after treatment with the combination therapy. All POSAS components showed a reduction in scar score, while scar relief, pain, itchiness, and surface area improved significantly ($P< 0.05$) in keloids. Significant improvement in hypertrophic scars was found in scar pigmentation, vascularization, pliability, thickness, pain, and surface area. Overall POSAS scores revealed statistically significant decreases between baseline and 3–4 months, 4–6 months, and >12 months after start of therapy in both keloids and hypertrophic scars.

Conclusions: This study reveals that combined therapy of triamcinolone and verapamil results in overall significant scar improvement with a long-term stable result.

Keywords: hypertrophic scars, keloids, kenacort, verapamil

INTRODUCTION

Keloids and hypertrophic scars are still a therapeutic problem. These scars are mostly disfiguring and are likely to cause severe psychological problems. Besides the psychological aspect, the physical and functional implications of keloids and hypertrophic scars often cause a notable burden for the patient.[1]

The management of hypertrophic scars and keloids remains an unsolved problem. Many therapeutic modalities have been described: intralesional therapy, pressure therapy, cryotherapy, radiotherapy, surgical excision, and even combinations of the earlier mentioned therapies.[2-6] This article focuses on the possibilities that intralesional injections can bring into the therapy of keloids and hypertrophic scars.

The anti-inflammatory and scar-enhancing properties of corticosteroids on hypertrophic scars and keloids have been investigated and documented thoroughly. They are considered a first-line strategy in the treatment of limited keloidal and hypertrophic scars. The most commonly used corticosteroid in this matter is triamcinolone acetonide, and its efficacy and usefulness as well as its limitations are well known.[7-8]

In contrast to corticosteroids, the efficacy of verapamil (a calcium antagonist) and the combination of verapamil and triamcinolone on hypertrophic scars and keloids is less studied. The beneficial effects of verapamil on hypertrophic scars and keloids are mainly addressed as empirically.

Verapamil appears to degrade extracellular matrix by inhibition of collagen production.[9,10] Furthermore, verapamil may prevent platelet aggregation and decrease neutrophil activity and thereby inhibit inflammation.[11]

The Maastricht University Medical Center offers an outpatient clinic exclusively focused on scar treatment and management. With the use of a specific injection regime, we reckon that combination therapy is likely to result in significant scar improvement over time in everyday practice. We believe the positive properties of triamcinolone and verapamil can have a synergetic enhancing effect on hypertrophic scars and keloids when used as combined intralesional therapy. Significant clinical evidence for effectiveness of combined intralesional therapy of triamcinolone and verapamil on hypertrophic scars and keloids in vivo is still lacking.

The aim of this study is to assess the efficacy of combined intralesional therapy of triamcinolone and verapamil in small bothersome hypertrophic and keloid scars.

METHODS

Design

In this retrospective study, conducted at the department of plastic surgery at the Maastricht University hospital (MUMC+), between July 2012 and December 2015, 58 patients underwent a combined therapy of triamcinolone and verapamil injections in order to improve their hypertrophic or keloid scar. The study includes 58 patients with involvement of in total 31 keloid scars and 27 hypertrophic scars.

Patients and treated sites

Eligible patients were men or women with keloid or hypertrophic scars, who had not been treated with triamcinolone and verapamil in an earlier stage of their scarring. All patients that received triamcinolone and verapamil treatment in order to improve their scar between July 2012 and December 2015 were included. Major exclusion criteria were the use of an additional scar treatment like pressure therapy or silicone sheets at the time the study started.

The scars of 28 patients had not been treated when the study started. From the remaining 30 patients, 8 of them had been treated solely with ointment and 10 patients were treated with combined silicone and pressure therapy. Other scar therapies, patients previously had included laser therapy, cryotherapy, physiotherapy, silicones, and pressure therapy separately and excision of the scar. Abovementioned therapies were all deemed unsuccessful, and additionally, those treatments took place in a distant earlier stage, causing no interference with the current study. Scar location and scar etiology are documented in Tables 1 and 2, respectively. The study conformed to good clinical practice guidelines and followed the recommendations of the Declaration of Helsinki. The protocol was approved by the local ethics committee.

Patients

The relevant patient group after exclusion consisted of 25 men and 33 women with a mean age of 28 years (9–82 years, Table 1) and a mean follow-up of 209 days (39–729 days, Table 3). All patients were diagnosed with hypertrophic or keloid scarring at the scar clinic by a team of experts, consisting of a senior plastic surgeon, a resident plastic surgeon, a prosthetist, and a physiotherapist specialized in scar therapy. Scars were present a mean time of 3.84 years when treatment started (Table 2).

Procedures

From July 2012 to December 2015, 58 eligible patients were assigned to triamcinolone and verapamil injections that consist of a 1:1 mixture of triamcinolone (Kenacort-A, Bristol-Myers

Table 1. Patient characteristics

	Sex		*Mean age*	*Scar location*						
	Male	Female	Years	Extremities	Face/head/neck	Pre-sternal	Shoulder	Sternum	Thorax	Abdomen	Back
No.	25	33	28.1 (9–82)	8	18	4	4	13	3	4	4

Table 2. Scar etiology and time scars were present when therapy started

	Etiology						
	Acne	Burns	Piercing	Spontaneous	Surgery	Trauma	Varicella
No.	5	1	4	3	33	11	1
	Mean time the scars were present at time therapy started (years)						
	3.84						

Squibb, New York, United States 40 mg/mL) and verapamil (2.5 mg/mL). The mean volume of the mixture injected in scars was between 0.1 and 0.2 mL.

All patients followed the same injection scheme: a first injection (*t*=0), the second injection a week after the initial injection, and an additional third injection 3 weeks after the first injection. As from 39 days after the first injection, scars were assessed at the scar clinic by the team of experts.

Adverse effects

During the study a small amount of patients experienced adverse effects. One patient experienced hardening of the scar. Another patient encountered minor indentation of the scar. Furthermore, a couple of patients experienced a short period of itchiness at the scar directly after the injection.

Follow-up

In total, 58 eligible patients completely followed the proposed injection scheme as they form baseline. Patients were followed as from 39 to a maximum of 729 days after start of the injection scheme (Table 3).

Based on duration of follow-up, five follow-up moments after baseline (*t*=0, end of the injection scheme, *n*=58) were chosen. Follow-up moments consisted of 1 to 3 months (*n*=17), 3 to 4 months (*n*=10), 4 to 6 months (*n*=11), 6 to 12 months (*n*=11), and >12 months (*n*=9).

Twelve patients were lost to follow-up because they went to an affiliated hospital for further follow-up, because the recruitment period of the study ended before patients were called for follow-up visit or because patients did not show up for follow-up visit.

Table 3. Follow-up information

	No. of patients	*Time after start of therapy (days)*	
		Mean	SD
Baseline	58	0	0
1–3 months	17	59.88	15.20
3–4 months	10	103.80	8.52
4–6 months	11	168.45	16.88
6–12 months	11	269.09	58.03
>12 months	9	502.67	108.98
Follow-up time	Days		
Min	39		
Max	729		
Mean	209		

Assessment of the scars

All the scars were evaluated prior to or on the day of the first injection by the previously validated Patient and Observer Scar Assessment Scale (POSAS).[12] The scar was rated numerically on a ten-step scale by both the patient and doctor on six items: vascularity, pigmentation, thickness, relief, pliability, and surface area on the Observer Scale. The Patient Scale consists of pain, itchiness, color, stiffness, thickness, and irregularity of the scar.

One of the reasons POSAS was chosen for scar evaluation is because it is the only scar assessment tool to include a component for patients to fill in. Furthermore, we chose POSAS because of its distinctive feature of reflecting subjective symptoms like pain and pruritus and because of its appropriateness for everyday practice.[13-15]

On each visit, an expert and the patient independently filled out a POSAS form in order to assess the scar.

Statistical analysis

The study was planned as a case-series study to evaluate the efficacy of triamcinolone and verapamil with respect to scar outcome. Scar scores at follow-up visits are presented as means with standard deviations. Those scores were compared with the use of ANOVA and Games-Howell post-hoc tests for significance in means. A value of $P< 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 22.0.0.0.

Table 4. Mean Patient, Observer and POSAS scores for keloids and hypertrophic scars

	Patient score		*Observer score*		*POSAS score*	
	Keloids	Hypertrophic scars	Keloids	Hypertrophic scars	Keloids	Hypertrophic scars
Baseline (t = 0)	40.73	43.93	27.03	26.67	67.77	70.59
SD	7.10	6,31	8.22	7.72	10.20	8.79
95% CI	38.08–43.38	41.43–46.42	23.96–30,10	23.61–29,72	63.96–71.58	67.12–74.07
1–3 months	29.90	35.14	21.80	21.57	51.70	56.71
SD	14.22	8.61	8.14	6.00	20.16	13.51
95% CI	19.73–40.07	27.18–43.11	15.98–27.62	16.03–27.12	37.28–66.12	44.22–69.21
3–4 months	28.57	21.33	18.00	22.00	46.57	43.33
SD	11.06	8.39	7.64	6.08	12.42	14.43
95% CI	18.34–38.80	0.50–42.17	10.94–25.06	6.89–37.11	35.08–58.06	7.48–79.19
4–6 months	28.50	29.00	20.00	19.80	48.50	48.80
SD	12.28	6.82	7.69	4.60	11.15	4.97
95% CI	15.62–41.38	20.53–37.47	11.93–28.07	14.08–25.52	36.80–60.20	42.63–54.97
6–12 months	28.80	34.83	17.40	14.17	46.20	49.00
SD	14,62	13.29	4.16	2.99	17.71	12.67
95% CI	10.65–46.95	20.89–48.78	12.24–22.56	11.02–17.31	24.21–68.19	35.71–62.29
>12 months	23.67	28.17	15.33	18.67	39.00	46.83
SD	3.79	11.99	2.31	7.69	6.08	14.63
95% CI	14.26–33.07	15.58–40.75	9.60–21.07	10.60–26.73	23.89–54.11	31.48–62.19

RESULTS

Outcome POSAS scores

The means and standard deviations for baseline and five follow-up moments are presented in Table 4. A one-way ANOVA was conducted to compare mean POSAS scores at baseline and five follow-up moments for keloid scars and hypertrophic scars separately. Post-hoc analyses using the Games-Howell post-hoc criterion were used to make comparisons between follow-up moments. This test was used because it does not assume equal variances and equal group sizes.

For keloids, there were statistical significant differences ($P< 0.05$) in POSAS scores between baseline (67.77, SD: 10.20) and subsequent times (3–4 months (46.57, SD: 12.42), 4–6 months (48.50, SD: 11.15), and >12 months (39.00, SD: 12.59)) (Figure 1). No statistical significant differences in subsequent times were found. Details about patient, observer, and total POSAS scores at different follow-up moments, standard deviations, and 95% confidence intervals are shown in Table 4.

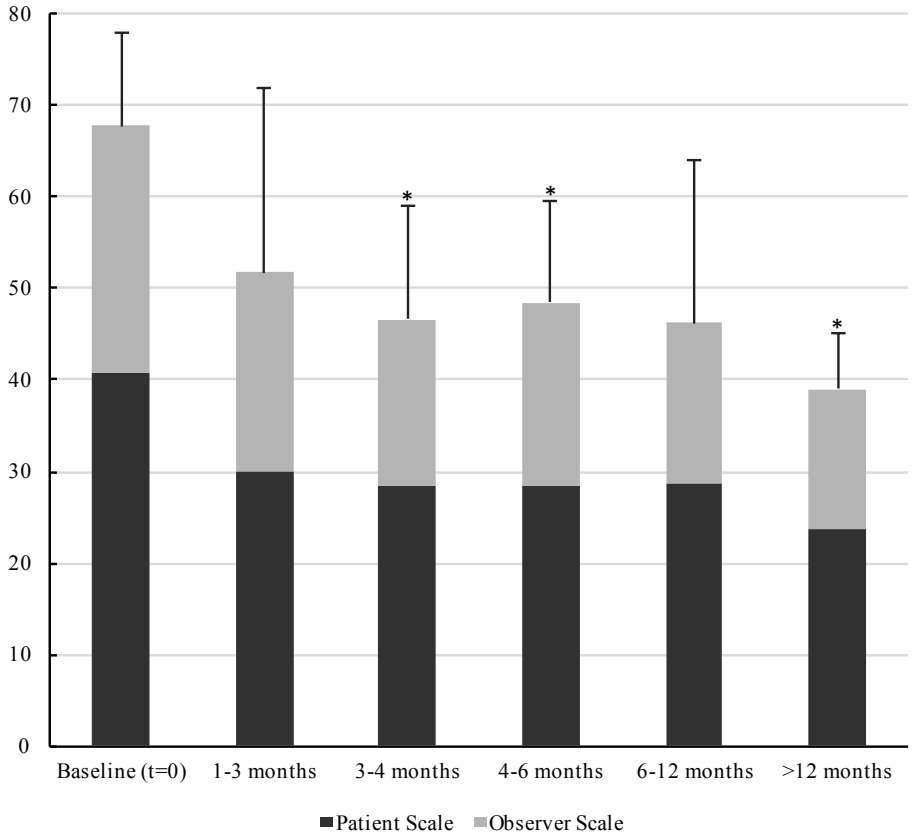


Figure 1. Mean Patient, Observer, and total POSAS scores are shown at baseline and four subgroup visits (early, medium, long, and late term) for keloid scars. A *single asterisk* indicates a statistical significant ($P< 0.05$) difference compared to baseline

Hypertrophic scars

For hypertrophic scars, significant improvement in POSAS scores was found between baseline (70.59, SD: 8.79) and subsequent times (3–4 months (43.33, SD: 14.43), 4–6 months (48.80, SD: 4.97), and >12 months (46.83, SD: 14.63)) (Figure 2, Table 4). Also, no statistical significant differences in subsequent times were observed.

