Innovative approaches in scar prevention and treatment from a plastic surgeon's perspective

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INNOVATIVE APPROACHES IN SCAR PREVENTION AND TREATMENT FROM A PLASTIC SURGEON'S PERSPECTIVE

Volkan Tanaydin

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**Innovative approaches in scar prevention and treatment from a
Plastic surgeon's perspective**

Volkan Tanaydin

Proefschrift

ter verkrijging van de graad van doctor
aan de Universiteit Maastricht,
op gezag van de
Rector Magnificus, Prof.dr. Rianne M. Letschert
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen

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“ *Dedicated to my parents*
For Noya Eliz ”

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CHAPTER 1

Introduction and outline of this thesis

INTRODUCTION

Scar treatment has always been and remains an important topic for plastic surgeons. Poorly-healed wounds leaving clearly visible scars can have significant negative effects on cosmesis and on patient self-esteem. Numerous scar treatment strategies have been developed and recommended. Some include only one modality, while most combine several modalities.¹⁻⁶ In addition, several pharmaceutical agents have been recommended to treat the aesthetic appearance of scars.⁷ Especially the use of pressure therapy is well documented and widely accepted as one of the preferred non-invasive treatments for preventing hypertrophic and keloid scarring^{8,9}

However, outcomes of the treatment modalities applied, suggest that so far few treatments lead to satisfactory aesthetic results.^{10,11} A much more effective approach is actually preventing a problem scar instead of treating it. This can be achieved for example by prevention of post-surgical healing complications. The present work seeks to investigate three innovative interventions that offer plastic surgeons viable treatment options: one preventive and two therapeutic treatment modalities to better manage the clinical treatment of scars.

Surgery always leads to scarring. Effective scar management is an important part of surgical incision site treatment.¹² Differences between normal and abnormal wound healing leading to undesirable scar formation may occur during the different phases of the wound healing process.¹² During the normal wound healing process, there is a balance between new tissue biosynthesis and degradation mediated by apoptosis and remodeling of the extra cellular matrix.¹³ A dysfunction of the underlying control mechanisms may lead to persistent inflammation, excessive collagen synthesis, deficient matrix degradation causing abnormal scarring^{12,13} which can lead to the formation of hypertrophic scars or keloids. The incidence of hypertrophic scars after surgery is reported to be 40-70%.¹² A hypertrophic scar is a red, raised, itchy scar confined to the border of the surgical incision. These scars usually occur in the first weeks, increase in size within 6 months and after a static phase, they gradually regress which may take up to 2 years. Keloids are more aggressive benign fibrous skin tumors which may begin at the site of the skin wound but grow beyond the margins of the wound

due to a dysfunctional scarring process that leads to an overabundance of collagen deposits.¹⁴ They do not regress spontaneously and tend to recur following excision. One of the most common anatomical sites includes the earlobes.^{15,16}

Preventive treatment modality of problem scars

Negative pressure wound therapy (NPWT) was considered as an option for treating post-surgical incision scars, such as those that develop from reduction mammoplasty (breast reduction). Breast reduction is a common cosmetic surgical procedure that reduces the size of the breast and remedies the discomfort caused by oversized, ill-shaped, and hanging breasts.¹⁷ The procedure carries a complication rate as high as 53 percent.¹⁸⁻²⁰ While most of these issues can be resolved by a proper selection of the procedure and gentle tissue-handling, complications from delayed wound healing are most common and incidences of hematoma, fat necrosis, nipple necrosis, cellulitis, and fungal dermatitis may also occur.²⁰⁻²² Hypertrophic scarring is common after inferior pedicle breast reduction in the inframammary scar and 15 percent of all scars are reported to be thick, itchy, or uncomfortable.¹⁸ The basic goal of the plastic surgeon in designing and closing breast incisions is to avoid creating tension at the junction between the horizontal and vertical incisions. The quality of scarring may be improved when lateral tension is minimized and wound healing is both effective and free of complications.

NPWT refers to the controlled application of sub-atmospheric pressure to promote wound healing.²³⁻²⁵ The intervention is widely known for its management of complex open wounds including reduction mammoplasty, where the intervention promotes wound healing and allows for surgical or secondary intentional closure.^{23,26,27} It is thought that one of the key mechanisms of action of NPWT over closed incisions is to minimize lateral tension. Reductions in lateral tension with incisional NPWT have been demonstrated using computer modeling and in vitro measurements,^{28,29} while animal studies have demonstrated increased breaking strength of wounds following the application of NPWT to closed incisions.^{30,31} When applied prophylactically to a closed incision, NPWT may decrease the incidence of wound complications, such as delayed wound healing, infections, and dehiscence. Further, a growing body of evidence supports the assertion that NPWT may

offer significant benefits to closed incisions,³²⁻³⁷ making NPWT an attractive option for treating post-surgical incisions in order to prevent unsatisfactory aesthetic results.

Therapeutic treatment modalities of problem scars

In treating keloidal scars, evidence suggests pressure therapy is an effective approach to address auricular keloids. Pressure therapy has been gaining notoriety as a post-surgical treatment option for keloids since its first use in 1678.³⁸ Since then, various compression devices have been developed and previously described, including spring pressure earrings³⁹, silicone-sheeted earrings⁴⁰, custom-made silicone ear molds⁴¹, magnetic disks^{42,43}, acrylic resin devices^{44,45}, U-loop devices⁴⁶, and aluminum finger splints.⁴⁷ Keloids treated with surgery alone have exhibit recurrence rates ranging from 45 to 100 percent.⁴⁸ When the post-surgical treatment is combined with a compression device, the recurrence rates drop to between 10 and 20 percent.^{42,44}

The principle issue with treating scars with pressure therapy effectively is to apply and maintain constant mechanical pressure directly on the target area. Especially, in the case of auricular scars, the convoluted shape of the ear makes it even more challenging. Additionally, most of the pressure devices mentioned above lack the ability to control the amount of pressure being applied to the keloid. While pressure therapy can prove successful at mediating post-surgical scars, inefficient compression may consequently lead to therapy failure and keloid recurrence. Recently, new ear pressure clips have been developed that show improved outcomes in terms of effectiveness, comfort, and cosmetic appearance. These innovative pressure therapy devices represent a more feasible option for post-surgical treatment of keloid scars.

The last treatment option considered in this work is topical vitamin E (tocopherol). Vitamin E as a topical agent is frequently prescribed as a treatment for scars. This is partially because a significant proportion of both medical professionals and patients believe that it can help improve the cosmetic outcome of a scar.⁷ In response to an injury, oxygen radicals are produced that decrease wound healing by damaging DNA, cellular membranes, proteins,

and lipids.⁴⁹ Antioxidants are thought to enhance wound healing by reducing the damage by free oxygen radicals that are released by neutrophils in the inflammatory phase of the healing process.⁵⁰

Vitamin E is the most important lipid-soluble membrane-bound antioxidant in the body.⁵¹ It is comprised of eight antioxidants whose stereoisomers are derived from tocopherols and tocotrienols. Among these forms, α -tocopherol has the most potent biological activity, because it is the only form maintained in the human body. Vitamin E acts as an anti-inflammatory agent and affects the remodeling of scars by interacting with phospholipids in cell membranes, including molecular packing and maintaining the stability of biologic membranes.^{52,53} Because of these properties, vitamin E has been used to accelerate wound healing, to prevent hypertrophic scarring, and to decrease pruritus.⁵⁴

Aim of our studies

Many scar treatments have been tried with limited success, suggesting a need for more effective treatments. The present work will examine innovative therapies that offer the best feasible option for improving the appearance of scars. First, we evaluated as preventive treatment option for problem scars the efficacy of single-use NPWT on the prevention of post-surgical healing complications (**Chapter 2**) and post-surgical scar quality (**Chapter 3**) in a multicenter study. In our center, we have extended the latter study to 1 year follow-up with adding objective measurements (**Chapter 4**). Then we evaluated as therapeutic treatment options the effectiveness of our custom-made pressure clips for post-surgical keloid treatment of the ear in a preliminary study (**Chapter 5**) and extended study (**Chapter 6**). Lastly, we performed a systematic review to critically analyze current literature about the effect of vitamin E on treating scars (**Chapter 7**).

Outline of this thesis

The most common aesthetic problem following injury or surgical intervention is the development of hypertrophic scars and keloids. An innovative option considered as preventive treatment for problem scars was that of negative pressure wound therapy (NPWT). The intervention is widely known for its management of complex open wounds, where it promotes wound heal-

ing and allows for surgical or secondary intentional closure. When applied prophylactically to a closed incision, NPWT may decrease the incidence of wound complications, such as delayed wound healing, infections, and dehiscence. Given these attributes, we performed a multi-center study to investigate the potential of a single-use NPWT device in the prevention of composite wound morbidity compared to standard care (**Chapter 2**). Follow-up assessments were conducted to evaluate the difference in incision healing complications up to 21 days post-surgery. Individual healing complications were assessed separately as secondary endpoints. In a similar study, we have assessed the feasibility of NPWT in scar treatment evaluating the aesthetic appearance and scar quality at 42 and 90 days (**Chapter 3**) using the Patient Scale and Observer Scale (POSAS) and the Visual Analogue Scale (VAS) questionnaires. In a subsequent study, for a sub-set of patients from our center only, scar quality was analyzed up to 1 year using additional scar objective measurement modalities, such as viscoelasticity (**Chapter 4**).

Keloids remains a challenge for both the clinician and the patient, especially when scarring is located on the ear. One of the major problems encountered during the therapy of earlobe keloids is the problematic and even sometimes impossible way of applying pressure to the postsurgical scar. This is mostly due to the specific shape of the ear that makes it difficult to apply pressure. In our center, we have designed a custom molded device made from uvex with adjustable pressure clips. This device was tested in a preliminary study (**Chapter 5**) and in an extended study using a significantly larger sample (**Chapter 6**). Our primary objective was to analyze the long-term efficacy of this pressure device for treating scarring following keloid excision. Our secondary objective was to identify risk factors which may explain the failure of treatment in the recurrence group.

The practice of prescribing vitamin E after surgery for scar prevention and treatment is widespread and increasingly popular among both the public and clinicians. However, very little evidence exists for this ritual. Therefore, we conducted a systematic review (**Chapter 7**) to critically analyze current literature on the effect of vitamin E, treating scars and to define consensus on the role of topical vitamin E (tocopherol).

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CHAPTER 1

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CHAPTER 2

Efficacy of single-use NPWT on the prevention of post-surgical healing complications in patients undergoing reduction mammoplasty: an intra-patient, randomized, comparative trial

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ABSTRACT

Background: It has been proposed that negative pressure wound therapy (NPWT) applied prophylactically to a closed incision may decrease the incidence of wound complications. Patients undergoing reduction mammoplasty are at risk of wound complications such as delayed healing, infection, and dehiscence, and the bilateral nature of the surgery allows for a within-patient randomized study to evaluate incisional NPWT's effect in reducing healing complications.

Methods: In this multicenter trial, 200 patients undergoing bilateral reduction mammoplasty were treated with PICO Single-Use NPWT System or standard wound-care dressings randomized to right or left breast for up to 14 days to enable within-patient comparison. Follow-up assessments were conducted to evaluate the difference in incision healing complications up to 21 days post-surgery. Healing complications (for the primary endpoint) were defined as delayed healing (incision not 100% closed by 7 days) and occurrence of dehiscence or infection within 21 days. Individual healing complications were assessed separately as secondary endpoints.

Results: Significantly fewer healing complications (primary endpoint) were noted in NPWT-treated breasts (113 [56.8%]) vs. standard care (123 [61.8%]). The difference of 10 (5.0%) patients with fewer healing complications using NPWT was statistically significant ($P = 0.004$). NPWT also resulted in a significantly lower incidence of dehiscence (secondary endpoint) compared to standard care (32 patients [16.2%] vs. 52 patients [26.4%]) by day 21, a relative reduction of 38% ($P < 0.001$).

Conclusions: This is the first major prospective, within-patient, randomized, controlled, multicenter study to provide evidence for an incisional NPWT strategy to reduce healing complications.

INTRODUCTION

Breast reduction or ‘reduction mammoplasty’ is one of the most common procedures carried out by plastic surgeons, with more than 103,077 women in the USA alone undergoing the procedure in 2015 for significant breast hypertrophy, and a further 148,967 for breast lift surgery.¹ Patients with symptomatic macromastia experience both physical and psychosocial issues including back, neck, and shoulder pain, and low self-esteem. Several studies have demonstrated breast reduction surgery to be a safe and effective procedure offering long-term relief for most patients and improving quality of life.^{2–4} Despite women undergoing breast reduction surgery being generally young and healthy, postoperative complications are relatively common, with reported overall complication rates after breast reduction surgery as high as 53%.^{2,5} Most complications are minor in nature, requiring minimal intervention, but some patients will require hospital readmission, endure discomfort from nonhealing wounds with scar and may require surgical revision.

Negative pressure wound therapy (NPWT) is most widely known for managing complex open wounds, where it is deployed to progress nonhealing wounds to a point of being ready for closure, either surgically or through secondary intention.^{6–8} However, growing evidence suggests NPWT may also offer significant benefits to closed incisions.^{9–15} The present study aimed to investigate the potential of a single-use NPWT device in preventing composite wound morbidity (infection, dehiscence, and delayed wound healing) compared with standard care (SC) in patients undergoing bilateral reduction mammoplasty. The bilateral nature of the surgery offers optimal clinical conditions to undertake a direct comparison of the 2 treatment arms on the same patient. The effects of NPWT on the medium-term aesthetic appearance and quality of the resultant scar compared with SC were also assessed and will be reported elsewhere.

PATIENTS AND METHODS

Bilateral Randomization

A multicenter study was conducted across 6 sites: United States ($n = 3$), France ($n = 1$), South Africa ($n = 1$), and the Netherlands ($n = 1$). Two hundred

eleven patients ($n = 211$) who were undergoing elective bilateral breast reduction were recruited from the population routinely seen by the investigators between June 1, 2012 and April 9, 2014. Ethics approval was first obtained at the institution of the principal investigator (R.D.G.), Institutional Review Board at Northwestern University, Chicago, (STU00062369 -5/22/2012), and at each of the other sites. Before entry into the study, all patients signed an informed consent form. Treatment randomization was within-patient (i.e. right or left breast) via a central Website, www.SealedEnvelope.com. NPWT covered the horizontal portion and junction of the inverted “T” incision. Surgeons were free to choose the pedicle technique appropriate for their patient.