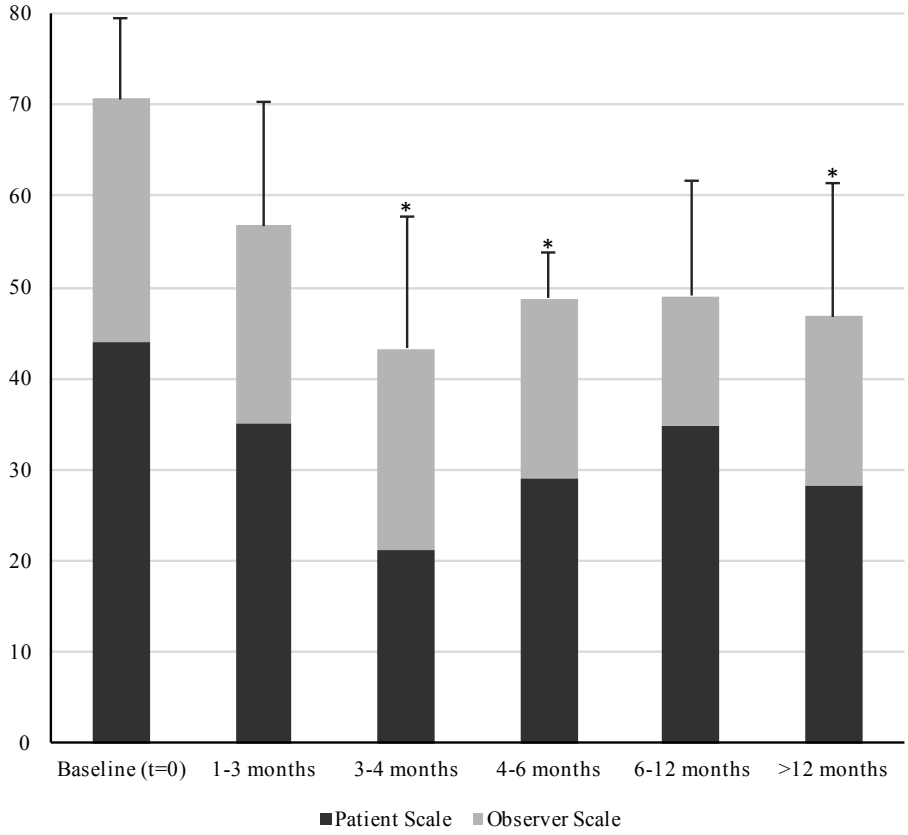


Figure 2. Mean Patient, Observer, and total POSAS scores are shown at baseline and four subgroup visits (early, medium, long, and late term) for hypertrophic scars. A *single asterisk* indicates a statistical significant ($P< 0.05$) difference compared to baseline

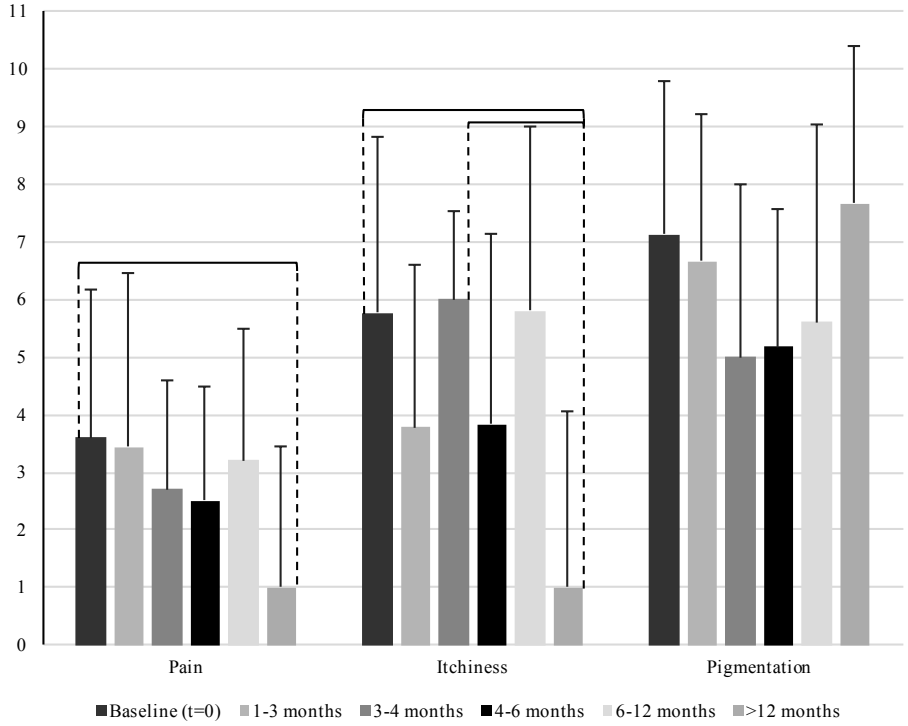


Figure 3
a Patient scar scores as part of the total POSAS score are displayed for keloid scars at baseline and five follow-up moments: 1–3 months, 3–4 months, 4–6 months, 6–12 months, and >12 months. Scars were rated on a ten-step scale. *Braces* indicate a statistical significant ($P< 0.05$) difference between follow-up moments.

Patient Scores

To evaluate the outcome of the patient component of the POSAS (pain, itchiness, pigmentation, pliability, thickness, and relief) all Patient Scores were compared on baseline and five follow-up moments. A one-way ANOVA with analyses using Games-Howell post-hoc test was used.

Keloids

All six components of the Patient Score decreased after baseline, significant differences were found in pain and itchiness (Figure 3).

Pain There was significant improvement in pain between baseline (3.60, SD: 2.58) and >12 months (1.00, SD: 2.44).
Itchiness Itchiness showed significant decrease between baseline (5.77, SD: 3.05) and >12 months (1.00, SD: 3.04) and between 3 and 4 months (6.00 SD: 1.55) and >12 months.

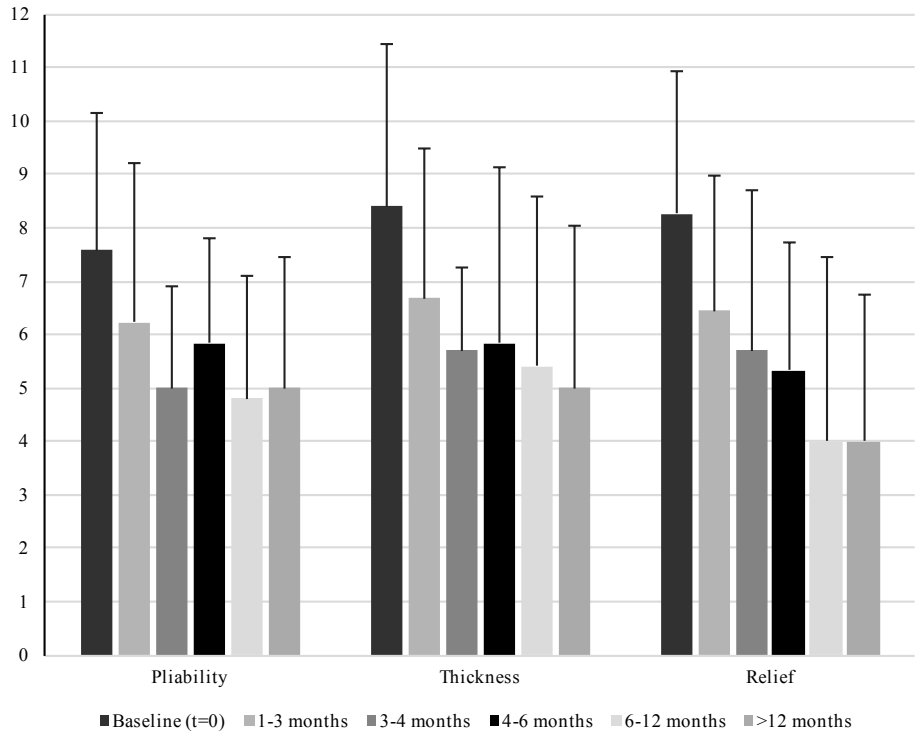


Figure 3
b Patient scar scores as part of the total POSAS score are displayed for keloid scars at baseline and five follow-up moments: 1–3 months, 3–4 months, 4–6 months, 6–12 months, and >12 months. Scars were rated on a ten-step scale. *Braces* indicate a statistical significant ($P < 0.05$) difference between follow-up moments

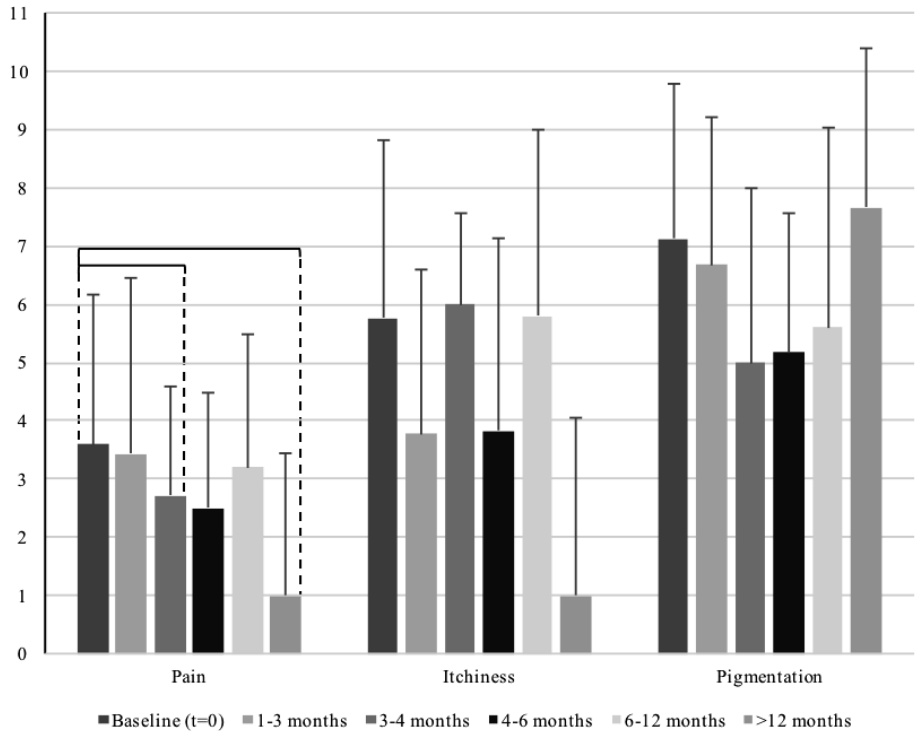


Figure 4
a Patient scar scores as part of the total POSAS score are displayed for hypertrophic scars at baseline and five follow-up moments: 1–3 months, 3–4 months, 4–6 months, 6–12 months, and >12 months. Scars were rated on a ten-step scale. *Braces* indicate a statistical significant ($P < 0.05$) difference between follow-up moments.

Hypertrophic scars

All of the components of the patient score decreased after baseline, significant differences were observed in pain, scar pliability, thickness, and relief (Figure 4).

Pain Significant decreases in pain were observed between baseline (3.60, SD: 2.58) and 3–4 months (2.71, SD: 1.89).
Pliability Hypertrophic scar pliability showed significant improvement between baseline (7.57, SD: 2.03) and >12 months (5.00, SD: 2.44).
Thickness There was significant improvement in scar thickness between baseline (8.40, SD: 1.38) and 3–4 months (5.00, SD: 2.41).
Relief Significant decreases were observed between baseline (8.27, SD: 1.86) and 3–4 months (5.71, SD: 2.69) and between 1 and 3 months (6.44, SD: 2.92) and 3–4 months.

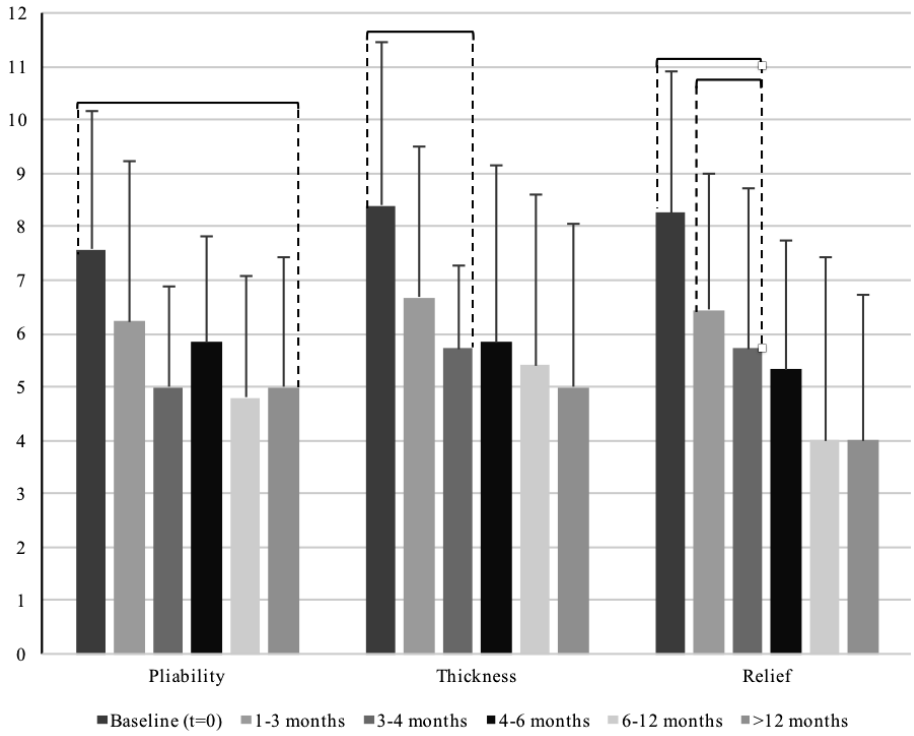


Figure 4
b. Patient scar scores as part of the total POSAS score are displayed for hypertrophic scars at baseline and five follow-up moments: 1–3 months, 3–4 months, 4–6 months, 6–12 months, and >12 months. Scars were rated on a ten-step scale. *Braces* indicate a statistical significant ($P < 0.05$) difference between follow-up moments

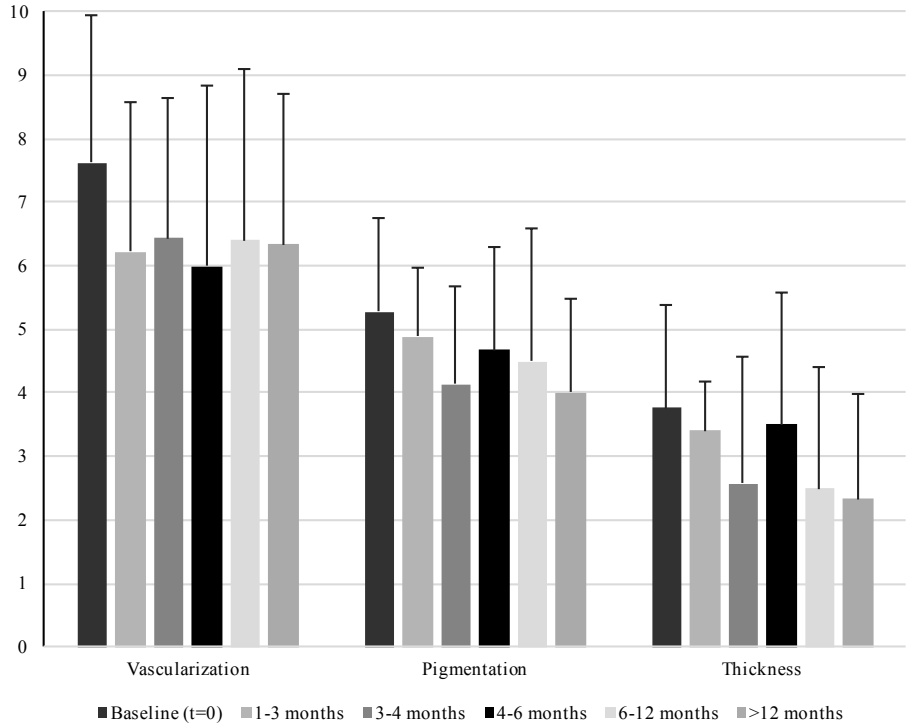


Figure 5
a Observer scar scores as part of the total POSAS score are displayed for keloid scars at baseline and five follow-up moments: 1–3 months, 3–4 months, 4–6 months, 6–12 months, and >12 months. Scars were rated on a ten-step scale. *Braces* indicate a statistical significant ($P < 0.05$) difference between follow-up moments.

Observer Scores

Corresponding to analyses of Patient Scores all Observer Score components (vascularization, pigmentation, thickness, relief, pliability, and surface area) were compared on baseline and five follow-up moments. A one-way ANOVA with analyses using Games-Howell post-hoc test was used.

Keloids

All six components of the observer score decreased after baseline, statistical significant differences were found in scar relief, pliability, and surface area (Figure 5).

Relief Scar relief showed significant improvement between baseline (5.00, SD: 1.91) and >12 months (2.00, SD: 1.88).
Pliability Significant improvement in scar pliability was observed between baseline (4.63, SD: 1.75) and 4–6 months (3.33, SD: 1.37).

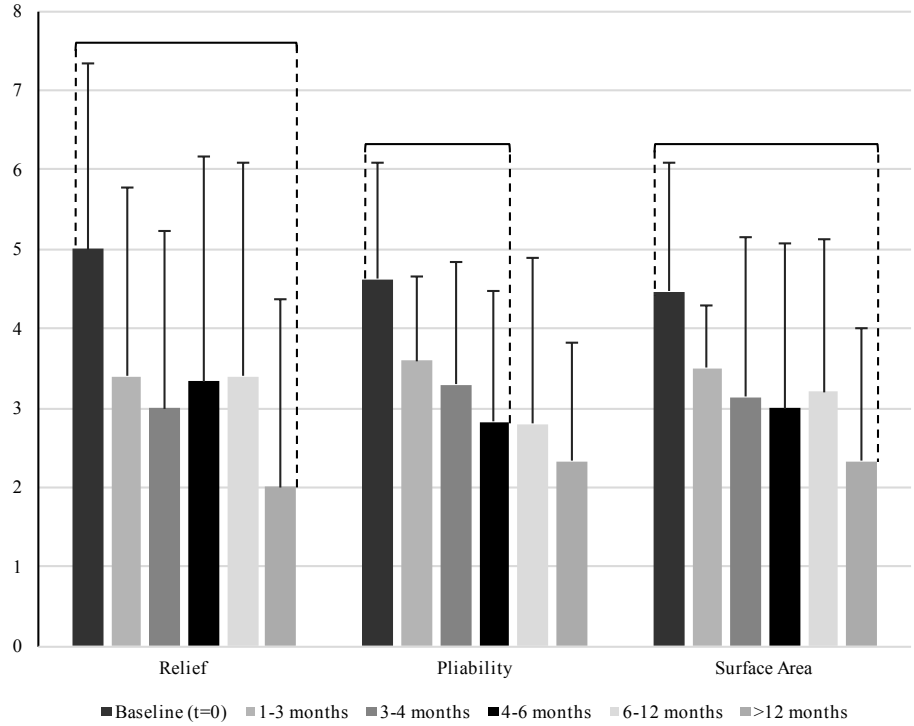


Figure 5
b Observer scar scores as part of the total POSAS score are displayed for keloid scars at baseline and five follow-up moments: 1–3 months, 3–4 months, 4–6 months, 6–12 months, and >12 months. Scars were rated on a ten-step scale. *Braces* indicate a statistical significant ($P < 0.05$) difference between follow-up moments

Surface area Surface area of the scar improved significantly between baseline (4.47, SD: 1.59) and >12 months (2.33, SD: 1.63).

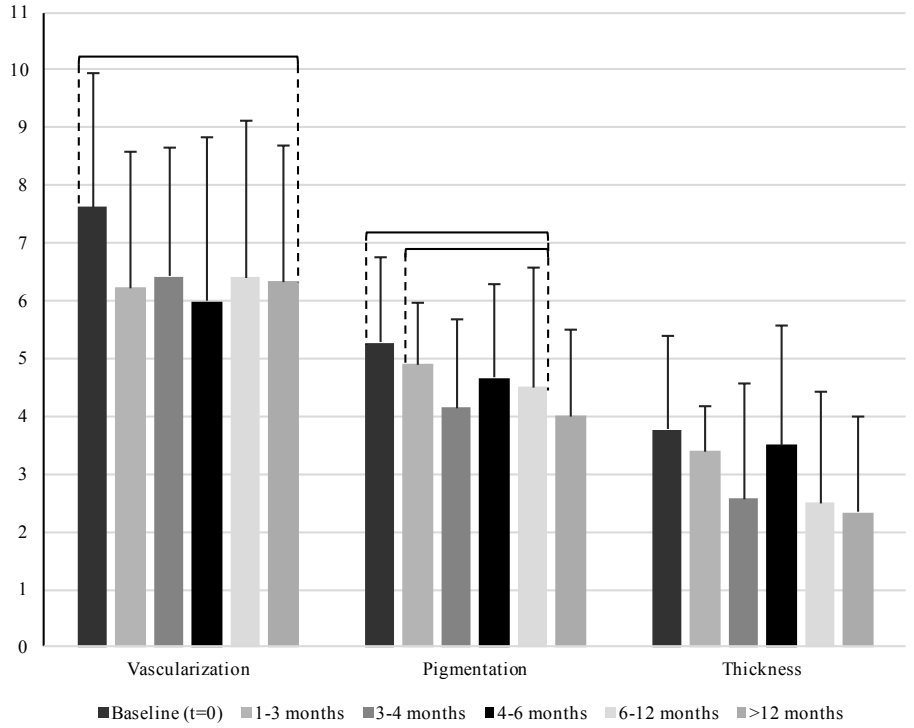


Figure 6
a Observer scar scores as part of the total POSAS score are displayed for hypertrophic scars at baseline and five follow-up moments: 1–3 months, 3–4 months, 4–6 months, 6–12 months, and >12 months. Scars were rated on a ten-step scale. *Braces* indicate a statistical significant ($P < 0.05$) difference between follow-up moments.

Hypertrophic scars

Every component of the observer score decreased after baseline, statistical significant differences were found in scar vascularization, pigmentation, relief, pliability, and surface area (Figure 6).

Vascularization There was significant improvement in vascularization between baseline (7.62, SD: 2.34) and >12 months (6.33, SD: 2.36).

Pigmentation Scar pigmentation showed significant improvement between baseline (5.28, SD: 1.46) and 6–12 months (4.50, SD: 2.08) and between 1 and 3 months (4.89, SD: 1.07) and 6–12 months.

Relief Significant decreases in scar relief were observed between baseline (5.00, SD: 1.91) and 4–6 months (3.33, SD: 1.37), 6–12 months (3.40, SD: 0.89) and >12 months (2.00, SD: 1.88).

Pliability There were significant differences in pliability between baseline (4.63, SD: 1.75) and 6–12 months (2.80, SD: 1.30) and >12 months (2.33, SD: 1.78).

Surface area Surface area of the scar showed significant improvement between baseline (4.47, SD: 1.59) and 1–3 months (3.50, SD: 1.57) and 6–12 months (3.20, SD: 1.30).

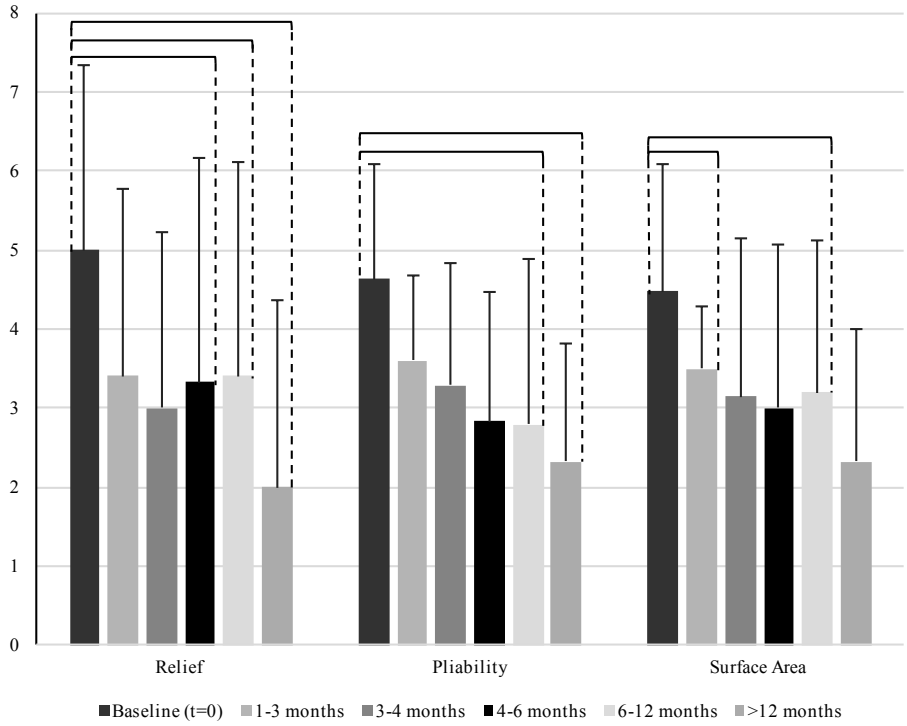


Figure 6
b. Observer scar scores as part of the total POSAS score are displayed for hypertrophic scars at baseline and five follow-up moments: 1–3 months, 3–4 months, 4–6 months, 6–12 months, and >12 months. Scars were rated on a ten-step scale. *Braces* indicate a statistical significant ($P < 0.05$) difference between follow-up moments

Summarizing, all POSAS scar aspects showed a decrease in scar score at some moment during follow-up visits, whereas pain, itchiness, pliability, relief, and scar surface area decreased statistically significant ($P< 0.05$) for keloids. For hypertrophic scars, significant decreases in POSAS scores were observed for pain, pliability, thickness, relief, vascularization, pigmentation, and surface area.