Sample Size

Sample size calculations showed that 197 patients would be required to detect an absolute difference of 10% in the complication rate between bilateral breasts treated either with NPWT or SC dressings, assuming 20% of wounds treated with SC dressings and 10% of wounds treated with NPWT develop a healing complication (a 50% reduction) and that there were 26% discordant pairs. This is on the basis of a 2-sided McNemar’s test at the $\alpha = 5\%$ level of significance and 80% power. The sample size was rounded up to 200.

Inclusion and Exclusions

Women aged > 18 years who had undergone elective surgery for bilateral reduction mammoplasty and having postsurgical incisions of similar length on each breast were included in the study. Presurgical exclusion criteria included pregnancy or lactation; using steroids or other immune modulators known to affect healing; history of radiation of the breast; tattoos in the area of the incision; skin conditions such as cutis laxa that would result in poor healing or widened scars; patients with a known significant history of scar problems (i.e. hypertrophic scarring or keloids) and known allergies to product components. Postsurgical exclusion criteria were incisions still actively bleeding and incisions > 12 inches (30 cm) maximum linear dimension.

NPWT Intervention and SC

The NPWT device was PICO (Smith & Nephew Medical Limited, Hull, United Kingdom), a portable single-use (disposable after 7 days) NPWT system

delivering -80 mmHg (nominal) negative pressure to the wound surface.^{16,17} Figure 1 shows the PICO device and a patient with the NPWT system in place (Fig. 1). Treatment commenced on day 0 and lasted for up to 14 days. The pump has a 7-day lifespan and the associated PICO NPWT dressing is left in place up to 7 days. Each PICO kit comes with 2 NPWT dressings, so, according to the needs of the individual patient and the level of exudate, dressing changes were permitted before 7 days at the investigator's clinical judgment. Participating physicians were advised to discontinue treatment on day 14 and return patients to SC (see below) if the incision was still not closed at this time point. The recommended comparator treatment (SC) was 3M STERI-Strip (3M Health Care, St. Paul, Minn.). STERI-Strips were placed along the entire axis of the incision and covered with a dry gauze dressing or nonadherent dressing. Alternatively, investigators could use a nonadherent dry dressing if STERI-Strips were not deemed appropriate by the principle investigator at that site. The majority of patients received prophylactic antibiotics ($n = 188$ [94.5%]). Sutures were used to close wounds in the majority of patients ($n = 168$ [84.4%]) or a combination of sutures and staples ($n = 28$ [14.1%]). Wound assessments were carried out at dressing application (day 0), first dressing change (3–7 days) and any subsequent dressing changes, and at day 21, 42, and 90 follow-up assessments.

Fig. 1. A, The PICO NPWT pump is lightweight (80 g) and measures 64 mm × 68 mm × 21 mm. It delivers -80 mm Hg and lasts for 7 days. There is no exudate canister and it is battery-powered. exudate evaporates from the upper surface of the multilayer NPWT dressing, which transmits negative pressure across the surface of the wound. B, A patient from the trial randomized to receive PICO to the right breast following the reduction procedure. The dressing covers the entire lower incision, the T-junction, and much of the vertical incision except the nipple.

In some centers, 1 surgeon performed both procedure and the closure; in other centers, attending physicians were involved either with closure or with surgery and closure with 1 breast. The maximum level of experience (including attending surgeon, assistant surgeon, and resident) was similar in both treatment and SC groups (median 11 years, mean 13.2 NPWT, and 12.0 SC). Use of drains was according to individual practice and uniform across both breasts: actual data = NPWT 80.9% and SC 80.4% breasts received a drain.

Study Endpoints

The primary objective was to assess whether an incision developed healing complications within 21 days of surgery for both incisional NPWT and the comparator dressing. A healing complication was defined as presence of at least one of the following conditions: infection (superficial or deep), dehiscence (partial, superficial, or deep), or delayed healing (incision not 100% closed within 7 days of the first surgical procedure). Secondary objectives were to assess the number and type of these complications individually including other postsurgical complications: skin necrosis, nipple and areola necrosis, cellulitis, abscess, suture abscess, or hematoma occurring within 21, 42, and 90 days postoperatively. Aesthetic appearance and scar quality were also assessed at 42 and 90 days and, for a subset of patients from a single center, scar quality was analyzed up to 1 year. The scar results will be reported separately elsewhere.

RESULTS

Patient Demographics

Two hundred patients were recruited into the study. Figure 2 shows participant flows. One patient withdrew before the first assessment. In total, 185 (92.5%) patients completed the day 21 assessment and 178 (89%) patients completed the full 90-day study. Table 1 shows patient demographics. Overall, the patient population was relatively young (mean age 35.7 years) and their general health was good. Of the 199 patients in the full analysis set, only 10 (5.0%) declared being smokers and 6 patients (3.0%) suffered

Fig. 2. Patient disposition. Safety analysis set, $n = 200$ patients; full analysis set, $n = 199$ patients. One hundred seventy-eight (89.0%) patients completed the 90-day study; 22 (11%) patients were withdrawn: reasons were given as adverse event, $n = 1$ (0.5%); patient's own request, $n = 4$ (2%); lost to follow-up, $n = 14$ (7%); and other, $n = 3$ (1.5%).

from diabetes (all type 2). Most patients (70.9%, $n = 141$) were classed as “a normal healthy patient” by the American Society of Anesthesiology Physical Status Score. Slightly fewer than half of patients had a body mass index (BMI) > 30 kg/m². Incision lengths were similar between treatment groups and centers (horizontal: NPWT mean 24.1 cm, SC mean: 23.9cm; vertical: NPWT mean, 7.3 cm, SC mean 7.2 cm). Ease of application, comfort, and acceptability during wear were also assessed; SC and NPWT were very similar (data not shown).

Table 1. Patient Demographics (n = 199)

Age (mean years, range)	35.7 (18–65)
Weight (mean kg, range)	79.3 (44.4–173.3)
Overall BMI (kg/m ² , range)	30.0 (18.1–57.3)
<20 (n, %)	4 (2.0%)
20–<25	35 (17.6%)
25–<30	80 (40.2%)
≥30	80 (40.2%)
Smokers (n, %)	10 (5%)
Diabetes (n, %)	6 (3%)
ASA Physical Status Score (n, %)	
Normal healthy patient	141 (70.9%)
Mild systemic disease	51 (25.6%)
Severe systemic disease	7 (3.5%)
Ethnic origin (n, %)	
Caucasian	66 (34.2)
African American	50 (25.9%)
Asian	0
Hispanic	22 (11.4%)
Other*	55 (28.5%)
Prophylactic antibiotics (n, %)	
Yes	188 (94.5%)
No	11 (5.5%)
Duration of surgery (mean minutes, range)	168.3 (49–445)
Mean tissue resection weight (n, %)	
<500 g	68 (34.2)
500–<1000 g	82 (41.2)
1000–<1500 g	31 (15.6)
>1500 g	18 (9.0)

*Many patients in the “other” category were of African origin.

The Effect of NPWT on Wound-Healing Complications

Differences between the breast incisions treated with NPWT and SC for both primary and secondary endpoints are compared in Figure 3. Use of NPWT on closed incisions resulted in a significant reduction in wound-healing complications within 21 days of surgery: 56.8% of NPWT-treated incisions (n = 113) experienced wound complications compared with 61.8% (n = 123) treated with SC ($P = 0.004$). The overall level of healing complications for SC (61.8%) seems high when compared with figures reported in the literature.^{2,5} In this study, delayed healing, which contributed to the primary endpoint of wound

complications within 21 days, was defined as a wound not closed with 100% epithelialization within 7 days of surgery. In practice, however, an incision could not be assumed to be closed if a patient failed to attend an assessment within 7 days of surgery. Therefore, any incision not assessed within 7 days was defined as having delayed healing and classed as a healing complication, even if the wound may, in fact, have been 100% closed. A sensitivity analysis aiming to address this issue was added to the analysis protocol so the time point for the delayed healing component was changed from 7 days to 10 days after surgery. By this point, all patients should have returned for at least 1 visit and have complete information regarding wound closure. The sensitivity analysis supports the theory that the frequency of delayed wound healing was overestimated. Using the sensitivity analysis definition of delayed wound healing within 10 days (all other complications within 21 days), the total number of complications fell from 123 (61.8%) to 89 (44.7%) in SC-treated incisions, and compares more closely to complication rates reported elsewhere.¹⁸ The treatment effect was maintained in the sensitivity analysis, with NPWT resulting in a 5% absolute reduction or 10 fewer patients (39.7%, $n = 79$) experiencing a wound complication within 21 days ($P = 0.033$).

The Effect of NPWT on Wound Dehiscence

In addition to the primary variable, the effects of NPWT were assessed on a range of specific complication secondary endpoints. Figure 3 shows that NPWT significantly reduced the incidence of wound dehiscence within 21 days of surgery (Fig. 3). In total, 16.2% of NPWT-treated incisions ($n = 32$) experienced dehiscence (partial, superficial, or deep) compared with 26.4% ($n = 52$) treated with SC [$P < 0.001$, 95% confidence interval (CI) of the difference, 5.1-15.9]. The difference of 20 fewer patients (10.2%) represents a relative reduction in dehiscence of 38% as a result of incisional NPWT. There were 4 (2.0%) NPWT-treated incisions that developed infection (superficial or deep) compared with 6 (3.0%) treated with SC within 21 days of surgery. The difference of 2 patients (1.0%) with fewer infections on NPWT treatment was not statistically significant ($P = 0.532$; 95% CI, -1.9 to 4.3) and, naturally, the numbers were low. It is clear that, in this study, the major complication in breast reduction driving the significant difference in the primary endpoint is dehiscence (rather than infection) and that the application of incisional NPWT was successful in reducing the frequency of this complication.

Figure 3. Frequency of complications during the post-surgical period in 199 patients treated with NPWT and SC. For the sensitivity analysis, the definition of delayed healing was changed from 7 days to 10 days after surgery, with the aim that all patients should have returned for at least 1 visit at this point and we would therefore have complete information regarding closure. Using this cutoff, the results remained statistically significant ($n = 79$, 39.7% vs. 89, 44.7% for NPWT and SC, respectively; treatment difference 5% [95% CI: 0.4;10.1]; $P = 0.033$).

Superficial dehiscence was the most common form of dehiscence observed in the SC group ($n = 35$, 17.8%), followed by partial ($n = 19$; 9.6%), then deep dehiscence ($n = 6$, 3%). NPWT resulted in a significant reduction in both superficial dehiscence ($n = 22$, 11.2%) and partial dehiscence ($n = 7$, 3.6%). The rate of deep dehiscence in the NPWT-treated group was 3% ($n = 3$), compared with 6% in SC, but did not reach significance with such low numbers. The effects of NPWT on dehiscence rates could be observed as far out as 42 days after surgery. Figure 4 shows the proportion of dehiscence wounds at 21, 42, and 90 days (Fig. 4). Figure 5 shows one of the patients who suffered deep dehiscence on the SC side but not on the NPWT-treated breast (Fig. 5). The dehiscence wound remained unhealed at day 90.

Fig. 4. Proportion of patients reporting a dehiscence at each individual assessment.

Patient Risk Factors for Wound Complications

It has been noted by many authors that a greater mass of tissue resected in reduction mammoplasty is associated with an increased incidence of wound complications.^{18–21} Data were captured for some of the common risk factors associated with reduction mammoplasty in the present study, including smoking, diabetes, high BMI, and high tissue resection weight. The numbers of patients reported to be diabetic ($n = 6$) or smokers ($n = 10$) were too few to make any associations with outcomes. Figure 6 shows that NPWT appeared to have the greatest effect on dehiscence in the higher BMI categories (Fig. 6). Figure 7 shows that, although there is an increasing likelihood of a dehiscence in higher weights of tissue resection, the effects of NPWT were similar across all tissue resection categories (Fig. 7). The effect of NPWT on preventing skin necrosis was noteworthy, despite it occurring infrequently in the study: 9/197 patients (4.6%) suffered skin necrosis within

Fig. 5. Example of a patient with deep dehiscence on breast treated with SC and good healing on breast treated with NPWT.

Fig. 6. Effect of body mass index on wound dehiscence.

Fig. 7. Effect of tissue resection weight on dehiscence.

21 days post-surgery, 7 (3.6%) instances of which occurred only in the incisions treated with SC, whereas 2 (1.0%) patients developed skin necrosis on both incisions (NPWT and SC) ($P = 0.008$). Six of the 9 patients developing skin necrosis were found to be in the highest BMI category (≥ 30 kg/m²) and 4/9 were in the highest category of tissue resection weight (≥ 1500 g). Data from the analysis of nipple and areola necrosis, hematoma, seroma, abscesses, suture abscesses or extrusions, and details of serious adverse events are in the Supplemental Digital Contents 1-3. (see document, Supplemental Digital Content 1, which shows data from the analysis of nipple and areola necrosis, hematoma, seroma, abscesses, suture abscesses, or extrusions, <http://links.lww.com/PRSGO/A600>; see table, Supplemental Digital Content 2, which shows a detailed description of serious adverse events localized to a treatment for 2 patients in the NPWT group and 7 patients in the SC group, <http://links.lww.com/PRSGO/A601>; see figure, Supplemental Digital Content 3, which shows center effects for incidence of dehiscence, <http://links.lww.com/PRSGO/A602>).

Adverse Events

The number of patients reporting a serious adverse event was $n = 7$ (3.5%) in the SC-treated incisions compared with $n = 2$ (1.0%) in NPWT-treated incisions. No adverse events were found to have a relationship to the device (NPWT or SC).