Strengths and limitations

This is the first clinical case-series to evaluate the effectiveness of an intralesional combination therapy for scars with triamcinolone and verapamil. There were several limitations of this study. The number of patients at each follow-up visit would preferably have been larger. Another limitation is the absence of a control group. However, a clear decrease in POSAS scores at all follow-up moments compared to baseline was observed for both keloids and hypertrophic scars. The strength of this study is that it shows clearly that the patients that underwent a full treatment according to our regimen had a fast improvement of their scars. And this was even seen in scars that were already treated with different types of scar therapy

before. In this study, the intralesional injections and scar assessments were always carried out by two separate experts.

Furthermore, we did see that patients followed up longer than 12 months also had a strong decrease in the POSAS score. This proves the effectiveness of the combination of triamcinolone and verapamil for intralesional treatment of hypertrophic scars and keloids in the long term.

DISCUSSION

In this retrospective study, a combined therapy with triamcinolone and verapamil injections resulted in significant scar improvement over time. A total of 116 POSAS scores were collected to evaluate hypertrophic and keloid scarring over a maximum period of 729 days. The most notable effects from combined triamcinolone and verapamil injection therapy in scar tissue for keloid scars were improvement in scar surface area, pliability, relief, pain, and itchiness (Figures 3 and 5).

The most notable effects in hypertrophic scars were improvement in pigmentation, vascularization, pliability, thickness, pain, and surface area.

Particularly improvement in thickness, irregularity and pliability can be seen as valuable progress in thickened hypertrophic and keloid scars with excessive collagen deposits.

This study suggests that the combined verapamil and triamcinolone therapy scheme to cause notable scar improvement in both keloid and hypertrophic scars in a relatively early stage (3 to 4 months after start of therapy) (Table 4, Figures 1 and 2). Our results suggest a beneficial effect on some of the clinical parameters of the Patient Scale, which is an encouraging observation since keloids and hypertrophic scars can cause significant psychological and functional distress.[16, 17]

In keloid scars, the same amount of statistically significant decreases in scar scores over time were observed at the Patient and Observer Scale (3; Figures 3 and 5). The Observer Scale showed significant decreases in relief, pliability, and scar surface area. Significant decreases observed in Patient Score included pain and itchiness.

For hypertrophic scars, the Observer Scale scores show more statistically significant decreases in scar scores over time than the Patient Scale (10 versus 5; Figures 4 and 6). Every aspect of the Observer Scale demonstrated significant decrease during follow-up, except for thickness. At the Patient Scale, non-significant decreases were observed in scar pigmentation and itchiness.

However, patients' overall opinions about their abnormal scar are not significantly influenced by itchiness and pigmentation. Instead, psychological distress is suggested to be the more influential characteristic in patients' overall opinion of their scars.[16-18]

Even though POSAS does not include a component of psychological distress or (lack of) quality of life the patient encounters, it is encouraging to see that Patient Scores (including scar pliability, thickness, and relief) reveal prominent improvements in scarring over time.

Multiple studies have proven the effect of triamcinolone and verapamil separately, whereas triamcinolone still is considered being a gold standard in non-surgical management for hypertrophic scarring and keloids. Nonetheless, verapamil has shown to be a promising extra modality in treatment of keloid and hypertrophic scar and it may even function as a suitable alternative to triamcinolone in the treatment of hypertrophic scars and keloids.[19, 20]

In an animal model, intralesional administration of verapamil has proven to suppress proliferation and viability of fibroblasts in mice. Furthermore, combination therapy of triamcinolone and verapamil exerted an efficacy equivalent or even better than double-dose verapamil alone in the treatment of hypertrophic burn scars in mice.[21]

Correspondingly, a randomized parallel group study concluded that both triamcinolone and verapamil could achieve scar flattening in hypertrophic scars and keloids, yet it needed to be clinically investigated if both drugs could be combined in a single injection to derive a synergistic and enhanced response.[22]

The results of the abovementioned studies confirm and rectify our choice to use combined therapy.

This study was planned to evaluate the efficacy of triamcinolone and verapamil with respect to scar outcome. According to our results, we assume a combination therapy of triamcinolone and verapamil is a useful modality to treat hypertrophic and keloid scars (Figures 7 and 8).

This retrospective study showed that a combination therapy of triamcinolone and verapamil results in important scar improvement with a long-lasting result. Future research by means of well-controlled double-blind clinical trials with larger study populations and with the presence of a control group would be ideal for further clinical appraisal of the efficacy of combination therapy of triamcinolone and verapamil.

Conflicts of interest

Authors Kant, van den Kerckhove, Colla, Tuinder, van der Hulst, and Piatkowski de Grzymala declare that they have no conflict of interest.

Informed consent

For this type of study formal consent is not required.

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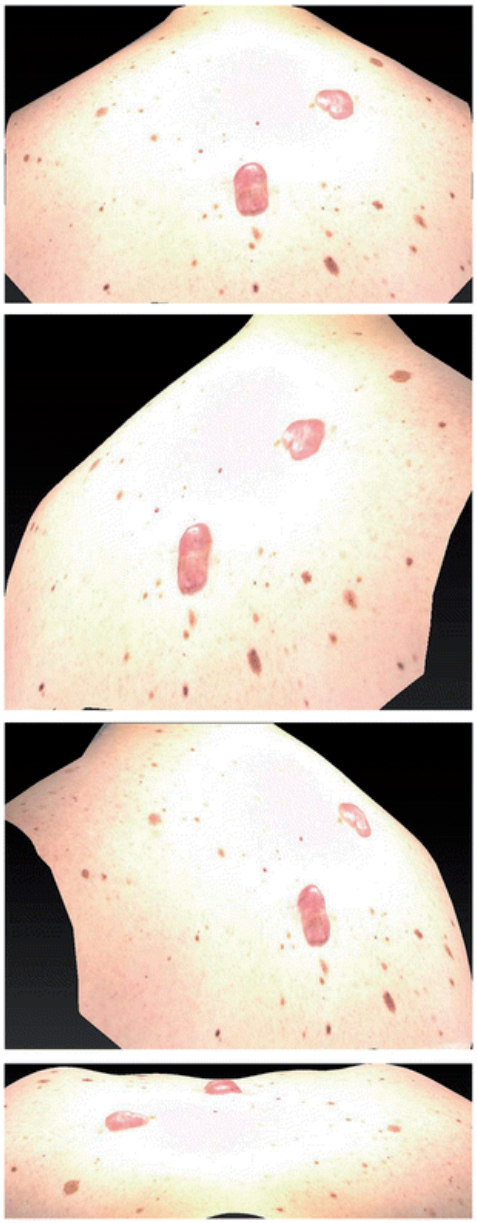


Figure 7. Keloids at the start of the injection scheme

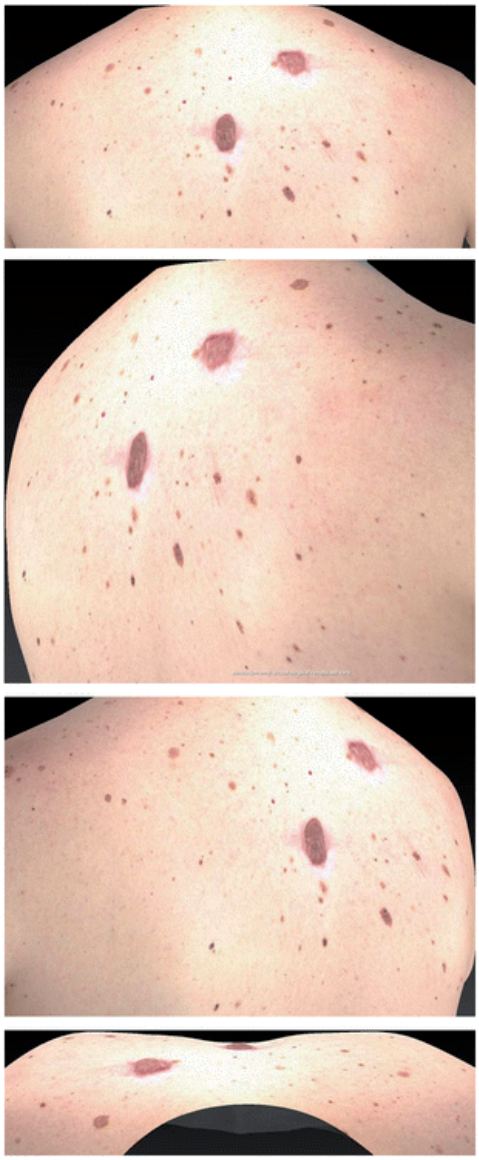


Figure 8. Keloids after patient completed full injection scheme

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CHAPTER 9



General discussion

Scars are inextricably linked with plastic surgery; however, their origin can differ. They can be the result of an operation, a trauma, or a burn, and they can be caused intentionally or unintentionally. An example in which scars are deliberately inflicted is the phenomenon of scarification: intentionally damaging the skin to obtain a permanent scar pattern.[1] Archaeologists have found evidence that this was already done by the Australian Aboriginals in 60,000 BC.[2] Scarification is done by cutting into the skin, removing (parts of) the skin, or chemically or thermally burning the skin. An explanation for this course of action that is widely supported by anthropologists is to thereby make the body "harder." For example, scarification is performed during the symbolic transition from child to adult. In some cultures, medically beneficial effects are associated with scarification. In Togo, for example, scarification is applied to the forehead to treat epilepsy. In Sudan, temporal incisions are made to treat headaches, and supraorbital scars are inflicted to improve vision. However, there is no scientific evidence for the effects of these treatments.[3]

Scars that symbolize emotions and attraction

The sight of a scar can evoke positive emotions: it can remind someone of a special event, such as the birth of a child after a Caesarian section, of a life-saving operation, or of an operation that has alleviated suffering from chronic pain. Scars also play a role in strengthening character traits in certain cultures. For example, the Maori men of New Zealand are known for the combination of facial tattoos and self-applied grooves in their faces which make them more attractive to women and frightening and impressive in combat. Male members of the Karo tribe in Ethiopia scarify their chest to show that they have killed members of rival tribes, and female Karo tribesmen scarify their torsos to be found attractive.[3] Members of the Yoruba tribe in Nigeria have typical self-inflicted facial scars called Kolo. Kolo can have many meanings, such as the demonstration of courage and perseverance, but they can also indicate feelings such as grief and sorrow.[4]

Psychological impact of facial scars

Facial scars are generally not considered desirable in today's Western society. Psychological research tells us that a scarred face causes (undesirable) fixation of the gaze on the face.[4] Facial scars can have a significant negative impact on the quality of life of people. For example, it was shown that even facial scars due to a benign disease such as acne can have a negative influence on relationships through reduced self-confidence and lead to avoidance behavior in others.[5,6]

Facial scars from burns appear to have even more severe effects on people's mental health. These scars can have disastrous effects on the self-confidence of the patient, cause unwanted attention, and may even trigger feelings of isolation.[7]

In the normal physiological formation of a scar, the scar and the direct wound area are red after a skin incision (due to the influx of blood platelets, coagulation factors, serum

proteins, and collagen). This is called the *inflammatory phase*. Cell migration to the wound results in an increase in fibroblasts with the production of extracellular collagen and proteoglycans, causing redness that persists and spreads in the direct wound area. This phase is called the *proliferative* or *granulation phase*, which also occurs early on (about 4 to 7 days after injury) and lasts about 3 to 6 weeks. After 2 to 3 months, the intensity of the scar's redness decreases, but the redness around the scar persists. After 4 to 5 months, the redness further decreases, and after 10 to 12 months, the scars become pale and thinner but they will remain visible.[8-10]

A disruption of the physiological process of scarring can result in hypertrophic and keloidal scars. Hypertrophic scars are often elevated, widened, and red. Keloids are also elevated but often extend over the margins of the initial wound. Furthermore, keloids are notorious for their clinical symptoms of itching and pain. In keloidal scars, the collagen synthesis is about 20 times greater compared to normal skin and about three times larger compared to hypertrophic scars.

In addition, there is a disrupted apoptosis mechanism of fibroblasts in hypertrophic scars and keloids.[11] This overproduction of collagen and reduced degradation of fibroblasts are partly responsible for the known external characteristics of keloids and hypertrophic scars (their pronounced elevation in relation to the surrounding skin). Extrinsically, mechanical stress on wound edges is one of the most critical factors involved in the formation of hypertrophic scars and keloids. For example, hypertrophic scars occur more often with wounds that are closed under tension.

Malignant degeneration of scars

In addition to the psychological consequences of scars, malignancies can arise from atrophic and unstable scars.[12] An example is the development of a *Marjolin's ulcer* : a malignant tumor (histologically, usually a squamous cell carcinoma) that requires wide surgical excision.[13] An extended wound healing period with inadequate wound treatment can result in chronic ulcers, and incomplete epithelialization may result in a Marjolin's ulcer. The Marjolin's ulcer is most common after the inadequate healing of severe burns. Jean Nicholas Marjolin discovered this type of skin tumor for the first time in chronic burn scars in 1828.[14]

Severe disorders that occur as scars

It is also possible for malignant lesions to present themselves clinically as keloids and hypertrophic scars. For this reason, knowledge of the presentation and clinical features of keloids and hypertrophic scars is crucial. The plastic surgeon should be aware of malignancies that can occur in keloids and hypertrophic scars as a misdiagnosed and mistreated "keloid" can have far-reaching consequences that can be life-threatening for the patient. Examples of such cases include an amelanotic malignant melanoma, a dermal leiomyosarcoma, and a dermatofibrosarcoma protuberans that were mistaken for a keloid.[15-17]

Adhesions and contractures

However, the aforementioned malignant degenerations are rather rare. More frequent (functional) problems of scar tissue are adhesions and contractures. In addition to the bothersome cosmetic aspects of scars, scar tissue can also be problematic underneath the skin. For example, after surgical intervention, adhesions may occur due to excessive growth of scar tissue. Adhesions are fibrous bands that form between internal tissue and organs that do not exist in a healthy situation. They occur regularly in the abdominal cavity after inflammation and repeated operations. Adhesions after tendon repair are a frequently occurring troublesome complication in plastic surgery. After surgical flexor tendon repair they occur on average in 30 to 40% of cases.[18] Tendon adhesions can significantly limit the biomechanical movement of the fingers, and they can reduce the functionality of the hand through stiffness.[19,20] Even with the help of extensive hand therapy by means of targeted active and passive mobilization, the problem of stiffness can persist and affect the function of the joint negatively.[21]

Another form of problematic scars underneath the skin are capsular contractions in breast implants. Capsular contractions express themselves through pain and discomfort in the patient.[22] Although mainly older types of implants were notorious for the occurrence of capsular contractures and the incidence of capsular contractions in new implants has been reduced, capsular contractions are still sometimes present and problematic.

Treatment of scars

Scars often heal without the presence of clinical symptoms. However, in some cases, when a normal wound healing cascade is derailed and problematic, pathological scars occur. The prevalence of pathological scars after burns is 77%.[23] Overall, a combination of patient-related factors (genetics, skin type, and hormonal imbalance), location-related factors (specific locations on the body), and environment-related factors (trauma, inflammation, burns, operations, increased wound stress) are at the root of an abnormal cellular response that can lead to the formation a pathological scar.[11] Pain and pruritus are the most common clinical symptoms of pathological scars. Finding a tailor-made therapy for a diverse patient population is a major challenge because of the many types of scar treatments that are currently available and the specific expectations of each patient, which depend on age, gender, and culture.

Invasive and non-invasive scar treatments

The history of scar treatment is believed to date back to a few thousand years ago, when beeswax was used by the ancient Egyptians and Greeks to promote wound healing and to prevent abnormal scarring. Since those days, multiple treatment methods have emerged, for which the scientific evidence of efficacy and efficiency varies from scant to relatively extensive. The most common scar treatments currently include non-invasive methods

such as the use of silicone sheets and gels, pressure therapy, and other topical treatments (vitamin E, vitamin A, onion extract, and imiquimod). On the other hand, there are invasive methods such as dermabrasion, surgical excision, intralesional injections (including corticosteroids, verapamil, bleomycin, 5-fluorouracil, and collagenase), radiotherapy, laser therapy, cryotherapy, lipofilling, and combinations of these techniques.[24-29] The wide range of options and the lack of knowledge of the mechanism of action of the various treatments can lead to uncertainty for the practitioner about the correct and most adequate and reliable therapy for the patient. Certainly, when problematic scars are located in a precarious location such as the face are, choosing the right treatment is a major challenge.

Better insight into the maturation period of hypertrophic scars

It is generally assumed that scars are best treated while they are still in their active "immature" phase, when the remodeling of scar tissue takes place. This active phase is characterized by erythema, increased thickness, and the presence of clinical symptoms (such as pain and pruritus).[30,31] However, estimates of the length of the remodeling phase are broad and inaccurate. The consensus is that scar maturation occurs within a year, although there are also studies indicating that the process can take several years.[32,33] In **Chapter 2**, it was noted that hypertrophic scar maturation could take significantly longer than is generally stated in the literature. For example, in this study, three years after the onset of a hypertrophic scar, 34% of patients still had an active, immature scar. This chapter also showed that older patients (>55 years) develop mature scars considerably faster than do young patients (>35 years) (on average, 22.53 months versus 35.76 months, respectively). This conclusion is consistent with a study by Bond et al., in where standardized scars were inflicted on 58 patients.[9] In our present study, the same age categories were used for young, middle-aged, and older patients. There are no other clinical studies on the estimated duration of scar maturation of a large patient group in the current literature. A possible explanation for the delayed maturation time in young patients is that their scar tissue may have a higher vascular density. As a result, more proliferative stimuli are received, causing the activity and growth of scar tissue to last longer. The clinical consequence of this is that we recommend a conservative approach with regard to the surgical management of hypertrophic scars over a more extended period. Also, we recommend the use of scar therapy for a longer duration.

With regard to maturation time and possible scar therapy applications, pressure therapy seems to ensure the most rapid scar maturation of the therapies examined in our study (23.20 months on average, compared to 30.59 months for combination therapy, 35.51 months for silicone therapy, 46.42 months for intralesional therapy, and 41.31 months for other therapies).

Pressure therapy is one of the most studied types of scar therapy with clear indications of positive clinical effects. These effects include reduction of pain, itching, and edema, as well as indications of an accelerated maturation time of scar healing.[30,34-36] The results of our

study confirm the choice of using pressure therapy for the treatment of hypertrophic scars. Nevertheless, there were some limitations. First, the retrospective nature of this study did not allow for the exact time of the onset of scar hypertrophy to be determined. In addition, the study population did not include a control group. Finally, patients in our study had a history of problematic scars (as they were referred to a specialized scar outpatient clinic). This could have influenced the maturation time negatively. In our opinion, this is the first clinical study in which the maturation of hypertrophic scars of such a large number of patients has been investigated over a prolonged period of time. Prospective research in which an attempt is made to standardize the various causes of scars is necessary to obtain an even more reliable estimation of the maturation period of hypertrophic scars.

What often precedes facial pressure therapy: Facial skin cancer

One of the main causes for major facial defects is (the surgical removal of) facial skin cancer, of which basal cell carcinoma is the most common type. When skin cancer is surgically removed, the resulting defect may be extensive due to the size and depth of the malignant growth. The consequence of this is the necessity of performing extensive facial reconstruction. It is known that skin cancer can cause a significant decrease in the quality of life of patients.[37] However, the effect of facial skin cancer on patients' perceived aesthetic appreciation of their face has never been thoroughly investigated with the use of a PROM.

In aesthetic surgery, multiple PROMs that assess quality of life and patients' satisfaction after aesthetic procedures such as rhinoplasty, skin rejuvenation, facelift, and blepharoplasty have emerged in recent years.[38] These PROMs help patients to quantify the possible positive effects of these aesthetic treatments. Techniques can be compared in this way and patients can thereby better assess whether these treatments would contribute to their quality of life. This can lead to a more conscious and well-informed choice before undergoing an aesthetic procedure. PROMs have also been developed for the treatment of non-melanoma facial skin cancer: the Facial Skin Cancer Index is the most specific tool for assessing quality of life after facial skin cancer.[39] This questionnaire includes items regarding the feelings of fear, shame, frustration, and worry caused by facial skin cancer. However, no studies in the current literature examine the influence of skin cancer on the aesthetic appreciation of the face in detail, such as the effect of facial skin cancer surgery on facial symmetry and proportions. At a time when there is an increasing demand for assessment of the effects of treatments and the capacity to inform patients about the consequences for the appreciation of their facial appearance after facial skin cancer surgery, it is valuable to obtain deeper insight into the effects of (the surgical removal of) facial skin cancer.

In **Chapter 3**, 47 patients (23 men and 24 women with an average age of 71 years) reported on the impact of the surgical removal of facial skin cancer on the appreciation of their face throughout FACE-Q questionnaires. Three component questionnaires of the FACE-Q were used. Questionnaires regarding satisfaction with facial appearance (in general

and in social situations) were filled out before surgery, at one month, and at three months after surgery. The third questionnaire, satisfaction with the result of surgery, was filled out by patients at one and three months after surgery. Patients were treated using standard surgical excision or Mohs' micrographic surgery for different types of histologically proven (non-melanoma) skin cancer.

The results showed that patients were significantly more satisfied with the aesthetic result at three months after surgery compared to one month. Also, removal of facial skin cancer does not appear to lead to a poorer appreciation of patients' facial appearance either in general or in social situations, as scores from both questionnaires showed no significant decrease between the baseline and one-month and three-month follow-ups. In addition, patients with larger skin cancer lesions (>10 mm in diameter) were significantly more satisfied with the end result at three months compared to one month after surgery. A possible explanation for this is a difference in patients' expectations. Patients who are aware that major facial reconstruction must take place may be relatively more positive about the result (because they might expect a "bad" result) than patients who undergo surgery for a smaller skin cancer lesion and may therefore expect that the result of surgery to be better. However, this hypothesis was not tested in this study. In the patient group with smaller skin cancer lesions (<5 mm and 5 to 10 mm), no significant differences in satisfaction with facial appearance (in general or in social situations) were observed at the two follow-up points.

The study showed that patients did not experience a significant change in appreciation of their facial appearance after surgical reconstruction due to facial skin cancer between the baseline and the two follow-up points. Furthermore, satisfaction with the result of therapy did not significantly change over a three-month period.

According to this study we can conclude that Mohs' micrographic surgery and standard surgical excision appear to be effective in maintaining an acceptable aesthetic result after facial skin cancer surgery in patients' perception. Given that basal cell carcinoma is the most common type of cancer and surgical excision is usually the only possible treatment, the results of this study (when extrapolated to all patients with basal cell carcinoma) are positive and encouraging for this patient group. During this study, no patients were administered facial pressure mask treatment.

When observing the influence of facial locations from where skin cancer was removed, the greatest improvement in satisfaction with the result is seen in patients with defects on the nose. However, this difference was not statistically significant. To make a clearer statement about the facial location where skin cancer surgery has the greatest impact on (dis)satisfaction with facial appearance, larger study populations are needed with a longer follow-up period. It would also be helpful to objectify the thickness, color, and pliability of the facial reconstruction sites by means of ultrasound, colorimeter, and cutometer, respectively, and to correlate these values with satisfaction with facial appearance. In this way, even better insight into the parameters that are most vital in preserving an acceptable

aesthetic result after facial skin cancer surgery can be obtained. The use of the FACE-Q in this study made it possible to investigate how the assessment of patients' facial appearance is affected by surgical reconstruction after facial skin cancer in a valid way. This is the first study to examine the effects of facial skin cancer surgery on aesthetic appreciation after facial skin cancer surgery over a period of three months.

Pressure mask therapy for the treatment of facial scars and deformities

Specifically when we look at facial scars, a unique and delicate approach is usually required, given the psychological implications of scars in this area.[40] When facial scars are relatively small, there may be a role for topical agents, intralesional injections, dermabrasion, surgical excision, radiotherapy, or laser therapy.[11,41-46] However, when large or multiple facial units are involved as, for example, with extensive burns, the key to treatment is often pressure therapy. Pressure masks (initially in the form of elastic hoods and later in the form of transparent plastic masks) have been used for scars due to burns for about 50 years.[70-72] In theory, exerting mechanical pressure on immature scars causes capillary occlusion, resulting in reduced blood flow to the scar tissue, which can result in a decrease in (myo)fibroblast proliferation and collagen synthesis.[10,47,48] Another suggested effect of pressure therapy is edema reduction. However, wearing a pressure mask for at least 12 hours a day is physically and mentally challenging. Proof of this is the low compliance rates observed in patients with hypertrophic scars due to severe facial burns,[49] although the number of studies assessing the effects of pressure masks using validated measuring instruments is also limited.

Chapter 4 presents a systematic review of the current literature regarding the clinically measured effects of pressure mask therapy on severe hypertrophic scars and other facial deformities. Only three studies (published in 2016 and 2017) describing assessment of the skin after pressure mask therapy using validated measuring tools were included. Two of the studies focused on the treatment of burns in minor and adult Chinese patients (n=12). One of these studies (n=2) did not describe any significant improvement in the average thickness of hypertrophic scars between one and three months after the start of the therapy, measured by ultrasound. The other study, that focused on burn scars, described a significant decrease in the thickness of hypertrophic scars on the forehead, eyes, nose, and mouth in the two treatment groups, again measured by ultrasound. In this study, one patient group consisted of patients being treated as quickly as possible (n=5), and the other group was comprised of patients that were treated one month later (n=5). In addition, the hardness of scars was found to improve significantly in both treatment groups (measured with a durometer), and there was a significant improvement in POSAS scores in both the Observer and Patient Scales for both groups. The third study described a cohort of 21 patients treated with a pressure mask because of conspicuous persistent scars and deformities arising after facial flap surgery (see the study in **Chapter 6**). The average total POSAS score and the average Patient Score decreased significantly in this study, with an

average follow-up of 46 weeks (from 48.87 to 30.31 and from 31.10 to 16.29, respectively). All studies used a pressure mask with added silicone on the inside. The duration of wearing the mask (from 10 to 20 hours of daily wear) and the amount of applied pressure underneath the mask varied (from 11.30 to 13.32 mmHg). The small number of studies that have investigated the clinical effects of pressure mask therapy with validated measuring instruments and the small patient groups in such studies limits the review. Therefore, it remains difficult to make a robust statement about the clinical effects of pressure mask therapy. The excluded and mainly outdated articles in which pressure masks were the subject of study were mostly clinical observations of the effect of pressure masks, a technique of manufacturing pressure masks, or the evaluation of different types of pressure masks without the clinical effects being thoroughly investigated.[50-54] Clinical trials with larger patient populations and control groups are necessary to confirm the suggested positive effects of pressure masks to treat facial scars. Because of the intensity and challenging nature of the therapy, it is necessary to gather more evidence about the clinical effects and the effects on the quality of life of patients in order to justify the use of this non-invasive therapy.