DISCUSSION

The aim of the present study was to investigate the potential of single-use incisional NPWT as a treatment modality for prevention of wound complications (delayed wound healing, dehiscence, and infection) following reduction mammoplasty. The relatively common bilateral procedure, with a high rate of non-life-threatening complications, provides an opportunity to conduct a within-patient randomized study. The total number of complications within 21 days (including delayed healing up to 10 days as per the sensitivity analysis) fell from 44.7% in incisions treated with SC to 39.7% in incisions treated with NPWT ($P = 0.033$). Clinically more significant were those

women experiencing dehiscence that could be of substantial impact, as the example in Figure 5 shows. NPWT significantly reduced the incidence of wound dehiscence within 21 days of surgery: 16.2% of NPWT-treated incisions ($n = 32$) experienced dehiscence (partial, superficial, or deep) compared with 26.4% ($n = 52$) treated with SC ($P < 0.001$), resulting in a difference of 20 fewer patients (10.2% or 38% relative reduction) sustaining a wound dehiscence as a result of NPWT treatment. The effects of NPWT on dehiscence rates could be observed as far out as 42 days after surgery (19.3% [$n = 38$] vs. 29.4% [$n = 58$], $P < 0.001$).

Avoiding tension at the T-junction between horizontal and vertical incisions remains a basic goal in the design and closure of breast incisions. It is thought that one of the key mechanisms of action of NPWT over closed incisions is to minimize lateral tension. Reductions in lateral tension with incisional NPWT have been demonstrated using computer modelling and *in vitro* measurements in both the PICO²² and other devices.²³ Animal studies have demonstrated increased breaking strength of wounds following the application of NPWT to closed incisions.^{24,25} Other potential mechanisms to explain this vulnerary effect are the ability of incisional NPWT to enhance tissue perfusion, which can be impaired at the T-junction site and flap edges in breast-reduction procedures, and the reduction of incisional edema, which is common to all surgical procedures and can further impede perfusion at the edges of the incision. It is notable that NPWT appeared to provide particular benefit in preventing wound complications in the higher tissue resection weight categories and in patients with higher BMI. There is, therefore, support for the concept that perhaps a combination of edema reduction, improved tissue perfusion, and minimizing lateral tension is key to NPWT's mechanism of action in preventing complications when larger amounts of tissue are resected. Based on the present study, it would appear that there are certainly grounds for considering such devices in mammoplasty where BMI is above 25 (Fig. 6) or resection weight is above 500 g (Fig. 7).

The ideal duration to apply incisional NPWT is presently unknown. Many studies have used between 3 and 7 days^{10–12} In the present study, sites could use up to 14 days. At most sites, overall duration of NPWT treatment was a median of 7 days (mean, 10.9 days). However, at site 5, a further NPWT treatment was nearly always applied even if the incision was closed or almost closed, so, in these patients, NPWT treatment duration (closed

wounds) was median 14 days (mean, 14.3 days). A sensitivity analysis was performed to see if the primary endpoint was different with or without data from site 5. The size of the overall treatment difference was slightly reduced if the overall data excluded site 5 but the result remained significant. Thus, there was no indication of a difference between 7 and 14 days' use, but this remains a topic for further research (analysis shown in the Supplemental Digital Content 1).

One limitation of the current study is that treatment could not be blinded. The use of a sham device would have been a possibility, but it would still have been obvious to the patient and physician which device was in operation. With these limitations in mind, the achievement of a statistically significant reduction in healing complications, in particular dehiscence, translates to significant clinical benefits when placed in context of the large number of breast-reduction procedures performed each year and provides high-level evidence supporting utilization of incisional NPWT in susceptible patients.

CONCLUSIONS

These findings support the growing body of evidence for the ability of incisional NPWT to reduce wound complications.^{10–12} This is the first major prospective, within-patient, randomized, controlled, multicenter study to provide evidence for a therapeutic strategy to reduce healing complications. Conducting a bilateral study allows for the most rigorous direct comparison of 2 treatment arms on the same patient and completely avoids subject-to-subject variability as a confounding factor when comparing 2 treatment types. Further studies within plastic surgery would be informative.

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CHAPTER 2

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CHAPTER 3

An intra-patient controlled, randomized study on scar quality following bilateral mammoplasty incisional treatment with negative pressure wound therapy compared to fixation strips

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ABSTRACT

Background: Wound complications following surgery can lead to delayed healing and an increased chance of developing wound dehiscence and wound infection, as well as sub-optimal scar formation. Single-use Negative Pressure Wound Therapy (NPWT) has been shown to result in fewer wound healing complications compared to standard care when used post-surgically following a range of procedures including hip and knee arthroplasty, C-sections and colorectal surgery. We recently reported the effects of single use NPWT on post-surgical healing complications following reduction mammoplasty. This paper presents the findings from scar assessments that were undertaken during the study up to 90 days post-surgery.

Methods: A multi-center, intra-patient, randomized, controlled study (RCT) compared aesthetic appearance and quality of scarring following bilateral breast reduction surgery in 200 patients who received post-surgical incision care with NPWT to one breast and standard care to the other. Aesthetic appearance and scar quality were assessed at 21, 42 and 90 days using the Patient Scale and Observer Scale (POSAS) and a multi-category Visual Analogue Scale (VAS).

Results: Incisional NPWT significantly improved scar appearance compared to standard care as measured by POSAS and VAS scoring systems, with significance achieved at both 42 days and 90 day assessments ($p < 0.001$). At 90 days post-surgery keloid scarring occurred in 3 (1.8%) incisions treated with standard care versus none using NPWT.

Conclusions: This prospective, within-patient, RCT involving anatomically matched pairs of surgical incisions offers a robust means in which to demonstrate the effects of NPWT on scarring outcomes in addition to wound healing complications following surgery.

INTRODUCTION

Breast reduction mammoplasty is a common and effective procedure that can offer significant long-term benefits to patients suffering from symptomat-

ic macromastia.¹⁻³ Appropriate selection of the procedure and gentle tissue handling may reduce common post-surgical complications, such as delayed wound healing, hematoma, fat and nipple necrosis and infections.⁴⁻⁶ Hypertrophic scar formation following mastopexy is reported at 15% and may be due to a number of factors which include; poor surgical technique and selection of the procedure, genetic factors, advanced age, anatomical site, and mechanical forces or lateral tension on the incision line.⁴⁻⁶ Quality of scarring may be improved when post-surgical inflammation and edema is reduced and wound healing is uneventful. Studies have substantiated the importance of mechanical forces in promoting scar formation by increasing lateral tension along the incision line.⁷

NPWT has been reported to promote wound healing in a wide array of acute and non-healing or stalled wounds.¹⁰⁻²² Since its introduction into clinical practice in the late 1990s, it has been advocated for use on various types of ulcers¹⁰⁻¹², open fractures¹⁴ and other post-traumatic wounds¹⁵, burns¹⁶, split-thickness skin grafts¹⁷, open abdominal wounds¹⁸, and sternal wounds.¹⁹ Clinical outcomes when using NPWT inspired some specialists to apply the technique to closed surgical incisions.⁹ The system serves as a preventative measure after high-risk procedures, or in patients with multiple comorbidities and/or risk factors such as obesity and use of steroids.⁴⁻⁷

One of the key mechanisms of action of NPWT over closed incisions is believed to be the reduction in lateral tension that is experienced by an incision under NPWT. The compressive forces applied under NPWT help to bolster the incisional line providing a splinting effect, which helps maintain tissue apposition and prevent tissue gaping.⁹⁻²⁰⁻²³ The effects of NPWT on incision healing complications following reduction mastopexy were recently reported.²⁴ NPWT treated sites showed significantly less wound healing complications up to 21 days post-surgery compared to standard care treated sites ($P = 0.004$).²⁴ It was hypothesized that any difference in wound healing complications between the NPWT treated incision sites and those that received standard care might be reflected in the quality of scarring. This paper will focus predominantly on the aesthetic outcomes and quality of scarring of the study assessed up to 90 days post-surgery.

METHODS

Study Population

As reported previously, this international study encompassed 200 patients who underwent breast reduction mammoplasty. Patients were recruited from centers in France (n=1), The Netherlands (n=1), South Africa (n=1) and the USA (n=2). Included were women >18 years of age undergoing bilateral reduction mammoplasty and having postsurgical incisions of similar length on each breast. Pre-surgical exclusion criteria included pregnancy or lactation; using steroids or other immune modulators known to affect wound healing; history of radiation of the breast; tattoos in the area of the incision; skin conditions such as cutis laxa that would result in poor healing or widening scars; patients with a known history of significant scar problems i.e. hypertrophic scarring or keloids and known allergies to product components.

Postsurgical exclusion criteria were incisions still actively bleeding; exposure of blood vessels, organs, bones or tendons at the base of the reference wound; and incisions >12 inches (30 cm) maximum linear dimension. Surgeons were free to choose the appropriate incision and pedicle technique for their patient.

Study Design

This was a prospective intra-patient controlled, randomized, comparative, multi-center study. Sample size calculation was based on the primary objective of the study.²⁴ On the basis of a 2-sided McNemar's test at the $\alpha = 5\%$ level of significance and 80% power, 197 (rounded up to 200) patients would be required to demonstrate a difference of 10% in incision healing complication rate between bilateral breasts treated either with NPWT or fixation strips. The study design is shown in Figure 1.

Interventions

The single-use NPWT system (PICO, Smith and Nephew Medical Ltd, UK) used in the study consists of a small portable pump, 2 adhesive dressings and 10 fixation strips. The pump weighs 70 grams, uses 2 AA batteries and is capable of delivering 80 mmHg negative pressure to the wound surface.

Fig. 1. Study design

A single start/pause button (with automatic restart after 1 hour) and alarm LEDs for leakage and low battery enable easy use. The system without canister manages low to moderate levels of exudate, mainly by evaporation through the multi-layer dressing and is designed to provide therapy for up to 7 days.²¹ Various size dressings are available. NPWT covered the horizontal portion and junction of the inverted “T” incision.

Comparator dressings were standardised across all study sites. Standard care involved the use of adhesive strips (STERI-Strip, 3M, St. Paul, MN, USA) placed along the entire axis of the incision, and covered with a dry gauze dressing or non-adherent dressing. ‘No-Sting’ protective wipes were supplied for use on the peri-wound skin prior to the application of any secondary fixation strips and were used at the discretion of the principal investigator at that site.

Randomization of Treatment

The patients served as their own control. Each patient underwent bilateral reduction mammoplasty and received post-surgical site treatment simultaneously with NPWT to one breast and standard care to the other. Treatment was randomly allocated. The information was accessed digitally at www.SealedEnvelope.com. The randomized treatment was applied following incision closure in the operating room. Both incision site treatment with NPWT and standard care commenced on day 0 and lasted for up to 14 days.

Outcomes

The primary objective of the study was to investigate the difference in incision healing complications (delayed wound healing, dehiscence or infection) between NPWT and standard care up to 21 days post-surgery. Secondary objectives were to assess the number and type of any incision healing complication occurring within 21, 42, and 90 days postoperatively. These study outcomes have been published elsewhere.²⁴

The aim of this report was to present a further secondary outcome of the study: Aesthetic appearance and quality of scarring following bilateral breast reduction surgery as evaluated at day 21, 42 and 90 days, comparing NPWT with standard care.

Assessment Schedule

Assessments of aesthetic appearance and quality of scarring took place during planned visits at days 21, 42 (± 3 days) and 90 (± 7 days) using various clinical scales. Treating physicians were asked to evaluate each scar using a modified Visual Analogue Scale (VAS), whilst both physicians and patients were asked to evaluate each scar using the Patient and Observer Scar Assessment Scale (POSAS) at 42 and 90 days post-surgery.²⁵⁻²⁹ Both the observer and patient scale of POSAS contains six items that are scored numerically and summed up in a total score (vascularity, pigmentation, thickness, relief, pliability and surface area). Besides the scale, category boxes are available to score nominal parameters (e.g. color). The patient and observer also score their 'Overall Opinion'. Each item of both scales has a 10-point score, with 10 indicating the worst imaginable scar or sensation. The lowest score is '1', and corresponds to normal skin (normal pigmentation, no itching etc.). The total score of both scales is the summation of the scores of each of the six items. The Total Score ranges from 6 to 60. Besides the six items, the 'Overall Opinion' on scar quality is scored separately by both patients and observers.²⁵⁻²⁹

The modified Visual Analogue Scale (VAS) used in this study is based on the Manchester Scar Scale (MSS), as a measure for scar aesthetics and quality. Each scar characteristic (colour, appearance, contour, distortion, texture) is assessed and assigned a score. The VAS total score is the summation of these characteristics, within the range 5 – 18, 5 being 'excellent' to 18 'poor'.

Global assessment of scar quality was performed by placing a vertical mark on a 10-cm line to represent the scar. For purposes of data collection in this study, the line was divided into 10 boxes, to represent a 10-point scale, to help aid in the accurate recording and interpretation of the data. The sum of the obtained scores formed the overall scar score.²⁵⁻²⁹

With respect to the scar type, treating physicians were asked to describe scars as being either normal (flat/white), immature hypertrophic scar (red), linear hypertrophic scar (red raised), minor or major keloid, at days 21, 42 (± 3 days) and 90 (± 7 days).

Data Analysis

Scar quality assessments were carried out up to 90 days post-surgery to evaluate and compared any treatment effects on scar formation following breast reduction surgery. For each treatment, the presence of diabetes, whether the patient smokes and body mass index was taken into account. Scar type and visual assessment scales²⁵⁻²⁹ were recorded and summarized for all incisions that were closed at the respective follow-up assessments at days 21, 42 and 90.

Statistical evaluation was performed using IBM SPSS. The Hodges-Lehman test was used to show a difference between treatments in the total patient and observer POSAS scar assessment scores, the total VAS scar score and the global scar assessment at the 42 and 90 days follow-up.²⁵⁻²⁹ Where the differences between treatments were not normally distributed, the Wilcoxon Signed-Rank test was used. Tests were carried out at the 5% significance level and a confidence interval of 95%.

Ethics

Ethics approval was first obtained at the institution of the principal investigator (R.D.G.), institutional review board (IRB) at Northwestern University, Chicago, (STU00062369 - 5/22/2012), and at each of the participating institutions.

Patients were assessed according to the eligibility criteria and were provided with study information and adequate time to read and understand the information. Inclusion in the study followed after the patients gave written consent.