Fabrication of a facial pressure mask

In addition to their frequent use in burn care, pressure masks are used at the MUMC+ for other purposes: the improvement of hypertrophic or postsurgical irregular scars and the reduction of skin thickness after facial flap surgery with unsatisfactory aesthetic results. The manufacturing of specific masks for such purposes is explained in **Chapter 5**. This technical article described how a transparent pressure mask with a custom inner layer of silicone is manually formed at the MUMC+. The manufacturing of such a mask which combines silicone and pressure therapy, has never been described to date. For manufacturing and econimical purposes, facial scanning is used more and more frequently in recent years. In this way, the digital model obtained can be adjusted using software and then 3D printed. This technique is minimally burdensome for patients and relatively fast. However, manually manufactured masks have several crucial advantages over this technique.

By manually applying liquid plaster to the face and shifting the underlying soft tissue during the hardening of the plaster, the orthotist/prosthetist facilitates the application of extra pressure to the desired parts of the face. A positive model is then formed by filling the negative model with liquid plaster so that it contains all the irregularities of the face. After this, the positive model is dried and corrected by means of sandpaper with very fine grit. A Uvex® transparent plastic sheet is then heated and applied over the positive model using a vacuum console in order to compress the mask to the model. After the removal of the excess Uvex® edges, the mask is complete. In a final step, a medical grade silicone sheet with a thickness of 1 mm is applied to the inside of the plastic mask and anchors are attached for fixing the head bandages enabling the adjustment of the pressure on the face of the patient.

Another major advantage of this technique over 3D printing is that it allows for minimal and precise manual adjustments to the positive plaster mask during therapy when scar thickness reduces. Thus, there is no need for a new mask to be fabricated when the appearance of the scars changes and the pressure underneath the mask decreases as a result. The manual technique is superior with regard to shifting and steering underlying tissue that requires an extra amount of pressure. In the case of 3D models, extra pressure can also be added at specific locations with the use of software. However, this is not accompanied by the shifting of underlying tissues. This shifting is important, for example, in patients with an ectropion caused by the contraction of scars. When using the manual technique, soft tissue under the lower eyelid can be shifted upward toward the lower eyelid during the formation of the negative mold to reduce ectropion.

Also, during each follow-up visit to the outpatient clinic, the positive mold ca be adjusted when scars and deformities are reduced. Then, the plastic mask can be heated and put over the adjusted positive mold so that the changed or diminished facial scars are also reduced on the plastic mask. By applying 2 to 3 monthly adjustments to the mask, the pressure on the desired parts of the face remains adequate at all times. A disadvantage of this traditional method is that it takes several weeks to manufacture a complete mask. Also, learning to form negative and positive molds is accompanied by a steep learning curve. Forming a mask via scanning of the face and 3D printing is less stressful for the patient and takes less time.

Clinical results of facial pressure mask therapy

As mentioned, this specific pressure mask is mainly used at the MUMC+ with patients who have unsatisfactory results after facial flap surgery for coverage of a skin defect. Such flaps can be transposition flaps (rhomboid flap, Z-plasty), rotation flaps (bilobed flap, nasolabial flap), advancement flaps (cheek advancement, VY-plasty), or combinations of these. In most cases, these flaps provide acceptable aesthetic results. In a small number of cases, the covering of large facial defects through flaps results in noticeably thickened, bulging reconstruction zones sometimes resulting in "pincushioning" and the formation of hypertrophic scars. In a study in which plastic surgical reconstruction after Mohs' surgery was examined in 446 patients, it appeared that a surgical revision was required in 4% of the patients and that pincushioning occurred in 11% of cases.[55-57]

In **Chapter 6,** the efficacy of a pressure mask for this specific group of patients who had unsatisfactory results after facial flap surgery (n=21) was investigated. This is the first clinical study to investigate the effectiveness of a pressure mask for this purpose. The effects of pressure masks have so far only been studied for patients with hypertrophic scars due to burns. The patient group (with an average age of 57 years) was followed up for an average duration of 46 weeks (from 11 to 112) during treatment with a custom-made pressure mask as described in **Chapter 5.** Patients wore the mask for an average of 12 hours a day,

although the daily duration of therapy was not registered. The facial reconstruction zones were assessed by means of the POSAS at the start and end of therapy.

With regard to the Patient Scale of the POSAS, it appeared that itching, pigmentation, pliability, thickness, and relief of the skin improved significantly after an average therapy duration of 46 weeks. The Observer Scale showed a significant improvement in the thickness, relief, and pliability of the reconstruction site after the completion of therapy. The total POSAS (the sum of the Patient Scale and the Observer Scale) also decreased significantly between the start and end of the therapy (from 48.86 to 30.13).

Ideally, this study would have had a control group and a larger research population. Nevertheless, it is a valuable result that patients were satisfied with the clinical results of therapy. Proof of this are the improvements in five of the six aspects of the Patient Scale of the POSAS. This therapy seems suitable for the small group of patients for whom facial flap surgery leads to substantial scars and deformities. However, the prerequisite is that patients are motivated to complete the therapy since the mask sometimes has to be worn daily for longer than a year. The alternative to this non-invasive but gradual soft-tissue correction is a surgical revision of the skin flap. However, there are multiple possible complications (ischemic, stress-related, hematological, and infections) that might occur as a result of a surgical revision.[55] Applying a pressure mask could possibly prevent surgical revision. The pressure mask has been shown to be effective in patients who were treated between one and three months after facial flap surgery and who still had active, immature scars in which scar remodeling could still take place. In this study, the pressure mask was not tested on patients with longer-existing or mature scars and deformities. For patients with severe and extensive scars and deformities for which pressure therapy, topical agents, intralesional injections, dermabrasion, radiotherapy, and laser therapy are not sufficient or indicated, surgical revision seems to be the only alternative.

Durability of pressure mask therapy

Since pressure mask therapy is demanding for the patient, it is essential that the clinical results of this therapy be long-lasting and that patients be satisfied with the end result of the treatment.

Chapter 7 answers the question, "Has wearing a pressure mask been worth it from the point of view of the patients?" This is the first study to investigate the results after treatment with a pressure mask using a Patient Reported Outcome Measure (PROM). The study population included 87 patients who underwent and completed treatment with a customized facial pressure mask between January 2012 and November 2017. The primary aim of this study was to examine patients' satisfaction with their facial appearance (in general and in social situations) after completing pressure mask therapy. An additional purpose was to assess patients' satisfaction with the outcome of therapy and their choice of pressure mask therapy. These were assessed via the completion of four different FACE-Q

questionnaires: a PROM developed to evaluate the results of aesthetic procedures from the patient's point of view. Patients were divided into five groups based on the time elapsed since the end of therapy (<1 year, 1 to 2 years, 2 to 3 years, 3 to 4 years, and 4 to 5 years). There appeared to be no significant differences among the five follow-up groups in the degree of satisfaction with facial appearance in general and in social situations. Therefore, it can be concluded that the aesthetic results are stable in a follow-up period of five years. The results showed that patients who completed therapy 3 to 5 years ago are significantly more satisfied with their facial appearance in general compared to patients who completed therapy less than one year ago. The "extended" maturation time of hypertrophic scars proposed earlier in this thesis wherein some patients it may take several years before some patients' scars become clinically inactive may explain the difference in satisfaction with facial appearance between the two aforementioned groups.

Another important finding of this study was that patients who indicated wearing the mask 12 to 16 hours daily were significantly more satisfied with the end result of therapy compared to patients who had worn the mask for only 4 to 8 hours a day. This suggests that a longer daily duration of therapy leads to better aesthetic results in patients' perception. However, there is no clear consensus in the literature regarding the number of hours a pressure mask should be worn daily. It could be assumed that this should be the same as the daily recommended duration for pressure therapy at locations elsewhere on the body. The recommendation for wearing pressure garments is, on average, 23 hours daily.[58] However, in this study, patients were advised to wear the mask for as long they could endure it, with a minimum continuous wearing time of 8 to 12 hours per day to make the therapy mentally bearable. Face and neck pressure therapy is known for its low compliance rates in patients, as was observed in the past by Stewart et al.[49] Our study found that seven patients (17% of the study population) reported wearing the mask less than the recommended time (4 to 8 hours per day instead of a minimum of 8 to 12 hours per day). Therefore, compliance was also a problem for some patients in this study.

Nevertheless, no significant differences were observed in the study with regard to the satisfaction with facial appearance (in general or in social situations) of patients wearing the mask for 4 to 8 hours, 8 to 12 hours, and 12 to 16 hours daily. However, patients who wore the mask for at least eight hours a day (8 to 12 hours and 12 to 16 hours) did report significantly higher satisfaction with regard to their choice of pressure mask therapy compared to patients who wore the mask for 4 to 8 hours a day. In addition, the mean Patient, Observer, and total POSAS scores decreased significantly between the start and end of therapy.

Although the clinical evidence on the effectiveness of pressure masks is scarce, as described in **Chapter 4**, this study showed that the results of pressure mask therapy in this specific population remained stable over a five-year follow-up period. On average, patients were also satisfied with their decision to undergo pressure mask therapy.

A new therapy for keloids and hypertrophic scars

If we look further into the treatment of problematic scars, the number of current modalities is extensive, and the practitioner's choices for appropriate therapy are challenging and often depend on their own experience.[59-62] In particular, the treatment of keloids remains problematic because of the severity of the clinical symptoms (especially pain and pruritus), the rapid growth of the scar tissue, and their recurrent character.[63] Hypertrophic scars and keloids, in particular, are known to have a significant negative impact on the quality of life of patients. For the treatment of such scars, intralesional injections are among the most commonly used options.[25,64,65] Steroids, and in particular, triamcinolone acetonide, have long been used in intralesional injections for keloids, and they have proven to be effective. However, atrophy and pigmentation changes are the most serious side effects.[66-69] The theory is that triamcinolone acetonide reduces the degradation of collagenase by decreasing the proteinase inhibitors alpha-2-macroglobulin and alpha-2-antitrypsin in scars.[70]

A less researched drug for intralesional injections is verapamil. This drug, which blocks calcium channels, is mainly used to treat hypertension. Verapamil has been shown to be capable of depolarizing actin filaments and changing the shape of fibroblasts from bipolar to spherical. This depolarization activates procollagenase gene expression in dermal fibroblasts, resulting in a decrease in the extracellular matrix of keloids and hypertrophic scars.[71-75] Verapamil also appears to cause fewer side effects when compared to triamcinolone.[66,76] The use of verapamil for the treatment of keloids was first described in 1997. It is an agent that has recently gained increasing popularity in the (intralesional) treatment of hypertrophic scars and keloids.[77] In recent years, various studies have been conducted examining the effects of verapamil with other therapies, such as silicone gel sheets, pressure therapy, and in combination with interferon and a steroid drug.[78-80] Verapamil is, therefore, a promising additional modality in the range of current scar treatments.[74,81]

In **Chapter 8**, a new therapy was proposed for the treatment of hypertrophic scars and keloids in which triamcinolone and verapamil were combined 1:1 and administered intralesionally according to a fixed schedule (an initial injection, an injection after one week, and a third injection three weeks after the first injection). Scars were assessed using the Patient and Observer Scar Assessment Scale (POSAS)based on six aspects on a scoring scale of 1 to 10 (where 10 is the worst possible result) by both the physician and the patient. The most important findings in the group of 58 patients (31 hypertrophic scars and 27 keloid scars) in this retrospective study with a maximum follow-up of 729 days were as follows: significant improvement in scar surface area, pliability, relief, pain, and itching in keloids and significant improvement in pigmentation, vascularization, pliability, thickness, pain, and surface area in hypertrophic scars. The results were found to persist in the long-term as the average total POSAS score in the patient group that was followed up over 12 months after the first injection showed a significant increase when compared to baseline. Although this

was a retrospective study, it is promising that a combination of these drugs provided stable long-term results in the treatment of problematic keloids and hypertrophic scars.

Given the promising capacities of verapamil concerning fibroblast degeneration and the sometimes unsatisfactory results of triamcinolone as monotherapy in the treatment of keloids and hypertrophic scars, the idea of adding verapamil has previously arisen. The first study in this vein was conducted in 2010 by Yang et al., who investigated the combined intralesional use of verapamil and triamcinolone on human hypertrophic scar tissue implanted in mice.[82] They demonstrated that combination therapy caused a significant decrease in fibroblasts compared to a control group. Although clinical evidence supporting combination therapy is still scarce, our results from **Chapter 8** justify the choice to use combination therapy. No other clinical comparative studies on the combined intralesional use of verapamil and triamcinolone on hypertrophic scars and keloids are available at the time of writing. Triamcinolone acetonide is the most researched drug to date with regard to intralesional injections for hypertrophic scars and keloids, and it is (although with considerable side effects) still considered the gold standard.[69] The ongoing KEV trial at the MUMC+, where the clinical effects of both triamcinolone and verapamil alone and the combination of both agents on hypertrophic scars and keloids are being studied, should provide more conclusive evidence regarding the clinical effects of the combined use of triamcinolone and verapamil compared to the separate use of these agents. The study in **Chapter 8** can be seen as a valuable first step in providing evidence of the beneficial clinical effects of intralesional combination therapy with triamcinolone and verapamil.

Conclusion

In conclusion, this thesis provides additional insights into the possible "extended" duration of hypertrophic scar maturation, and into the appreciation by patients of their facial appearance after facial skin cancer surgery. Also, the thesis contributed to knowledge regarding the fabrication, clinical effectiveness, and long-term results of facial pressure mask therapy. Finally, the thesis provided insight into a relatively new combined intralesional scar therapy for keloidal and hypertrophic scars.

Clinical relevance

1. The maturation time of hypertrophic scars appears to be significantly longer than initially thought, with older people (>55 years) demonstrating the fastest development of mature scars. A more conservative approach regarding surgical revision is therefore recommended.
2. Removal of facial skin cancer by means of standard surgical excision or Mohs' micrographic surgery did not seem to adversely affect patients' perceived facial aesthetic appearance in a follow-up assessment at three months.

3. Facial pressure masks can provide significant improvement in hypertrophic scars and facial deformities in patients undergoing facial flap surgery to cover facial defects.
4. It has also been found that patients up to five years after completion of facial pressure mask therapy remain satisfied with the result and that longer daily wearing of the mask leads to a better result, according to the patients.
5. Therapy with combined intralesional injections of triamcinolone and verapamil into hypertrophic scars and keloids can lead to significant and stable improvement.

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CHAPTER 10

10

English summary

Chapter 1: Introduction

This chapter aims to introduce the reader to the consequences of scarring and to highlight the importance of scar therapy in plastic surgery. The formation of scars is discussed, and insight is provided about the wound healing cascade. The chapter also focuses on the influence of different cultures on the perception of scars and their (functional, symptomatic, and cosmetic) consequences as well as the psychological impact of scars on patients. The different types of scars are then addressed, and the current surgical and non-surgical options are discussed for the treatment of problematic scars. In addition, a specific way of treating facial scars with a pressure mask is discussed. Finally, the aims of this thesis are formulated.

Chapter 2: Better understanding of the maturation time of hypertrophic scars

This chapter aims to provide more insight into the least understood phase of the wound healing cascade: the remodeling or maturation phase. In the current literature, estimates of the duration of this phase are wide-ranging and unclear. During this active phase, scar remodeling is still possible, and scars are susceptible to appropriate therapy. In the retrospective study in **Chapter 2**, in which 361 patients with hypertrophic scars were followed, it was shown that the maturation of hypertrophic scars takes significantly longer than stated in the literature. Older patients (>55 years) form mature scars at a significantly faster pace than do younger patients (<35 years): 22.53 months versus 35.76 months, respectively. Pressure therapy (23.20 months) provides the fastest maturation of hypertrophic scars when compared to combination therapy (30.59 months), silicones (35.10 months), intralesional therapy (46.42 months), and other therapies (41.31 months). This is the first clinical study to investigate the course of hypertrophic scars in a large group of patients. Prospective studies examining the natural course of standardized scars are important for the further unraveling of the wound healing cascade.

Chapter 3: Aesthetic results after facial skin cancer surgery

Chapter 3 focuses on patients' perceived effects of surgical removal of facial skin cancer. Surgical removal of skin cancer needs to be as radical as possible. A consequence of this is that large defects can occur. Particularly in the face, this can have disastrous consequences for the anatomical proportions of the face. In **Chapter 3,** we examined the influence of the surgical removal of facial skin cancer on patients' perceived facial appearance using FACE-Q questionnaires. This study showed that patients are significantly more satisfied with the result of the facial reconstruction three months after surgery compared to one month after. Satisfaction with patients' facial appearance in general, and in social situations is not significantly affected by the removal of facial skin cancer in the period between baseline, one month, and three months after surgery. It appears that skin cancer surgery for larger lesions (>10 mm in diameter) leads to a significant improvement in satisfaction with the result between one and three months after surgery. The influence on patients' perceived facial

appearance regarding the facial location where skin cancer occurred was also investigated. Removal of skin cancer on the nose appears to have the greatest effect on the appreciation of the face when compared to the other anatomical locations in this study (frontal/temporal, eyelids, and nasolabial). However, this difference was not statistically significant. Studies with larger patient populations and studies with a longer follow-up duration should reveal more about the possible aesthetic consequences of the surgical removal of skin cancer from different facial sites.

Chapter 4: Systematic review of the clinical effects of pressure masks

Facial scars are known for their potential disastrous consequences for patients' quality of life. The therapy for extensive facial scars is pressure therapy—a physically and mentally challenging therapy. However, the evidence of the clinical effects of this therapy, measured with validated instruments, is limited. **Chapter 4** summarizes the current literature on the clinical effects of transparent rigid pressure masks by means of a systematic review. Only three articles that address small patient groups were included. It was, therefore, challenging to make a robust statement about the clinical effects of pressure masks on facial scars. However, two of the three studies described a significant improvement in terms of decreased in thickness, improved hardness, and improved POSAS scores for hypertrophic facial scars after treatment with a pressure mask.

Chapter 5: The fabrication technique of a specialized facial pressure mask

At the MUMC+, pressure masks are often used to reduce the thickness of the skin after facial flap surgery and to improve hypertrophic facial scars and irregularities. **Chapter 5** explains the fabrication technique of such a custom-made mask. Sequentially, the fabrication process includes the fabrication of a negative mold, a positive mold, the production of the Uvex® outside of the mask, the addition of the silicone inner layer, and the finishing of the mask. Soft tissue is manually shifted during the formation of the negative mold. When forming the positive mold, it is important that irregularities are removed from the mold. The finishing of the mask consists of attaching anchors for the Velcro® in order to apply pressure to the face. For the shifting and steering of soft tissue, a hand-made mask like the one described above is superior to 3D-printed masks based on face scanning. In addition, manual adjustments can be made more easily during therapy. However, the manufacturing of such a mask is accompanied by a steep learning curve.

Chapter 6: The clinical effects of a specialized facial pressure mask

The number of studies assessing the clinical effects of transparent pressure masks (as described in **Chapter 4**) is small. **Chapter 6** describes the clinical effectiveness of a facial pressure mask for patients with aesthetically unsatisfactory results after facial flap surgery. These patients had symptoms of noticeable hypertrophic scars and thickened, bulging

reconstruction sites after facial flap surgery to cover a defect usually caused by (the removal of) skin cancer. Twenty-one patients were included in a retrospective study over an average treatment duration of 46 weeks. Significant improvements in POSAS scores and, in particular, in the Patient Scale of the POSAS were observed in this study. Although facial flap surgery usually provides acceptable results, and although face mask therapy is only suitable for a relatively small number of (motivated) patients, it is a promising result in our study that patients following pressure mask therapy show clinically significant improvements.

Chapter 7: Quality of life after therapy with a specialized facial pressure mask

At the MUMC+, patients undergoing pressure mask therapy are advised to wear the mask for 12 hours per day. Sometimes therapy is necessary for longer than a year. Many patients experience wearing a full-face mask as a hideous and socially disruptive experience. In addition, prolonged positive facial pressure can be experienced as unpleasant. Moreover, pressure mask therapy is often long-term treatment. In **Chapter 7**, 87 patients who completed face mask therapy within the past five years were asked about satisfaction with their facial appearance in general and in social situations. They were also questioned about satisfaction with the choice of pressure mask therapy and satisfaction with the end result after treatment. The results reveal that a longer daily duration of therapy (8 to 12 hours per day versus 4 to 8 hours per day) leads to greater satisfaction with the end result from the patients' perspective. Patients' satisfaction with their facial appearance in general and in social situations appears to be stable over a follow-up period of almost five years. This study supports the choice of pressure mask therapy for the treatment of problematic facial scars.

Chapter 8: A new treatment for hypertrophic and keloid scars

Hypertrophic and, in particular, keloid scars are known for their negative effect on patients' quality of life. Keloids also have a recurrent nature, often with the presence of itching and pain. Intralesional injections with steroids (of which triamcinolone acetonide is the most studied steroid drug) are part of the standard treatment of thickened and elevated hypertrophic scars and keloids. With triamcinolone, varying results have been achieved, and side effects regularly occur. The addition of verapamil, a calcium antagonist that also has positive effects on scar tissue and thereby has a more favorable side effect profile, is discussed in **Chapter 8**. Intralesional injections of 1:1 triamcinolone and verapamil appear to result in significant and long-lasting improvements in hypertrophic and keloidal scars. This was measured by means of POSAS scores, with a maximum follow-up period of 729 days. A prospective comparative study of the clinical effects of verapamil and triamcinolone alone, as well as the combination of these drugs, should provide even more robust evidence of the effectiveness of these intralesional injections for hypertrophic scars and keloids.

Chapter 9: General discussion

In this chapter, the main findings from this thesis are discussed. Also, its relationship with the current literature on scarring, the aesthetic results after facial skin cancer, pressure mask therapy, and intralesional injection therapy is reviewed and situated.

APPENDICES



Appendices

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Nederlandse samenvatting

Hoofdstuk 1: Introductie

Dit hoofdstuk heeft als doel de lezer te introduceren over de gevolgen van littekens, alsmede het belang van littekenbehandeling in de plastische chirurgie te benadrukken. De vorming van littekens wordt besproken en er wordt inzicht gegeven in de wondhelingscascade. Het hoofdstuk is tevens gericht op de invloed van verschillende culturen op de perceptie van littekens en op de (functionele, symptomatische, en cosmetische) gevolgen en de psychologische impact van littekens op patiënten. De verschillende types van littekens worden doorgenomen en de huidige chirurgische en niet-chirurgische mogelijkheden ter behandeling van problematische littekens worden bediscussieerd. Daarnaast wordt er een specifieke behandelmethode voor littekens in het aangezicht door middel van een drukmasker besproken. Tenslotte worden de doelen van dit proefschrift vermeld.

Hoofdstuk 2: Een beter begrip omtrent de uitrijpingsduur van hypertrofische littekens

Dit hoofdstuk heeft als doel het verkrijgen van meer inzicht over de minst begrepen fase van de wondhelingscascade: de remodellerings- of maturatiefase. In de huidige literatuur zijn de inschattingen van de duur van deze fase breed en onduidelijk. Tijdens deze actieve fase kan remodellering van littekens nog plaatsvinden en zijn littekens vatbaar voor de juiste therapie. In de retrospectieve studie in **Hoofdstuk 2**, waarin 361 patiënten met hypertrofische littekens werden gevolgd, wordt gezien dat de uitrijping van hypertrofische littekens significant meer tijd in beslag neemt dan vooraf werd gesteld in de literatuur. Oudere patiënten (>55 jaar) vormen significant sneller uitgerijpte littekens dan jongere patiënten (<35 jaar): 22,53 maanden versus 35,76 maanden, respectievelijk. Druktherapie (23,20 maanden) zorgt voor de snelste uitrijping van hypertrofische littekens, vergeleken met gecombineerde therapie (30,59 maanden), siliconen (35,10 maanden), intralesionale therapie (46,42 maanden), en overige therapieën (41,31 maanden). Dit is de eerste klinische studie waarin bij een grote groep patiënten het verloop van hypertrofische littekens wordt onderzocht. Prospectieve onderzoeken waarbij het natuurlijk verloop van gestandaardiseerde littekens wordt onderzocht is van belang voor de verdere ontrafeling van de wondhelingscascade.

Hoofdstuk 3: Esthetische resultaten na chirurgie vanwege huidkanker in het gelaat

Hoofdstuk 3 richt zicht op de door de patiënt ervaren gevolgen van chirurgische verwijdering van huidkanker in het gezicht. Chirurgische verwijdering van huidkanker dient zo radicaal mogelijk plaats te vinden. Het gevolg hiervan is echter dat dit kan resulteren in

grote defecten. Met name in het gezicht kan dit zorgen voor desastreuze gevolgen voor de anatomische verhoudingen. In **Hoofdstuk 3** wordt de invloed onderzocht van chirurgische verwijdering van huidkanker in het gezicht met betrekking tot de waardering van het gezicht door de patiënt, door middel van FACE-Q vragenlijsten. Dit onderzoek toonde aan dat patiënten significant meer tevreden zijn met het resultaat van een reconstructieve operatie in het gezicht drie maanden na de operatie vergeleken met één maand na de operatie. Tevredenheid met het gezicht in het algemeen en in sociale situaties werd niet significant beïnvloed door verwijdering van huidkanker in het gezicht in de periode tussen start van de studie, één maand, en drie maanden na de operatie. Het lijkt dat verwijdering van huidkanker voor grotere laesies (>10 mm in diameter) leidt tot een significante verbetering in tevredenheid met het resultaat tussen één en drie maanden na de operatie. De invloed op de beoordeling van de waardering van het gezicht met betrekking tot de lokalisatie van huidkanker op het gezicht werd ook onderzocht. Verwijdering van huidkanker op de neus blijkt het grootste effect te hebben op de waardering van het gezicht, vergeleken met de andere anatomische locaties in dit onderzoek (frontaal/temporaal, oogleden, en nasolabiaal). Echter was dit verschil niet statistisch significant. Onderzoeken met grotere studiepopulaties en met een langere follow-up duur zullen meer duidelijkheid moeten geven over de mogelijke esthetische consequenties met betrekking tot de chirurgische verwijdering van huidkanker op verschillende locaties in het gezicht.