RESULTS

Two hundred patients were recruited into the study. Patients were treated between June 1, 2012, and April 9, 2014. Full analysis set was performed for n=199 patients. One patient withdrew prior to attending any post-base-line assessments. The majority (n=178; 89%) of patients completed the 90 days follow-up study period. Using the American Society of Anesthesiology Physical Status Score, most (n=141, 70.9%) of the included patients were healthy. Of the included patients 51 (25.6%) had mild systemic disease and 7 (3.5%) patients had severe systemic disease.

No relevant medical conditions were reported for 123 (61.8%) of the included patients (Table 1). The number of patients reporting a serious adverse event was n = 7 (3.5%) in the fixation strips treated incisions compared with n = 2 (1.0%) in NPWT-treated incisions. No adverse events were found to have a relationship to the device (NPWT or standard care).

Table 1. Patient Demographics (n=199)

Mean age (years, [range])	35.7 [18–65]
Mean weight (kg, [range])	79.3 [44.4–173.3]
Mean BMI (kg/m ² , [range])	30.0 [18.1–57.3]
<20 (n, %)	4 (2.0%)
20–<25	35 (17.6%)
25–<30	80 (40.2%)
≥ 30	80 (40.2%)
Smokers (n,%)	10 (5%)
Type 2 Diabetes (n,%)	6 (3%)
ASA Physical Status Score (n,%)	
Normal Healthy Patient	141 (70.9%)
Mild systemic disease	51 (25.6%)
Severe systemic disease	7 (3.5%)
Ethnic Origin (n,%)	
Caucasian	66 (34.2)
African American	50 (25.9%)
Asian	0
Hispanic	22 (11.4%)
Other	55 (28.5%)
Prophylactic antibiotics (n,%)	
Yes	188 (94.5%)
No	11 (5.5%)

VAS and POSAS outcomes

Scar quality was measured by the VAS and POSAS scoring scales up to 90 days post-surgery. Both at day 42 and day 90, VAS scores on scar characteristics such as contour, distortion and scar texture, showed a better quality of scarring for the NPWT treated incisions compared to standard care (Table 2).

At day 42 the (Hodges-Lehmann) estimate of the difference in the VAS total score between NPWT and standard care (within a single patient basis) was -1.5 units; demonstrating that NPWT had a 1.5 unit more favorable scar quality than those incisions treated with standard care. This was found to be statistically significant ($p < 0.001$, 95% CI: -2.0 to -1.0). At day 90 the (Hodges-Lehmann) estimate of the difference in patient total VAS score between NPWT and standard care was -1.5 (95% CI: -2.0 to -1.0), which was statistically significant ($p < 0.001$). These results were in line with the patient scores on scar characteristics.

At day 42 assessment the (Hodges-Lehmann) estimate of the difference in the VAS global assessment score between NPWT and standard care (within a single patient) was -1.0 (95% CI: -1.5, -1.0) and at day 90 -1.0 (95% CI: -1.0 to -0.5), which was also found to be statistically significant for both ($p < 0.001$) (Table 3).

POSAS observer scale scores on scar characteristics (vascularity, pigmentation, thickness, relief, pliability and surface area), were recorded at day 42 and day 90 on a scale of 1 -10 and in addition, each characteristic was categorized. At day 42 for NPWT treated incisions the (Hodges-Lehmann) estimate of the difference in observer total score between NPWT and standard care was -4.0 units ($p < 0.001$, 95% CI: -5.0 to -2.5).

At day 90 the (Hodges-Lehmann) estimate of the difference in observer total score between NPWT and standard care was -2.5 units, which was statistically significant ($p < 0.001$, 95% CI: -3.0 to -1.5) (Table 4). POSAS patient scores were in line with the observer scores. POSAS observer total and overall opinion as well as the patient scores for these items at day 42 and day 90 are shown in Table 5.

The within-patient differences in modified VAS and POSAS total and global scores for scar quality assessment between NPWT and standard care at 42 and 90 days follow-up are shown in Figure 2.

Table 2. Visual Analog Scale - Scar Characteristics

Visual Analog Scale (VAS)	Scar Characteristics Day 42		Scar Characteristics Day 90	
	N (%) of incisions		N (%) of incisions	
Scar Characteristics	NPWT	Standard Care	NPWT	Standard Care
Colour Obvious/gross mismatch	51/173 (29.5%)	70/172 (40.7%)	40/173 (23.1%)	53/172 (30.8%)
Appearance Shiny	43/173 (24.9%)	50/171 (29.2%)	25/174 (14.4%)	35/173 (20.2%)
Contour hypertrophic/keloid	9/173 (5.2%)	17/172 (9.9%)	14/174 (8.0%)	17/174 (9.8%)
Level of Scar distortion Moderate/ severe	17/173 (9.8%)	28/172 (16.3%)	16/174 (9.2%)	26/174 (14.9%)
Texture of scar distortion Firm/hard	17/170 (10.0%)	30/170 (17.6%)	10/166 (6.0%)	14/166 (8.4%)

Table 3. Visual Analog Scale - Total Score and Global Assessment

	Day 42 follow-up			Day 90 follow-up		
	NPWT	Standard Care	Median difference	NPWT	Standard Care	Median difference
VAS Total Score	9 (5 – 15) N=169	9 (5 – 17) N=168	-1.5 (CI: -2.0, -1.0) p<0.001	9 (5 – 13) N=165	9 (5 – 13) N=164	-1.5 (CI: -2.0, -1.0) p<0.001
VAS Global Assessment	3 (1 – 10) N=169	4 (2 – 10) N=169	-1.0 (CI: -1.5, -1.0) p<0.001	3 (1 – 9) N=171	3 (1 – 8) N=169	-1.0 (CI: -1.0, -0.5) p<0.001

The Visual Analog Scale (VAS) total score is the summation of scar characteristics (colour, appearance, contour, distortion, texture) scores, within the range 5 – 18, 5 being 'excellent' to 18 'poor'.

CHAPTER 3

Table 4. POSAS Observer Scar Characteristics Scores

POSAS observer scores	Day 42		Day 90	
	NPWT	Standard Care	NPWT	Standard Care
Vascularity Median, mean (range)	3, 3.4 (1-9)	4, 3.8 (2-8)	3, 2.8 (1-9)	3, 3.2 (1-7)
Pigmentation Median, mean (range)	3, 3.1 (1-8)	3, 3.5 (1-9)	2, 2.7 (1-7)	3, 2.9 (1-6)
Thickness Median, mean (range)	3, 3.2 (1-8)	3, 3.5 (1-8)	3, 2.8 (1-7)	3, 3.2 (1-8)
Relief Median, mean (range)	3, 3.1 (1-9)	3, 3.7 (1-10)	3, 2.7 (1-8)	3, 3.1 (1-8)
Pliability Median, mean (range)	3, 3.3 (1-8)	3, 3.7 (1-9)	3, 2.7 (1-7)	3, 3.1 (1-7)
Surface Area Median, mean (range)	3, 3.1 (1-9)	3, 3.7 (1-10)	3, 2.8 (1-8)	3, 3.2 (1-8)

POSAS, Patient and Observer Scar Assessment Scale.

Each item has a 10-point score, with 10 indicating the worst imaginable scar or sensation. The lowest score is '1', and corresponds to normal adjacent skin.

Table 5. POSAS total and overall observer and patient scores at Day 42 and 90

POSAS	Day 42 follow-up			Day 90 follow-up		
	NPWT	Standard Care	Median difference	NPWT	Standard Care	Median difference
Observer Total	19 (10 – 50) N=163	20 (12 – 53) N=154	-4.0 (CI -5.5, -3.0) p<0.001	16 (7 – 44) N=164	18 (9 – 37) N=157	-2.0 (CI -3.0, -1.0) p<0.001
Patient Total	19 (6 – 54) N=161	24.5 (6 – 50) N=154	-4.0 (CI: -5.0, -2.5) p<0.001	15 (6 – 51) N=167	19 (6 – 50) N=159	-3.0 (CI -3.5, -2.0) p<0.001
Observer Overall Opinion	3 (2 – 8) N=163	4 (1 – 10) N=155		3 (1 – 8) N=165	3 (1 – 6) N=157	
Patient Overall Opinion	3 (1 – 10) N=163	4 (1 – 10) N=153		2 (1 – 10) N=165	3 (1 – 10) N=157	

POSAS, Patient and Observer Scar Assessment Scale.

POSAS, items were scored on a 10-point scale, with 10 indicating the worst imaginable scar or sensation. The lowest score is '1', and corresponds to normal skin. The Total Score ranged from 6 to 60.

*All differences between NPWT and standard care at each time point were statistically significant, $p < 0.001$.

POSAS, Patient and Observer Scar Assessment Scale; VAS, Visual Analog Scale. The modified Visual Analogue Scale (VAS) is based on the Manchester Scar Scale (MSS), as a measure for scar aesthetics and quality.

Figure 2. Within-patient differences in modified VAS and POSAS scores for scar assessment between NPWT and standard care at 42 and 90 days follow-up for 199 patients following breast reduction surgery

Scar type

Application of NPWT post-surgery resulted in marked improvements in scar appearance compared to standard care. Scar type assessment at day 21 showed that 119/155 (76.8%) of the NPWT treated incisions were classed as 'normal (flat/white)', compared to 103/133 (77.4%) for those treated with standard care. No keloid scars (minor or major) were observed at day 21. At the 42 days assessment, 114/161 (70.8%) of the NPWT treated incisions were classed as 'normal (flat/white)' compared to 97/145 (66.9%) of the standard care treated incisions. One (0.6%) NPWT treated incision

was classed as a ‘minor keloid’ compared to 2 (1.4%) of the standard care treated incisions. At the 90 day assessment 123/174 (70.7%) of the NPWT treated incisions were classed as ‘normal (flat/white)’ compared to 106/171 (62.0%) of those treated with standard care. There were no keloid scars observed in the NPWT treated incisions compared to 3 (1.8%) minor keloids in the standard care treated sites (Table 6).

Table 6. Scar type at follow up assessments

Scar type	Day-21 follow-up		Day-42 follow-up		Day-90 follow-up	
	NPWT	Standard Care	NPWT	Standard Care	NPWT	Standard Care
Normal (flat/white)	119 (76.8%)	103 (77.4%)	114 (70.8%)	97 (66.9%)	123 (70.7%)	106 (62.0%)
Immature hypertrophic scar (red)	28 (18.1%)	20 (15.0%)	37 (23.0%)	33 (22.8%)	32 (18.4%)	38 (22.2%)
Linear hypertrophic scar (red raised)	8 (5.2%)	10 (7.5%)	9 (5.6%)	13 (9.0%)	19 (10.9%)	24 (14.0%)
Minor keloid	0	0	1 (0.6%)	2 (1.4%)	0	3 (1.8%)
Major keloid	0	0	0	0	0	0
N (%)	155 (100%)	133 (100%)	161 (100%)	145 (100%)	174 (100%)	171 (100%)

Handling and Comfort During Use

Dressings were very similar with respect to ease of application, comfort, and acceptability during wear. Dressings were changed for ‘routine’ reasons in 90.7% of NPWT and 97.4% of fixation strips dressing changes. Pain on dressing removal was similar between treatment groups. Management of exudate was deemed acceptable by physicians for both treatment arms.

DISCUSSION

This intra-patient controlled, randomized, comparative, multi-center study evaluated and compared aesthetic appearance and quality of scarring following bilateral breast reduction surgery in N=200 patients. Compli-

cations in reduction mammoplasty have been reported to be as high as 53%.⁵ Of these complications, the most common is delayed wound healing, which may lead to thick, itchy or uncomfortable scars.^{5,6} Psychosocial effects of unaesthetic scarring include diminished self-esteem, stigmatization and disruption of daily activities.³¹ Depending on the individual patient and scar severity, hypertrophic and keloid scars can be treated with compression, silicone gel, intralesional steroid injections, fractional or pulse-dye laser therapy, and surgery.^{31,34} Scar treatment can take a long period of time and results may vary greatly.³¹ Depending on the individual patient factors there is a risk for recurrence especially in those with keloid scars.³¹

It was hypothesized that the difference in wound healing complications in favor of incisional care with NPWT compared to those treated with fixation strips might be reflected in the quality of scarring. We previously reported a significant reduction in wound healing complications associated with NPWT treatment of incisions²⁴. Of the wound-healing complications observed in the study a significantly lower incidence of wound dehiscence (partial, superficial or deep) was shown for the NPWT treated incisions (16.2% (n=32)) compared to standard care (26.4% (n=52)). The difference was 10.2 percentage points (95% CI: 5.1-15.9) and was statistically significant [$p<0.001$].

At day 42 and day 90 assessments the incision sites treated with NPWT showed a statistically significant ($p<0.001$) better quality of scarring and aesthetic appearance, as measured by POSAS and VAS scales, compared to the incisions treated with fixation strips. The present within-subject trial design, involving anatomically matched pairs of surgical incisions, sought to minimize variance in scarring arising from differences in age, race, sex, surgical technique, anatomical location and other extraneous factors, thereby successfully isolating the effects of NPWT on clinical outcomes. Scar assessments were carried out with validated scales²⁵⁻²⁹ that were particularly suitable for linear incisions as well as patient and physician-related scores.

Although most complications can be overcome with the correct selection of the procedure and with gentle tissue handling, effective scar management is an important part of surgical incision site treatment.^{5,6} A pre-and

post-surgical site regime aimed at prevention of infection, reduction of inflammation, edema, and risk of scarring, is required to enable optimal outcomes.³⁰ Differences between normal and abnormal wound healing leading to undesirable scar formation may occur during the different phases of the wound healing process.³¹ During the normal wound healing process, there is a balance between new tissue biosynthesis and degradation mediated by apoptosis and remodeling of the extracellular matrix.³¹ A dysfunction of the underlying control mechanisms may lead to persistent inflammation, excessive collagen synthesis or deficient matrix degradation, and remodeling causing abnormal scarring.^{32,33}

The mechanism(s) by which NPWT improves quality of scar formation is not understood. Proposed mechanisms of action, such as enhancement of skin hydration, reduction of inflammation and edema, stem from studies using silicone sheeting or compression.³¹⁻³⁴ Further actions influencing the quality of scarring are enhanced local pressure on the incision line and reduction of traction.^{7,23}

The results of this rigorous randomized controlled trial help to address the evidence gap, by demonstrating that NPWT is an effective treatment in improving scar quality and the appearance of closed incisions amongst patients undergoing breast reduction surgery.