Hoofdstuk 4: Systematische review van de klinische effecten van drukmaskers

Littekens in het gezicht kunnen, zoals bekend, catastrofale gevolgen hebben voor de kwaliteit van leven van de aangedane patiënt. De behandeling voor uitgebreide littekens in het gezicht is druktherapie; een zowel fysiek als mentaal uitdagende therapie. Echter is het klinische bewijs voor de effecten van deze therapie, gemeten met gevalideerde instrumenten, schaars. **Hoofdstuk 4** vat de huidige literatuur omtrent de klinische effecten van transparante rigide drukmaskers samen middels een review van de huidige literatuur. Slechts drie artikelen met kleine studiepopulaties werden geïncludeerd. Daardoor was het moeilijk een krachtige uitspraak te doen over de klinische effecten van drukmaskers op littekens in het gelaat. Toch beschreven twee van de drie onderzoeken een significante verbetering van hypertrofische littekens met betrekking tot afgenomen dikte, verbetering in hardheid, en verbetering in POSAS scores na behandeling met een drukmasker.

Hoofdstuk 5: De vervaardiging van een gespecialiseerd drukmasker

In het MUMC+ worden drukmaskers veelal gebruikt ter reductie van de dikte van de huid na lapoperaties in het gezicht en ter verbetering van hypertrofische littekens en oneffenheden. **Hoofdstuk 5** beschrijft de fabricatietechniek van een dergelijk drukmasker. Opeenvolgend bevat het fabricatieproces de vorming van een negatieve mal, een positieve mal, de productie van de Uvex® buitenzijde van het masker, de toevoeging van een siliconenlaag

aan de binnenzijde, en het afwerken van het masker. De weke delen in het gezicht van de patiënt worden handmatig verplaatst tijdens de vorming van de negatieve mal. Tijdens het vormen van de positieve mal is het belangrijk dat oneffenheden worden verwijderd uit de mal. Het afwerken van de mal bestaat uit het bevestigen van ankers voor het klittenband, zodat druk kan worden uitgeoefend op het gezicht. Vanwege de mogelijkheid tot het verschuiven en modelleren van de weke delen is een manueel vervaardigd masker superieur en opzichte van 3D-geprinte maskers die door middel van scanning van het gezicht worden gevormd. Tevens kunnen er handmatige aanpassingen aan het beschreven drukmasker worden gedaan gedurende de therapie. Echter gaat het vervaardigen van een dergelijk masker gepaard met een steile leercurve.

Hoofdstuk 6: De klinische effecten van een gespecialiseerd drukmasker
Het aantal onderzoeken dat de klinische effecten van transparante drukmaskers heeft onderzocht (zoals beschreven in **Hoofdstuk 4**) is gering. In **Hoofdstuk 6** worden de klinische effecten van drukmaskers beschreven bij patiënten met esthetisch onbevredigende resultaten na lapchirurgie in het gezicht. Deze patiënten hadden klachten van hypertrofische littekens en opvallende, uitpuilende reconstructieplekken na lapchirurgie in het gezicht in verband met de bedekking van een defect na (verwijdering van) huidkanker. Eenentwintig patiënten werden geïncludeerd in een retrospectief onderzoek waarbij de gemiddelde behandelduur van patiënten 46 weken was. Significante verbetering in POSAS scores en, in het bijzonder, in de Patient Scale van de POSAS werden geobserveerd in dit onderzoek. Alhoewel lapchirurgie in het gezicht meestal leidt tot acceptabele esthetische resultaten en hoewel drukmaskertherapie alleen geschikt is voor een relatief klein aantal (gemotiveerde) patiënten, is het een hoopgevend resultaat dat er significante klinische verbeteringen aantoonbaar zijn na deze therapie.

Hoofdstuk 7: Kwaliteit van leven na behandeling met een gespecialiseerd drukmasker
In het MUMC+ wordt patiënten die drukmaskertherapie ondergaan geadviseerd het drukmasker 12 uur per dag te dragen. Soms is de noodzakelijke therapieduur langer dan een jaar. Veel patiënten zijn van mening dat een drukmasker afzichtelijk en sociaal storend is. Tevens kan langdurige druk in het gezicht als onaangenaam worden ervaren. Daarbij is drukmaskertherapie vaak langdurig. In **Hoofdstuk 7** werden 87 patiënten die drukmaskertherapie hadden ondergaan in de afgelopen vijf jaar gevraagd over de tevredenheid met hun gezicht in het algemeen en in sociale aangelegenheden. Ook werd hen vragen gesteld over de tevredenheid met de keuze voor maskertherapie, en werd hen gevraagd over de tevredenheid met het eindresultaat na deze behandeling. De resultaten laten zien dat het langer dagelijks dragen van het masker (8 tot 12 uur per dag versus 4 tot 8 uur per dag) leidt tot een grotere tevredenheid met het eindresultaat volgens de patiënten zelf. De tevredenheid met het uiterlijk van de patiënten (in het algemeen en in

sociale situaties) blijkt stabiel te zijn gedurende een follow-up periode van bijna vijf jaar. Deze studie ondersteunt de keuze voor drukmaskertherapie voor de behandeling van problematische littekens in het gezicht.

Hoofdstuk 8: Een nieuwe behandeling voor hypertrofische en keloïdale littekens

Het is bekend dat hypertrofische en, met name, keloïdale littekens kunnen zorgen voor negatieve effecten op de kwaliteit van leven van patiënten. Keloïden keren vaak terug, waarbij ze vaak zorgen voor jeuk en pijn. Intralesionale injecties met steroïden (waarvan triamcinolone acetonide het meest onderzochte middel is) zijn onderdeel van de standaardbehandeling voor verdikte en verheven hypertrofische en keloïdale littekens. Met triamcinolone zijn er wisselende resultaten behaald. Bijwerkingen komen veel voor. De toevoeging van verapamil, een calciumantagonist die tevens positieve effecten heeft op littekenweefsel en tevens een gunstiger bijwerkingenprofiel heeft dan triamcinolone, wordt onderzocht in **Hoofdstuk 8**. Intralesionale injecties middels 1:1: triamcinolone en verapamil blijken te resulteren in significante, langdurige verbeteringen bij hypertrofische en keloïdale littekens. Dit werd gemeten door middel van POSAS scores, waarbij de maximale follow-up periode 729 dagen betrof. Een prospectief, vergelijkend onderzoek omtrent de klinische effecten van verapamil en triamcinolone afzonderlijk, alsmede de combinatie van beide middelen, moet meer robuust bewijs leveren over de effectiviteit van deze intralesionale injecties voor hypertrofische en keloïdale littekens.

Hoofdstuk 9: Algemene discussie

In dit hoofdstuk worden de voornaamste bevindingen uit dit proefschrift uiteengezet. Tevens wordt de verhouding met de huidige literatuur betreffende littekenvorming, de esthetische resultaten na huidkanker in het gezicht, drukmaskertherapie en intralesionale injecties onder de loep genomen en besproken.

Valorization

Scars can be itchy, painful, or aesthetically unpleasing, but they can also have a disastrous effect on one's self-confidence. Fortunately, numerous therapies have been developed to minimize the aforementioned negative effects of scars. Age, sex, and cultural environment are important factors in the assessment of the severity of scars and in the choice for choosing the appropriate scar therapy.

In a time where, in the Western world, there is a lot of attention for (the preservation of) a youthful appearance, the number of different scar treatments is increasing. This is reflected by a predicted global annual growth percentage of the scar treatment market of 8.2% between 2018 and 2026.[1] Although therapeutic options for problematic scars are increasing, there is little scientific support for many of them. In this thesis, more insight was given into the healing and treatment of problematic scars, with an emphasis on facial scars. This chapter is aimed to discuss the value of the scientific results that can be obtained by this thesis.

In Chapter 2, the mean duration of hypertrophic scar maturation was examined. This chapter suggested hypertrophic scar maturation to occur considerably more gradually than previously believed. This leads to the assumption that a more conservative approach with respect to surgical scar revision is justified. If this approach is followed, in general, less surgical complications could occur and consequently morbidity could decrease.

When skin cancer is diagnosed, therapy can rarely be non-surgical. Chapter 3 discusses the effects of surgical facial reconstruction after the excision of non-melanoma skin cancer with respect to the aesthetic outcome as perceived by patients. Facial reconstructive surgery can be challenging mostly because of the anatomic complexity of the face, as it contains nine facial units and twenty-six facial subunits.[2] One of the pitfalls of facial reconstructive surgery is that a facial reconstruction following a skin defect can cross multiple facial (sub) units, resulting in poorer aesthetic results. However, the study in Chapter 3 displayed that patients' perceived aesthetic appreciation of their face didn't significantly decrease after surgical reconstruction following facial skin cancer in a small study population. With the annually rising incidence of basal cell carcinoma and as a result the increasing need for facial reconstructions are put in mind, these results can be promising.

This thesis was mainly focused on the treatment of scars, with emphasis on the treatment of facial scars and deformities by means of a custom fabricated facial pressure mask (Chapter 4, 5, 6 and 7). However, little is known about this demanding therapy with respect to the

clinical evidence. A literature review in Chapter 4 summarizes the sparse clinical evidence of facial pressure mask therapy and describes the necessity for further clinical research with controlled study populations. In this way, the cost-effectiveness could be investigated as well as an evidence-based guideline for the use of facial pressure masks in the treatment of facial scars and deformities could be developed. Chapter 5 provides insight into the process of the manual fabrication of a facial pressure mask. Although the manual fabrication technique takes significantly longer to complete when compared to formation of a mask by 3D-printing, a manual fabricated facial pressure mask as described in Chapter 5 is a more sustainable therapy when compared to 3D-printing, because of the regular modifications that are done to the mask during therapy. However, it requires a skilled orthotist/prosthetist that has to undergo a steep learning curve.

Chapter 6 provides assessment of the clinical effects of facial pressure mask therapy in patients with severe facial scars and deformities after facial flap surgery. The retrospective study shows significant reconstruction site improvement measured by means of POSAS scores. Although facial flap surgery usually provides decent aesthetic results, it is valuable that there is a promising non-surgical therapy for this small group of patients that didn't have pleasing results after facial flap surgery. This therapy can result in noticeable reconstruction site improvement, without the need for recurrent surgery. In this way, post-op morbidity can be decreased. As earlier mentioned, a facial pressure mask is a sustainable device because it can undergo slight adjustments during therapy. Chapter 7 displays the aesthetic results of this therapy as judged by patients are also sustainable in the course of 5 years after therapy was completed. In this chapter, patients who completed pressure mask therapy assessed their facial appearance in general and in social situations, their satisfaction with the decision to undergo face mask therapy, and their satisfaction with the end result of therapy. The results also show pressure mask therapy to give aesthetically more pleasing results when patients adhered to a longer daily therapy duration (12 to 16 hours, when compared to 4 to 8 hours).

The clinical effects of a relatively new combination of two known drugs; triamcinolone acetonide and verapamil, on hypertrophic scars and keloids was studied in Chapter 8. This therapy regime displayed significant improvement in scar appearance in both doctor and patients' view. Triamcinolone acetonide monotherapy belongs to the 'gold standard' in intralesional therapy as it has proven to effective in improving problematic scars. However, adverse effects were observed in over 50% in some studies. The addition of verapamil, a calcium channel blocker that also has scar tissue enhancing properties and causes less adverse effects, has delivered preliminary success in the treatment of keloids and hypertrophic scars. Chapter 8 showed encouraging results in the combined therapy of triamcinolone and verapamil in pathologic scars, as significant scar improvement was

observed by both patients and physicians with little adverse effects. We thereby believe the assumed synergistic response of combination therapy of triamcinolone and verapamil to offer a useful new modality in the treatment of keloid and hypertrophic scars. However, more clinical research is needed in order for combination therapy to be able to replace triamcinolone monotherapy as the gold standard.

Concluding, we believe pursuing the best possible facial scar treatment to be crucial. People with conspicuous facial scars are more likely to have depression-related symptoms, to have work-related problems, and are likely to experience negative effects on overall emotional well-being.[3,4] We hope to have provided insightful information about the healing, effects, and therapy of problematic (facial) scars and we hope we provided a foundation for further clinical research by means of this thesis.

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About the author

Sander Bjorn Kant was born on January 17th 1992 in Zwijndrecht, the Netherlands. After finishing secondary school in the East of the Netherlands, he started studying Biomedical Sciences at Maastricht University in 2011. In 2012, he was enrolled into Medicine at Maastricht University. During his first year in medical school, because of his special interest in plastic surgery, he got the opportunity to visit the specialized scar outpatient clinic of the MUMC+, led by Prof. Eric van den Kerckhove and Carlo Colla, several times. Under the supervision of Dr. Andrzej Piatkowski, he was given the chance to perform clinical research on scars at the plastic surgery department of the MUMC+, from February 2013 and on. He performed clinical elective rotations at the ENT department of Oranjestad, Aruba, and at the plastic surgery department of Zuyderland MC. Then he returned home to Rotterdam for his final clinical elective rotation at the plastic surgery department of the Erasmus MC, where he finished his medical studies in November 2018. Since then he has worked as a general surgical resident at the IJsselland Ziekenhuis, in order to lay a solid foundation for future work as a plastic surgical resident. In January 2020, he will start working as a plastic surgical resident (ANIOS) at the Erasmus MC. He resides in Rotterdam-Zuid, where you will find him at the Kuip every other weekend.

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