A longer follow-up period of 1 year for scar assessment of N=32 patients confirmed that the treatment effects observed in this study are maintained.³⁵

Limitations

Whilst scar assessment was intended to be carried out by an independent physician, in practice, the treating physician carried out the assessments due to scheduling difficulties. This may lead to some bias since the treatment itself could not be blinded. Independent panel assessments of photographs could be employed to limit this bias or validate clinician assessments but would be limited to 2D assessments. The study may have benefited from providing training on scar assessments to ensure consistency in measuring and using the assessment tools across the sites.

CONCLUSIONS

Findings from the present study demonstrated significantly improved scarring outcomes, for NPWT treated incisions compared to standard care, for patients undergoing breast reduction mammoplasty. Statistically significant differences in both observer and patient VAS and POSAS scores in favor of the NPWT treated incision sites were demonstrated compared to standard care. There were no keloid scars observed in the NPWT treated incisions compared to 3 (1.8%) keloids in the standard care treated sites. The use of NPWT translated to significant clinical benefits over standard care when used after surgical procedures to effectively support wound healing and promoting optimal scar formation.

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CHAPTER 4

Randomized controlled study comparing disposable negative-pressure wound therapy with standard care in bilateral breast reduction mammoplasty evaluating surgical site complications and scar quality

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ABSTRACT

Background: Negative Pressure Wound Therapy (NPWT) for post-surgical incision treatment has demonstrated benefits. A prospective randomized study was developed including 32 patients who underwent bilateral breast reduction mammoplasty. Patients served as their own control and received NPWT to one breast and fixation strips to the other breast.

Methods: Primary outcome was the number of wound healing complications within 21 days when comparing NPWT treatment with fixation strips. Secondary outcome was aesthetic appearance and quality of scarring using questionnaires (VAS and POSAS) scored at day 42, 90, 180 and 365 days follow up using additional scar measurement modalities, such as viscoelasticity.

Results: For the 32 included patients the number of wound complications was significantly lower ($p<0.004$) for the NPWT treated sites compared to fixation strips. POSAS and VAS scores at 42 and 90 days revealed a significantly better quality of scarring in the NPWT treatment breasts than fixation strips. At 180 days follow up there was a significant improvement in total VAS scores. No consistent significant improvement in scar quality was demonstrated with the assays that were used.

Conclusions: Our study showed less complications and a significant improvement in quality of scarring in favor of the NPWT treated sites. The results indicate NPWT to be an attractive option for these patients.

INTRODUCTION

Breast reduction is a common cosmetic surgical procedure to reduce the size of the breast and to overcome discomfort caused by oversized, ill-shaped and hanging breasts.¹ Although most complications can be overcome with proper selection of the procedure and with gentle tissue handling, reported percentages of complications are as high as 53%.²⁻⁴ The most common complication is delayed wound healing and other complications include hematoma, fat necrosis, nipple necrosis, cellulitis, and fungal dermatitis.⁴⁻⁶ Hypertrophy is common after inferior

pedicle breast reduction in the inframammary scar and 15% of all scars are reported to be thick, itchy or uncomfortable.² The assumption is that quality of scarring may be improved when wound healing is effective, without complications. Negative pressure wound therapy (NPWT) refers to the controlled application of sub atmospheric pressure to promote wound healing and has been applied in a wide array of acute and chronic wounds.⁷⁻⁹ Over the years clinical success of NPWT encouraged specialists to apply the technique to closed surgical incisions. It serves as a preventative measure after high risk procedures, mainly in trauma and cardiothoracic surgery, or in patients with multiple comorbidities and/or risk factors such as obesity and use of steroids.^{10,11} Stannard et al^{12,13} published two studies on different high risk skeletal traumas in which they concluded that there were significantly less infections and cases of dehiscence in the NPWT group compared to the sites treated with standard care. A recent development in the field of NPWT is a portable disposable system. An early study evaluating the performance and clinical benefits of the system showed promising results.¹⁴

A study was developed including 32 patients undergoing bilateral reduction mammoplasty, to evaluate the effectiveness of post-surgery incision treatment comparing a portable disposable NPWT system with standard care, using fixation strips. Patients were followed up to 365 days post-surgery.

METHODS

Study Population

The prospective randomized, controlled, comparative study included 32 patients >18 years of age, who underwent bilateral superomedial pedicle wise-pattern breast reduction mammoplasty and had postsurgical incisions of similar length on each breast. Patients received treatment at VieCuri Medical Centre in the Netherlands. Exclusion criteria included: pregnancy or lactation; using steroids, or other immune modulators known to affect wound healing; history of radiation of the breast; tattoos in the area of the incision; skin conditions such as cutis laxa, that would result in poor healing or widen scars; patients with a known significant history of hypertrophic scarring or keloids; postsurgical incisions still actively bleeding; exposure of blood vessels, organs, bone or tendon at the base of the reference wound; and incisions > 12 inches (30 cm) maximum linear dimension.

Study Design

This was a level II therapeutic study. The patients served as their own control, with both breasts included in the study. For this long term (365 days) follow up study the sample size available for analysis (n=32) represents the number of patients enrolled into the larger multicentre RCT at VieCuri Medical Centre in the Netherlands. No a-priori sample size calculation was performed. As the long term follow up was a single center study this number of patients allowed to keep recruitment time and study duration manageable. Post-hoc sample size calculations using nQuery 4.0, confirmed that the present study had sufficient (greater than 80%) statistical power to detect a difference between NPWT and standard care, based on the data observed, in terms of the scar quality and aesthetic appearance outcomes (VAS and POSAS) in the shorter term, 42 and 90 days, follow up. Further post-hoc sample size calculations showed that the same outcomes at the longer term follow up, 180 and 365 days, would require a larger study ranging between n=50 and many hundreds of patients, depending on outcome and time point, to be sufficiently powered.

Each patient received post-surgical treatment with both NPWT and standard care. Randomization was used for allocation of NPWT and fixation strip to the right or left breast incision site per patient, using sealed envelopes. Treatment site information was accessed digitally (www.sealedenvelope.com) upon the start of the treatment post surgically. As NPWT and fixation strips are optically different, blinding of the physician and patients was not feasible, however data analysis was performed blinded. All included patients (N = 32) had follow-up visits and assessments at screening (pre-surgery), day 0 (baseline, post-surgery), day 7, 21, 42, 90, 180 and 365 days post-surgery (Fig. 2).

Study Interventions

The study product is a single-use NPWT system without an exudate canister, allowing the portable pump to be small and light weight (PICO, Smith and Nephew Medical Ltd, UK). It is indicated for use on both open and closed wounds with low to moderate levels of exudate and comes with two adhesive dressings and ten fixation strips (Fig. 1a). The pump weighs 70 grams, uses two AA batteries and is capable of delivering 80 mmHg negative pressure

Fig. 1. (a) the PICO dressing in place on lower horizontal incision; (b) PICO pump. (Reprinted with permission of Smith & Nephew).

to the wound surface. A single start/pause button (with automatic restart after one hour) and alarm LEDs for leak and low battery enable easy use (Fig. 1b). The system, without canister, is able to manage low to moderate levels of exudate generated by the wound, mainly by evaporation through the specially designed multi-layer dressing. The system is programmed to provide therapy for up to seven days. Various size dressings are available.

As standard treatment, fixation strips (STERI-Strip, 3M, St. Paul, MN, USA) were used. These sterile skin closure strips have a porous, non-woven backing coated with a pressure-sensitive, hypoallergenic adhesive and is reinforced with polyester filaments for added strength.

Study Outcomes

The primary outcome of the study was the number of surgical site complications within 21 days post-surgery when comparing NPWT versus standard care using fixation strips. The secondary outcome was aesthetic appearance and quality of scarring, assessed at day 42, 90, 180 and 365 days.

Assessment Tools

Questionnaires and scales

Clinicians assessed surgical site condition for wound healing status at 21 days, scoring on a clinical scale. Cosmetic result and scar quality was assessed using two different types of questionnaires.

The Patient Scale and Observer Scale

The Patient Scale and Observer Scale (POSAS) is a comprehensive scale designed for the evaluation of scar quality by professionals (observer scale) and by patients (patient scale). Both scales contain six items that were scored numerically and made up a 'total score'. The POSAS has category boxes to score nominal parameters (e.g. color of the scar). Each item of both scales had a 10-point score, with 10 indicating the worst imaginable scar or sensation and 1 corresponding to normal scar or skin (normal pigmentation, no itching etc.). The total score of both scales was calculated by summing up the scores of each of the six items and ranges from 6 to 60. The patient and observer also scored their 'overall opinion'.^{15,16}

Photograph-based scale

The multi-category Visual Analogue Scale (VAS) is a photograph-based scale derived from evaluating standardized digital photographs in four categories (pigmentation, vascularity, acceptability, and patient comfort) plus contour. It sums up the individual scores to get a single overall score ranging from "excellent" to "poor." It demonstrated high observer reliability and internal consistency when compared to expert panel evaluation, but has only moderate reliability when used among lay panels.¹⁷⁻¹⁹

Additionally, scar assessment was performed by placing a vertical mark on a 10-cm VAS line to represent the scar. For the purposes of study data collection, the line was divided into 10 boxes, to represent a 10-point scale, to enable accurate recording and interpretation of the data. The sum of these scores then forms the overall scar score.

Quantitative scar measurements

To obtain quantitative information on scar quality the Cutometer® MPA 580 system (Courage+Khazaka electronic GmbH, Cologne, Germany) was used. The system has a wide variety of probes measuring different skin characteristics. For the study, three probes were used to assess scar viscoelasticity, water content level of the upper skin layers, and Trans Epidermal Water Loss (TEWL). The measurements were recorded in a data file (MS Excel).²⁰⁻²² PO-

Negative Pressure Wound Therapy, NPWT; Adverse events; AES, Serious adverse events, SAES

Fig. 2. Schematic profile of study disposition. Negative Pressure Wound Therapy, NPWT; Adverse events; AES, Serious adverse events, SAES

SAS, VAS scores and quantitative scar measurements took place during follow up visits on day 42, 90, 180 and 365 (end of study) (Fig. 2).

Data Collection and Analysis

The POSAS and VAS scores were summarized at the 42, 90, 180 and 365 days follow-up assessment. For each treatment the presence of diabetes, whether the patient smokes, and body mass index were taken into account. Statistical evaluation was performed using IBM SPSS. A paired T-test was used to calculate the difference between treatments for POSAS and VAS scores. If the differences between treatments were not normally distributed, the Wilcoxon Signed-Rank test was used. Tests were carried out at the 5% significance level and a confidence interval of 95%.

The measurements for viscoelasticity, water content, and TEWL were transferred from the device's software to a database and analyzed using IBM SPSS. The standard locations for measurements with the device were: (a)

normal skin between the breasts just below the sternum as reference (b) on the horizontal scar 5 cm laterally of the vertical scar in each breast.

Ethical Issues

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with The Declaration of Helsinki and its later amendments or comparable ethical standards. Institutional review board approval was obtained. The study registration ID number is NL40698.068.12 / METC 12-3-026. The start date of the study was June 1, 2012, the completion date was April 9, 2014.

Patients were assessed according to the eligibility criteria and were provided with study information and adequate time to read and understand the information. Inclusion in the study followed after the patients had received answers to their questions and gave written consent.

RESULTS

The included patients had a mean age of 40.9 years, ranging from 18-61 years (Table 1). All patients were Caucasian, had American Society of Anesthesiologists (ASA) Physical Status classification scores of 1 or 2 and did not have Diabetes Mellitus. Of the 32 patients, 28 (87.5%) did not have a medical history prior to the surgical procedure. Only two patients (6.25%) smoked approximately 5 cigarettes a day. Four patients (12.5%) used medication, however none of the medications are known to influence wound healing.

Tabel 1. Baseline characteristics for N = 32.

	Mean (range)
Age	40,9 (18-61)
BMI	26,5 (19,5-31,2)
Cup size	E-F (E-I)
Clavicle-areola distance	28,2 cm (23-35)
Resection weight	447,0 gr (113-1260)
Duration procedure	97,8 min (49-157)
Length of incision	19,7 cm (13-24)

Surgical Site Complications

Follow-up assessments were carried out to evaluate the difference in incision healing complications between the NPWT and fixation strips treated sites, up to 21 days post-surgery. Wound healing complications were defined as delayed healing (surgical incision not 100% closed at day 7 post-surgery), or occurrence of dehiscence or infection within 21 days post-surgery. Superficial wound dehiscence occurred in 10 (31.3%) patients. There was significantly less dehiscence ($p<0.001$) for the breasts treated with NPWT compared to the sites treated with fixation strips. Of the patients who presented with wound dehiscence, 5 (15.6%) had this complication in both breasts.

Of those five patients who had bilateral wound dehiscence, in 2 (40%) patients the NPWT treated site healed faster than the site treated with fixation strips. The 5 patients who had this complication in one breast, all had post-surgery treatment with fixation strips on this breast. The total number of wound complications was significantly lower ($p<0.004$) for the NPWT treated breasts.

Scar Quality and Aesthetic Appearance

The scar quality and aesthetic appearance as assessed using POSAS (Fig 3) and VAS (Fig 4) at 42 and 90 days revealed a significantly ($p<0.05$) better quality of scarring in the NPWT treatment breasts compared to standard care, using fixation strips. The total VAS score was also significant at 180 days. Skin viscoelasticity (Fig 5), trans-epidermal water loss and hydration measurements (Fig 6) at follow-up visits day 42, 90, 180 and 365, showed no consistent significant improvement. The results are illustrated in a typical case (Fig 7). NPWT was easy to use. Patients reported the tested NPWT system to be comfortable to wear. NPWT removal did not cause much pain or skin irritation. The overall acceptance of the NPWT system both by physicians and patients scored high.

Fig. 3. N = 32 Scar quality POSAS scores at 42, 90, 180 and 365 days. Patient and Observer Scar Assessment Scale (POSAS)

Fig. 4. N = 32 VAS scored at 42, 90, 180 and 365 days, Visual analog scale, VAS

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Fig. 5. N = 32 Skin viscoelasticity scored at 42, 90, 180 and 365 days

Fig. 6. N = 32 Trans-epidermal water loss and skin hydration

Fig. 7. Case 42, 90, 180 and 365 days

DISCUSSION

NPWT refers to the controlled application of sub atmospheric pressure to promote wound healing in a wide array of acute and complex wounds.⁷⁻⁹ Since its introduction into clinical practice in the late 1990s it has been advocated for use on various types of ulcers^{7-9, 23}, open fractures and other post-traumatic wounds^{24,25}, acute burns²⁶, split thickness skin grafts²⁷, open abdominal wound²⁸, and sternal wounds.²⁹ Over the years the clinical success of NPWT encouraged some specialists to apply the technique to closed surgical incisions. It serves as a preventative measure after high risk procedures and patients at risk for post-surgical complications.^{10,11,29} Stannard et al^{12,13} published two studies on different high risk skeletal traumas in which they concluded that there were significantly less infections and cases of dehiscence in the NPWT group compared to standard care. A retrospective review of 57 patients who received NPWT postoperatively after a sternotomy by Atkins et al³⁰ showed no superficial wound infections while they were in a high risk group. (37) Favorable outcomes were also presented by Reddix et al^{31,32} in a series of 19 morbidly obese patients who received surgery for acetabular fractures and later in a large group of patients who underwent the same procedure. A Cochrane review specifically focused on studies involving the use of NPWT on closed incisions and skin grafts found no sig-

nificant evidence for its effectiveness. The authors stated: “given the cost and widespread use of NPWT, there is an urgent need for suitably powered, high-quality trials to evaluate the effects of the newer NPWT products that are designed for use on clean, closed surgical incisions.”³³

For this purpose our study selected bilateral reduction mammoplasty patients who are at risk for post-operative wound complications.¹⁻⁶ The study included thirty-two patients, who served as their own control. The patients were suitable candidates for incisional NPWT treatment and standard care using fixation strips. In line with a wider RCT published recently³⁴, this study showed significantly fewer wound healing complications had occurred in the NPWT treated sites, compared to standard care with fixation strips at 7 and at 21 days post-surgery assessment. Treatment with NPWT resulted in significantly lower incidence of dehiscence compared to standard care. Scar quality as scored by VAS and POSAS was shown to be significantly better for the NPWT treated sites than for fixation strips treated sites. However no consistent significant improvement in scar viscoelasticity was demonstrated.

Cost of wounds is measured in pain, distress, embarrassment, anxiety and prolonged hospital stay. Further costs are related to wound infection, increased levels of exudate, pain and odour and prolonged inflammation, frequently resulting in further surgical interventions and poor scarring. Surgical infection affects 30-40 patients per 1000 operations with a mean additional length of stay of 11 days.³⁵ It was beyond the scope of the paper to report on cost implications of the NPWT treatment that was used. Cost-efficacy, specifically on prevention of wound dehiscence will be covered in a further publication.

Limitations

Surgical technique is a recognized factor in post-surgery wound healing.²⁻⁴ POSAS and VAS scores showed a better quality of scarring in the NPWT treated sites compared to fixation strips, indicating wound healing was mainly uneventful. Given the nature of the treatments it was not possible to conduct a double blind trial. Ideally, a control group with the same non-activated device would have been better, but this would still have been noted by the patient and physician. Therefore investigator and patient bias scoring POSAS and VAS cannot be ruled out. Our intention was to at least blind the

investigator, which was unsuccessful due to practical reasons, such as the assessor was not available. Instead the investigator did not know the randomization schedule and the patients were asked not to reveal it. No consistent significant improvement in scar viscoelasticity was demonstrated. This could be due to measurements being performed with different probes and other external factors influencing results. Even after standardizing measurement locations it proved difficult to exactly measure the same section of scar/skin during follow-up. Moreover some patients had such a fine scar that the probes were overlapping onto normal skin. Although we tried to keep a steady room temperature and air humidity, thereby minimizing environmental factors, this was practically impossible at the out-patient clinic. During the follow-up period seasons changed making the comparison of TEWL in serial follow-ups difficult. Some patients were stressed because they were late or had put on body lotion when they were not supposed to.

CONCLUSIONS

Our study showed less wound healing complications and a statistically significant improvement in the aesthetic appearance and quality of scarring for the NPWT treated sites versus those breasts that received standard care with fixation strips. The results indicate NPWT to be an attractive option for closed surgical incision treatment. Being able to minimise scarring as well as postsurgical outcomes has great clinical significance to the patient. Although the clinical significance of reduced scarring may be not of utmost importance for the surgeon, it is imperative for the patient's emotional well-being and quality of life.

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Conflict of Interest

All authors have no conflict of interest to report regarding the presented study.

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CHAPTER 5

Management of ear keloids using custom-molded pressure clips: a preliminary study

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ABSTRACT

Background: The application of mechanical pressure by compression devices has gained popularity in the treatment of keloid scars. In this present study, we analyze the long-term efficacy of our custom-molded pressure clip for ear keloids. Our secondary objective is to identify risk factors for the failure of the treatment in the group of the recurrence.

Methods: The patient group consisted of 9 men and 19 women with a mean age of 27 years and a mean follow-up of 8.5 years. For evaluation of the scars, scoring ratings, Patient and Observer Scar Assessment Scale (POSAS), and SF8-questionnaire have been used.

Results: Follow-up observations showed that 71 % were treated successfully. There were significant differences in the Fitzpatrick scale, cause of the ear keloids, overall opinion, and openness for re-treatment between the recurrence and nonrecurrence group. Furthermore, treatment with our custom-molded pressure ear clip resulted in a statistically significant improvement of all the item scores of the POSAS in both the patient and observer scales. Severe complications such as infections or necrosis were not noted.

Conclusions: In this study, we show that the results of adjuvant pressure therapy with our custom-molded ear clips are comparable with the recurrence rates of other studies recently published. The strength of this study is the long follow-up.

Level of Evidence: Level III, therapeutic study

INTRODUCTION

Keloids are a disease well known to mankind for a long time. The first description of abnormal scar formation in the form of keloids was recorded in the Smith papyrus regarding surgical techniques in Egypt around 1700 B.C. Even almost 4000 years later management of keloids remains a challenge for both the clinician and the patient. Keloids are defined as benign fibrous

skin tumors which grow at the site of a skin-wound, but beyond the margins of the wound. The aspect is mostly darker in color in comparison to normal skin. It is known that keloids are the result of a dysfunctional scarring process that leads to an overabundance of collagen deposits ¹, which results in growing of this scar causing discomfort and disfigurement.

The exact incidence of keloids remains to be unknown, but several studies show an incidence of approximately 2-2,5% ^{2,3} and at 4.5% to 16% in the black and Hispanic populations in several large series ⁴. Different types of injury can be the cause of keloids: e.g. ear piercing, burns, trauma, surgery, tattooing, vaccination or even insect bites. Since skin and wound tension is considered a critical factor in the formation of keloids, the most susceptible sites are the central chest, the back, the shoulders and interestingly also the ear lobes ⁵.

Numerous therapeutic modalities have been used to treat auricular keloids including intralesional corticosteroid injection ⁶, pressure therapy ^{7,8}, cryotherapy ⁹, radiotherapy ^{3,10,11}, laser therapy ^{12,13}, surgical excision or a combination ¹⁴⁻¹⁶. The variety of treatments for keloids suggests that none of these widely used therapies is satisfactory ^{7,17-19}. One of the major problems encountered during the therapy of earlobe keloids is the problematic and even sometimes impossible way of applying pressure to the keloid. This is mostly due to the peculiar shape of the ear that makes it difficult to give compression. This results in higher rates of therapy-failure and recurrence of keloids. Nowadays, new ear pressure clips have been developed ¹⁷⁻²⁰ with different results in terms of effectiveness, comfort and cosmetic appearance.

In recent years there has been the development of adjuvant pressure therapy by using a custom-made methyl methacrylate stent as published by Kadouch et al ¹⁷. This study uses a different device which shares the same principle as the device published by Kadouch et al. but includes more patients and has a longer follow-up.

Most of the pressure devices lack the control of the amount of pressure applied to the keloid, however our device has been optimized in order to allow the pressure to be adjusted. Furthermore, using our device makes it possible to also treat retro-auricular keloids (Figure 1 and 2).

Fig. 1. Our custom molded pressure clip. Note the different pressure mechanisms.

In this present study we analyzed the long-term efficacy of this pressure device for ear keloids. Our secondary objective was to identify risk factors explaining for the failure of the treatment in the recurrence group.

METHODS

Between 2003 and 2006 we treated 28 consecutive patients using a combination therapy of excision and our custom-molded pressure clip. Two weeks after excision of the keloid, a plaster cast of the ear was made. Then, by using the cast as a mold, a silicon liner was fabricated matching the surface of the ear. When fitted over the ear, the silicon liner was covered on both sides of the ears with two custom-made artificial auricles: one pre- and one retro-auricular. The fitting of which was enabled by the thermoplastic properties of the fabric as well as by a one-way click-and-fit system. In addition, these auricles could be pressure adjusted by a U-shaped screw-and-pin system.

Fig. 2. *Left side:* Keloid in the upper pole/helix of the ear and retro-auricular area. *Right side:* Appearance after therapy with our custom-molded pressure ear clip

The custom molded clips ensure a hydrated environment due to the choice for a silicon fabric. In addition, their effectiveness relies on the adjustability of the pressure on exactly those points where keloid recurrence is anticipated. Hence, the pressure can be variably adjusted during daytime ensuring a maximum capacity of the device to reduce keloid recurrence. The pressure is adjusted based on the patient's discomfort. However, we anticipated that most of the discomfort is related initially to the patient's awareness of the clip upon wearing. Therefore we designed a habituation scheme: On the first day the pressure is maximized to enable a wearing time of 1 h. The next day it is adjusted so that it can be worn for 2 h, and then for 3 h the following day and so on until it can be worn for a consecutive 12 hours with a minimum amount of discomfort. After 2 weeks, the pressure is augmented again until the pressure area in and around the scar blanches, but without discomfort and pain. This is the onset of therapy. Subsequently, any evidence of keloid recurrence is closely monitored in follow-up. If present (i.e. scar thickness increases),

this means that the scar area may not be targeted properly and pressure adjustments are made accordingly either by relocating the pressure or by increasing it. During therapy, an interdisciplinary team assessed the keloid every 3 months in our outpatient clinic. The therapy is continued for an average of 12-15 months (12-16 h/day). Normally, the scar is then free of edema, colorless and pliant. Post-therapy follow-up is pursued each year for 3 years. Within therapy, discontinuation standards comprise the following: 1) keloid recurrence in spite of corticoid injections, 2) more than two times therapy-related pressure ulcer occurrence and 3) no-show of patients in follow-up. Before participation in the present study, informed consent was obtained from all patients and the medical record was retrieved from the archive. Follow-up was performed at the outpatient clinic or by telephone interview.

Statistical Analysis

Continuous variables are presented as means with standard deviations or as medians with interquartile ranges. Categorical variables are presented as percentages. Continuous variables were compared between groups using unpaired Student's *t* tests or Mann-Whitney *U* tests as appropriate. Categorical variables were compared between groups using chi-square tests or Fisher's exact tests as appropriate. Changes in continuous variables before and after treatment were compared using paired Student's *t* tests. A *P* value of 0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 20.0.

RESULTS

The patient group consisted of 9 men and 19 women with a mean age of 27 years (18 – 66 years) and a mean follow-up of 8,5 years (6,9 -12,3 years). All patients were classified according to the Fitzpatrick scale (types I-VI). Additional questions, in terms of comfort, appearance overall opinion of the ear clip have been scored from 1 (worst) to 10 (best) and are documented in Table 1. Furthermore by using the SF-8 questionnaire, we asked the patients if they would undergo the same treatment again and if the treatment had affected their quality of life ²¹. Follow-up

CHAPTER 5

Table 1. Patient characteristics and risk factors between the recurrence and nonrecurrence groups and *P* values. (The figures in brackets mean the standard deviation or the first and third quartile)

	Recurrence N=8 (29%)	Non-recurrence N=20 (71%)	P
Gender (male)	50%	25%	0.37
Age (years)	25 (8)	27 (11)	0.50
Positive family history (%)	0	15	0.54
BMI (kg/m²)	22 (5)	24 (4)	0.22
Fitzpatrick scale	III (III-IV)	III (II-III)	0.05*
Anatomical location (%)			0.32
Upper pole	25	20	
Lobule	25	55	
Retro-auricular	50	25	
Cause (%)			0.04*
Ear piercing	25	60	
Otoplasty	75	25	
Trauma	0	15	
Previous treatment (%)			0.76
None	63	65	
Surgical excision	13	10	
Injections	25	15	
Brachytherapy	0	10	
Patient compliance (%)			0.60
<8 h a day	13	15	
8-12 h	50	30	
>12 h	38	55	
Therapy duration (months)	18 (10)	15 (6)	0.44
Comfort	5.00	6.75	0.11
Appearance	4.13	5.25	0.23
Overall opinion	4.63	8.05	0.02*
Open for re-treatment (yes)	37.5 %	100 %	0.01*
Enhanced quality of life (yes)	25 %	60 %	0.21

observations showed that 20 patients (71%) were treated successfully and 8 patients (29%) developed recurrence. For evaluation of possible differences between the recurrent and nonrecurrent group, variables defining the patient population were evaluated and risk factors for failure of treatment were identified. There were significant differences in Fitzpatrick scale, cause of the ear keloids, overall opinion and openness for re-treatment between the recurrence and nonrecurrence group. No significant differences were found for the further parameters. In the nonrecurrence group (55 % > 12 h of wearing) patients are more compliant to therapy compared to the recurrence group (38 % > 12 h of wearing). In the nonrecurrence group, patients were generally satisfied (8.05; overall opinion), but disliked the appearance of the ear clip (5.25; appearance). The comfort of the ear clip was acceptable, but should be improved (6.75; comfort). In the recurrence group patients were generally discontent (4.63; overall opinion). However, comfort and appearance were judged similarly as in the nonrecurrence group. Of note, 37,5 % of the patients in the recurrence group repeat the treatment and 25 % of these patients experienced an enhanced quality of life.

In this study, the Patient and Observer Scar Assessment Scale (POSAS) was used to evaluate the scars (Table 2, 3, and 4). The POSAS is a comprehensive scale designed for the evaluation of all types of scars by professionals as well as patients ^{22,23}. Treatment with our custom molded pressure ear clip resulted in a statistically significant improvement of all the item scores of the POSAS in both the patient and observer scales. The total score of the POSAS before treatment showed no statistically significant differences between the recurrence and nonrecurrence group. Lastly, the complaints or side effects of the ear clips were evaluated and documented in Table 5. Sixty-one percent of the patients were found to have discomfort during the application of the pressure clip. A relatively small number of patients complained about pruritus (14 %), skin irritation (25 %) and transient pressure ulcer with no permanent damage or scarring to the ear (18 %, Fig. 3). Severe complications such as infections or skin necrosis leading to scarring and poor cosmetic results were not noted.

CHAPTER 5

Table 2. Identifying risk factors between the recurrence and nonrecurrence groups and *P* values

Patient Scale	Before therapy	Last follow-up	P value
Pain	4.25	1.11	<0.001*
Itching	5.04	2.00	<0.001*
Color	5.79	1.54	<0.001*
Stiffness	8.39	3.25	<0.001*
Thickness	8.54	3.00	<0.001*
Irregularity	8.00	2.54	<0.001*
Overall opinion	9.14	3.07	<0.001*

* $p \leq 0.05$

Table 3. Comparison of the POSAS observer scale before therapy and the last follow up and *P* values.

Observer Scale	Before therapy	Last follow-up	P value
Vascularity	3.82	2.18	<0.001*
Pigmentation	3.04	1.82	0.01*
Thickness	6.89	3.32	<0.001*
Relief	5.75	3.00	<0.001*
Pliability	6.93	3.18	<0.001*
Surface area	7.07	3.25	<0.001*
Overall opinion	7.00	3.29	<0.001*

* $p \leq 0.05$

Table 4. Total scores of the POSAS before therapy, on last follow-up, and relative reduction in POSAS as well as *P* values

	Recurrence	Nonrecurrence	P value
POSAS score before treatment	81.50	92.90	0.08
POSAS score last follow-up	56.13	28.70	0.01*
POSAS score reduction	25.38	64.20	0.01*

* $p \leq 0.05$

Table 5. Side effects from using our custom molded pressure ear clip

Side effect	Number (%)
None	6 (21%)
Discomfort	17 (61%)
Pruritis	4 (14%)
Skin irritation	7 (25%)
Transient pressure ulcer	5 (18%)
Scarring with poor cosmetic results	0 (0%)
Infection	0 (0%)

Fig. 3. Pressure ulcer as a complication

DISCUSSION

Since the use of pressure therapy by Ambroise Paré for the first time in 1678²⁴, the application of mechanical pressure by compression devices has gained popularity in the treatment of keloid scars. Surgery alone leads to recurrence rates ranging from 45 to 100 %²⁵. Combined with compression devices recurrence rates drop to 10-20 %^{17,19}. Nowadays, pressure earrings are widely used as an adjunct to surgery in the treatment of auricular keloids. Chalian et al⁷ postulated that the ideal characteristics of pressure earrings should be; “*noninflammable, strong enough to resist distortion, light in weight, comfortable to wear, and easy for the patient to apply and remove. It must provide uniform adjustable compression and it must*

not interfere with normal hearing. It should also be inexpensive, easy to fabricate, esthetically acceptable, and easy to clean for proper hygiene". Various compression devices have been described in literature: spring pressure earrings ⁸, silicone sheeted earrings ¹⁶, custom made silicone ear mold ²⁰, magnetic disks ^{19,26}, acrylic resin devices ^{15,27}, u-loop devices ¹⁸, zimmer splintage ²⁸, aluminum finger splints ²⁹ and methyl methacrylate stents ^{17,30}. Our pressure device consists of a custom molded silicone with up to three separate adjustable pressure mechanisms.

In a similar study to ours using a methyl methacrylate stent, Kadouch et al had an overall success rate of 83 % with a mean follow-up of 23 months. In our study, we observed a 71 % success rate with a mean follow up of 8,5 years. It might thus appear that our method is less effective than theirs, but as we have seen in this study, keloid recurrence can occur as late as 3 years after primary therapy. The success rate of Kadouch et al may thus in fact be lower than presented. We advise a long follow-up to evaluate the effectiveness of therapy methods in scar treatment.

While a positive family history for keloids has been associated with keloid recurrence, we were not able to confirm this ¹⁷. On the other hand, we could confirm that darker-skinned patients were more prone to recurrence than lighter-skinned patients. This appears logical since people with a higher Fitzpatrick skin type also have a higher incidence of keloids ⁴. We also have found that keloids resulting from otoplasty had a higher recurrence rate than other causes. This is probably related to a more extensive damage to the soft tissue of the ear in comparison to smaller injuries caused by ear piercings for example. Another possible explanation is a more prolonged immunologic reaction on dissolvable suture material used in otoplasty. As for the therapy compliance rates, there is a trend towards a correlation between compliance and nonrecurrence, although this does not reach statistical significance. This further highlights the link between therapy effectiveness and outcome, and if true, doctors should encourage patients to wear the device as long as needed.

Using the POSAS score, we observed a statistically significant improvement in all the items of the POSAS between before therapy and the last follow-up. This confirms the efficacy of our custom-molded device. Since the total POSAS score before therapy showed no statistically significant difference

between the recurrence and nonrecurrence groups, we can conclude that recurrence does not depend on clinical presentation upfront. Therefore, someone with a high or low POSAS does not predict recurrence. In other words, it does not matter how bad the POSAS score is preoperatively, the chances for success are equal.

In addition, patients rated the comfort, appearance and overall opinion as acceptable, but people with recurrence had less comfort. A possible explanation could be that the adjustments had not been made appropriately, and therefore, the containment of the wound was suboptimal, resulting in a higher chance of recurrence. Put differently, the compression in these patients was maybe not centered on the point of interest.

Sixty-one percent of patients first complained about discomfort which seems very high; however, because our device can adjust the pressure, we can relieve this, in contrast to most pressure ear clips lacking the ability of applying accurate and independent pressure on the ear keloids. Another benefit is the prevention of severe complications such as tissue necrosis with permanent damage, because of the application of a homogenous pressure. Therefore, it is our opinion that our custom-molded ear clip in terms of effective applied pressure on the keloids, is superior to conventional ear clips.

The main drawback is the size of our custom-molded ear clip and the relatively unattractive aesthetic appearance of this device. In comparison to Park's device using magnets ¹⁹ our device is more obvious and unattractive, but as previously prescribed, Park's device lacks the ability to adjust the pressure. However, most of the other existing devices such as the U loop pressure clip ¹⁸ and the methyl methacrylate stent ¹⁷ are in our opinion a bit more or equally cosmetically appealing. However, most of the patients were satisfied with this therapy in general. To support this finding, we have found that 37,5% of patients with recurrence would choose the treatment again. This means that even if we consider recurrence as a failure, actually for the patient this is not the case. These patients are satisfied or at least free from the keloid for several years and if they would have to undergo the treatment again, they would.

In summary, in this study we show that the advantages of our custom-molded pressure ear clip are the retro-auricular treatment option, adjustable

pressure and minimal severe complication rate. The main disadvantage is the unattractive appearance. The results of adjuvant pressure therapy with our ear clips are comparable with the recurrence rates of other studies recently published.^{17,19} The strength of this study is the long follow-up. Since the number of patients is moderate, a larger patient group is needed to more accurately investigate and determine the efficacy of adjuvant pressure therapy for treatment of ear keloids.

Conflict of interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest.

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CHAPTER 6

Efficacy of custom-made pressure clips for ear keloid treatment after surgical excision

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ABSTRACT

Background: Mechanical pressure is increasingly applied as a means to prevent or treat keloid scars.

Aim: To analyze the long-term efficacy of our custom molded pressure-adjustable earclips to prevent keloid recurrence after surgical excision.

Methods: 88 patients who had undergone ear surgery for keloid scars were treated for 12 hours a day during a total period of 6-18 months using our custom molded earclip. The mean follow-up was 6.5 years. Primary outcome was recurrence of keloids. Secondary outcome was patient satisfaction as assessed by POSAS (Patient and Observer Scale)

Results: Keloid scars did not recur in 70.5% of treated patients. The Fitzpatrick scale, which classifies human skin by type, was significantly different between the recurrence and non-recurrence group. Differences in other patient characteristics were not found between both groups. All items of the POSAS patient scale drastically improved after therapy. Severe side effects of therapy were not observed.

Conclusion: Our pressure-adjustable earclip model is an effective tool in the prevention of ear keloid recurrence and is associated with high patient satisfaction. Its benefits should prompt further studies on its value as an adjuvant therapy to surgery in keloid treatment.

Level of Evidence: Level III on the Evidence Rating Scale for Therapeutic Studies.

INTRODUCTION

Both the clinician and the patient face challenges in the management of keloid scars of the ear because of the ear's intricate anatomical structure. Common treatments include occlusive dressings, intralesional corticosteroid injection¹, fluorouracil injections², pressure therapy³, radiotherapy⁴, laser therapy⁵, surgical excision⁶ or a combination of these therapies⁷. However,

the variety of treatments suggests that so far none of these single treatments lead to satisfactory esthetic results^{8,9}. When mechanical pressure is used, one of the major challenges is the exertion of constant pressure to the keloid, because of the convoluted shape of the ear. Inefficient compression may consequently lead to therapy failure and, therefore, keloid recurrence.

In recent years, ear pressure clips have been developed with different outcomes in terms of effectiveness, comfort and cosmetic appearance⁸⁻¹¹. These include clips made from methyl methacrylate, which has the advantage of being molded to the ear's shape and can therefore evenly distribute pressure to the keloid[8]. We have designed a device made from uvex, which shares the same principles, but has the additional benefit of ensuring pressure adjustment. In this study, we analyzed the long-term efficacy of this new pressure-adjustable device to prevent recurrence after surgical excision of keloid scars. In this study, we focus on the impact of the device in addition to surgery.

METHODS

In this retrospective study, we collected the data on patient records and planned outpatient clinic appointments to investigate 88 consecutive patients who were treated for keloid scars of the ear between 2000 and 2011 in the Academic Medical Center Maastricht in the Netherlands. A combination therapy consisting of surgical excision and pressure therapy with the custom-molded earclip was used, which started 4-5 weeks after surgery (Figure. 1). After 3-4 weeks Three of surgery, a plaster mold of the ear was taken that served to fabricate the pressure clip with a silicon liner matching the shape and surface of the ear. The silicone liner was then covered with an artificial pre- and retro-auricular thermoplastic auricle. The fitting of the clip was optimized by the properties of the silicone elastomer called uvex, as well as by an optimal combination of liner and thermoplastic orthosis. In addition, a U-shaped screw-and-pin system made pressure adjustment possible exactly on these points where keloid recurrence was suspected. The effectiveness of the earclips relies on their adjustability of pressure. The pressure is adjusted based on patient's discomfort and the blanching of the scar area with the option to readjust by turning the screw-and-pin system appropriately. To get accustomed to the device and minimize discomfort, a gradual buildup of therapy was recommended.

Fig. 1. Before earclip treatment.

On the first day of wearing the clip, the pressure was maximized to a degree upon which the patient could wear it comfortably for 1 h. On the second day, the pressure was adjusted to the extent that the patient could wear it for 2 consecutive hours. A further increase in time of wearing the clip was then achieved by gradually adjusting the pressure in the following days until it could be worn for twelve consecutive hours with a minimum amount of discomfort. Patients were instructed to use the pressure clip for at least 12 h a day for a total period of 6 -18 months. Follow-up was every 3 months in our outpatient clinic or by telephone interview as appropriate. An assessment was conducted on the area of excision of the former keloid and keloid recurrence was monitored closely by a multidisciplinary team specialized in scar treatment. If recurrence of scarring was suspected, the pressure was readjusted or relocated on the pressure points in case the scar area was not targeted properly.

Despite the treatment, the primary outcome was the recurrence of keloid scars. Differences between the recurrence and nonrecurrence group were identified

by assessing the demographic and clinical variables of the patient population as a means to define risk factors for failure of treatment in the recurrence group. Secondary outcomes were perceived comfort and appearance of the earclip, side effects, quality of life, and satisfaction with the treatment outcome. Comfort and appearance of the earclip were scored on a 1 (worst) to 10 (best) scale. Patients were also screened for side effects of the therapy. Quality of life was assessed using the Short-Form (SF)-8 questionnaire. The Patient and Observer Scar Assessment Scale (POSAS) was used to evaluate satisfaction with the treatment outcome (i.e., subjective experience of changes in keloid morphology measured by the patient and an independent doctor)^{12,13}.

All patients gave written informed consent before inclusion in the study. The study was approved by the Medical Ethical committee of the University of Maastricht and has been performed in accordance with the ethical standards following the Declaration of Helsinki.

Statistical Analysis

Continuous variables are presented as means with standard deviations or as medians with interquartile ranges, as indicated by the distribution of the data according to the Kolmogorov-Smirnov test. Categorical variables are presented as percentages. Continuous variables were compared between groups using unpaired Student *t*-tests or Mann-Whitney U tests as appropriate. Categorical variables were compared between groups using Chi-squared tests or Fisher's exact tests as appropriate. Changes in continuous variables before and after treatment were compared using paired Student's *t*-tests. *P*-value of 0.05 was considered statistically significant. Data analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Demographic and clinical characteristics of patients with keloid scars.

Table 1 presents patient demographics at the time of admission for the study, as well as clinical outcome data. The patient group consisted of 29 men and 59 women with a mean age of 24 years (8 - 69 months) who underwent exci-

Table 1. Demographic and clinical characteristics of patients with keloid scars.

Gender (male)	33%
Age (yrs)	24 (8-69)
Positive family history	17%
BMI (kg/m ²)	23 (15-37)
Fitzpatrick scale	3 (3-4)
Anatomical location	
Upper pole	19%
Lobule	35%
Retro-auricular	44%
Cause	
Ear piercing	43%
Otoplasty	51%
Trauma	6%
Previous treatment	
None	73%
Surgical excision	15%
Injections	6%
Brachytherapy	7%
Patient compliance	
<8 h a day	10%
8 - 12 h	44%
>12 h	46%
Therapy duration (months)	13 (4-36)
Comfort of the earclip	6.7
Appearance	4.7
Overall opinion	7.2
Open for retreatment (yes)	89%
Enhanced QOL (yes)	46%

sion and pressure therapy of ear keloids between 2000 and 2011 with a mean follow-up of 6.5 years (11 months - 12.3 years). Mean body mass index (BMI) was 23. The upper pole of the ear was affected in 19% of the cases with 35% lobule and 44% retro-auricular keloids. The etiologies of keloid scars were ear piercing in 43%, otoplasty in 51%, and trauma in 6%. While 73% of the patients had not undergone previous treatment, 15% had undergone surgical excision, 6% intralesional corticosteroid injections, and 7% brachytherapy. The mean therapy duration was 13 months during which only 10% of the group wore the earclip <8 h a day. The total group scored the comfort of the earclip as 6.7 (on a 10- point scale variable from 1 as worst to 10 as best) and 4.7 for the appearance. The overall opinion was 7.2. A total of 89% of the

group was open to future re-treatment and 46% experienced an enhanced quality of life after treatment.

New custom molded pressure clips prevent recurrence of keloids scars after surgery.

Follow-up observations after ear surgery and pressure treatment for keloid scars showed that 62 patients (70.5%) were treated successfully without recurrence and 26 patients (29.5%) developed recurrence (Table 2) with a

Table 2. Risk factors between the recurrence and nonrecurrence group.

	Recurrence N=26 (29,5%)	Nonrecurrence N=62 (70,5%)	P
Gender (male)	35%	32%	0.83
Age (yrs)	24 (12-44)	24 (8-69)	0.82
Family history	15%	18%	1.00
BMI (kg/m ²)	23 (15-37)	24 (16-37)	0.58
Fitzpatrick scale	3 (3-4)	3 (2-3)	0.02*
Anatomical location			0.82
Upper pole	23%	18%	
Lobule	31%	37%	
Retro-auricular	46%	44%	
Cause			0.33
Ear piercing	46%	42%	
Otoplasty	54%	50%	
Trauma	0%	8%	
Previous treatment			0.51
None	81%	69%	
Surgical excision	8%	18%	
Injections	8%	5%	
Brachytherapy	4%	8%	
Patient compliance			0.50
<8 h a day	8%	11%	
8 - 12 h	54%	40%	
>12 h	39%	48%	
Therapy duration (months)	14 (5-36)	13 (4-28)	0.36
Comfort (1 worst, 10 best)	6.1	7.0	0.07
Appearance earclips	4.1	4.9	0.10
Overall opinion	5.6	7.9	0.01*
Open for re-treatment (yes)	65%	98%	<0.001*
Enhanced QoL (yes)	19%	57%	<0.001*

*Statistically significant.

mean follow-up of 6,5 years (11 months – 12.3 years). There were significant differences in Fitzpatrick scale between the recurrence (3-4) and nonrecurrence group (2-3) with a median of 3. No significant differences in other variables were found between both groups.

Overall opinion, POSAS scores and comfort of wearing the ear clips.

As shown in Table 2, the patients in the nonrecurrence group scored better in comfort (7.0 (6.0 - 8.0) vs. 6.1 (5.0 - 8.0)), appearance (4.9 (4.0 - 6.3) vs. 4.1 (1.0 - 6.0)) and overall opinion of the earclip (7.9 (7.8 - 8.3) vs. 5.6 (3.0 - 9.0)) compared with the recurrence group. Concomitantly, 65% of the patients in the recurrence group would repeat the treatment, and 19% of these patients experienced an enhanced quality of life; 98% and 57%, respectively, in the nonrecurrence group. In the nonrecurrence group, treatment with our pressure-adjustable custom-molded earclips resulted in a statistically significant improvement of all the item scores of the POSAS in both the Patient and Observer Scale. Figures 2 and 3 show the keloid before treatment

Fig. 2. An example of our custom-molded device during the treatment.

Fig. 3. After earclip treatment

and the results after treatment. The total score of the POSAS before treatment showed no statistically significant differences between the recurrence and nonrecurrence group (Tables 3 and 4). As shown in Table 5, 46% of the patients were found to have discomfort during the application of the pressure. Other complaints were pruritus (22%), skin irritation (25%), and pressure sores (9%) (Figure 4). Severe complications such as infections or necrosis were not observed.

Table 3. Comparison of the POSAS Patient and Observer Scale before therapy and the last follow-up and p-values.

Patient Scale	Before therapy	After therapy	P
Pain	3.9 (2.8)	1.7 (1.6)	<0.001*
Itching	4.4 (2.7)	2.2 (2.1)	<0.001*
Color	5.5 (3.1)	2.3 (2.0)	<0.001*
Stiffness	7.2 (2.5)	3.5 (3.0)	<0.001*
Thickness	7.8 (2.3)	2.9 (2.5)	<0.001*
Irregularity	7.1 (2.6)	2.8 (2.5)	<0.001*
Overall opinion	8.4 (2.2)	3.4 (3.0)	<0.001*
Observer Scale			
Vascularity	3.4 (1.7)	2.2 (1.3)	<0.001*
Pigmentation	2.9 (1.8)	1.8 (1.1)	<0.001*
Thickness	6.5 (1.6)	3.4 (2.2)	<0.001*
Relief	5.6 (2.0)	3.0 (2.1)	<0.001*
Pliability	6.5 (1.8)	3.1 (2.3)	<0.001*
Surface area	6.6 (1.7)	3.3 (2.2)	<0.001*
Overall opinion	6.6 (1.5)	3.3 (2.2)	<0.001*

*Statistically significant.

Table 4. Total scores POSAS before therapy, on last follow up and relative reduction in POSAS as well as p-values

	Recurrence	Non-recurrence	P-value
POSAS score before treatment	81,38	82,68	0.78
POSAS score last follow-up	62,38	29,18	<0.001*
POSAS score reduction	19,00	53,50	<0.001*

*Statistically significant.

Table 5. Side effects from using our custom-molded pressure earclip

Side effect	Number (%)
None	35 (40%)
Discomfort	40 (46%)
Pruritis	19 (22%)
Skin irritation	22 (25%)
Pressure sores	8 (9%)
Necrosis	0 (0%)
Infection	0 (0%)

DISCUSSION

This study shows that our treatment strategy with the use of custom-molded and adjustable pressure clips prevents recurrence of ear keloids after surgery in 70.5% of patients. Previous studies have shown that surgery alone leads to recurrence rates ranging from 45 to 100% ¹⁴. Combined with compression devices, recurrence rates drop to 10 - 20% ^{8,10}.

Fig. 4. Pressure ulcer complication earclip

Therefore, pressure earclips have been widely used as an adjunct to surgery in the treatment of auricular keloids. For example, a comparable device to ours has been described by Kadouch et al., who had an overall success rate of 83% in keloid recurrence. This is higher in comparison to the success rate reported here, but the study only had a mean follow-up of 23 months. In this study, the mean follow-up was 6.5 years. In addition, we observed that recurrence can occur as late as 3 years after the start of therapy. Therefore, there is a possibility that the higher success rates reported by Kadouch et al., and Park et al. may have been biased due to a short follow-up period in their studies. Nonetheless, the relatively high success rates in their and our studies highlight the effectiveness of ear pressure in keloid treatment.

We found that darker-skinned patients were more prone to recurrence in comparison to lighter-skinned patients, which corroborates with previous findings that higher Fitzpatrick skin types have a higher incidence of keloids¹⁵.

As we noted no differences in therapy duration and patient compliance between the recurrence and nonrecurrence group, the success of the therapy did not seem to depend on other factors. However, a limitation of this study is that we have not recorded ethnicity in the study. This may have shed more light on the value of the Fitzpatrick scale as an independent risk factor for recurrence within a subgroup consisting of patients with the same ethnical background. A possible complementary strategy in future studies of the impact of our earclip model on keloid prevention would therefore be to first divide patients based on ethnicity before commencing the study, and then monitor those with a higher Fitzpatrick scale more closely to improve outcomes in this group.

As exemplified above, various compression devices have been developed and described in the literature^{1,3,8-11,16-21}. From these studies, we can deduce ideally, the pressure earclip characteristics as follows: They should be non-inflammatory, resistant to distortion, light in weight and comfortable to wear, and easy to use. They should provide uniform adjustable compression and must not interfere with normal hearing. In addition, they should be affordable, easy to fabricate, aesthetically acceptable, and easy to clean in order to maintain hygiene[3]. Our pressure device possesses most of these features and is unique in the sense that it consists of a custom-molded silicone liner (inside part) with up to three separate thermoplastic adjustable pressure

Fig. 5. (a) Earclip treatment of keloids in all the anatomical positions of the ear. **(b)** Earclip treatment of keloids in all the anatomical positions of the ear.

screw-and-pin mechanisms as a part of the thermoplastic orthosis (outside part). Another advantage of the earclip is its usage in the treatment of keloids in all the anatomical positions of the ear, including the difficult retro-audicular position and earlobes¹⁷ (Figure 5a and b).

We observed a significant improvement in all the parameters mentioned in the POSAS between before therapy and the last follow-up. This suggests the efficacy of the custom-molded device. In addition, patients rated the comfort, appearance, and overall opinion as acceptable, but people with recurrence scored worse for comfort. A possible explanation could be that the adjustments had not been made appropriately and therefore the covering, and subsequently the pressure on the wound, was suboptimal resulting in a higher chance of recurrence. Closer monitoring may prevent this in the future. A drawback is the size of our custom-molded earclip which results in a relatively unattractive aesthetic appearance of this device. But it seems that this is not a reason for the patients to discontinue the therapy. In fact, we showed that 89% of the patients would agree for re-treatment if necessary.

We observed minor side effects, which we felt to be acceptable in comparison to other devices¹⁰. In the study of Park et al. cases of tissue necrosis and wound dehiscence following hematoma are described when using pressure magnets. A total of 46% of patients complained about discomfort, but severe complications such as tissue necrosis were not observed, possibly because of the application of a homogenous pressure on the ear.

In conclusion, although the results of adjuvant pressure therapy with the custom-molded earclips are comparable with the recurrence rates of other studies recently published ^{88,10}, we believe that the relatively large group of patients and longer follow-up favor our earclip in comparison to other devices at this time. In addition, the custom-molded earclip is superior to conventional earclips in terms of adjustable and equally applied pressure on keloids, which prevents the formation of pressure sores. This study supports further study in a larger number of patients, which will more accurately determine the efficacy and safety of our earclip device in keloid treatment and prevention.

CONCLUSIVE REMARKS

Our earclip model is an effective tool with high patient satisfaction in the prevention of ear keloid recurrence and is therefore recommended as an adjuvant therapy for surgical excision.

Conflict of interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest.

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CHAPTER 6

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CHAPTER 7

The role of topical vitamin E in scar management: A systematic review

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ABSTRACT

Background: The practice of prescribing vitamin E after surgery for scar prevention and treatment is widespread and increasingly popular among both the public and clinicians. However, very little evidence exists for this “ritual.”

Objectives: This review was undertaken to critically analyze the current literature about the effect of vitamin E on treating scars.

Methods: The Cochrane, Medline, and PubMed databases were searched based on the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P). The studies and levels of recommendation were graded according to the American Society of Plastic Surgeons (ASPS) criteria. Only prospective studies were included.

Results: Only six studies met the inclusion criteria. Of these six included studies, three reported a significant improvement in the cosmetic appearance of scars when using vitamin E: one study used topical vitamin E in white children as monotherapy, and two studies used vitamin E in an adult population as combination therapy. The other three selected studies showed no significant improvement in scar appearance when using topical vitamin E as monotherapy. Two of the six included studies reported adverse events of vitamin E application: contact dermatitis and increased incidence of itching and rash.

Conclusions: We conclude that there is not yet sufficient evidence that monotherapy with topical vitamin E has a significant beneficial effect on scar appearance to justify its widespread use. Further prospective studies with vitamin E monotherapy and/or combination therapy are warranted to draw better conclusions regarding the value of vitamin E in the management of scar healing.

Level of Evidence: 2

INTRODUCTION

Scar treatment has always been and still is an important topic for plastic surgeons, because poorly healed, clearly visible scars can have significant negative effects on cosmesis and patient self-esteem. In recent years, several scar treatment strategies have been developed and recommended. Some of these treatment options include only one modality,¹ whereas others combine several modalities such as surgery,² laser treatment,³ radiation therapy,^{4,5} pressure therapy,⁶ cryotherapy.⁷ In addition, several pharmaceutical agents are recommended to treat scars, such as topical vitamin E, steroids, antioxidants, moisturizers, and so on. It has been demonstrated that a significant proportion of medical professionals and many patients believe that treatment of scars with topical vitamin E can help to improve the cosmetic outcome of a scar.⁸

Vitamin E, or tocopherol, is the most important lipid-soluble membrane-bound antioxidant in the body.⁹ It consists out of eight antioxidants, from which the stereoisomers are derived from the tocopherols and the tocotrienols. Among these forms, α -tocopherol has the most potent biological activity, because it is the only form maintained in the human body. Vitamin E acts as an anti-inflammatory agent and affects the remodeling of scars by interacting with the phospholipids in cell membranes, inducing molecular packing and maintaining the stability of biologic membranes.^{10,11} Vitamin E is used cosmeceutically to accelerate wound healing, to prevent hypertrophic scarring and to decrease pruritis.¹²

However, to date, there is neither a consensus nor good scientific evidence for the use of vitamin E in the treatment of scars. Therefore, this review was undertaken to evaluate the evidence from prospective studies regarding the effect of topical vitamin E on the outcome of scars.

METHODS

Search Strategy

The Cochrane, Medline, and PubMed databases were searched in January 2016 using possible combinations and search terms covering the use of

vitamin E in the treatment and management of scars. The following search terms were used to: scar, hypertrophic scar, keloid, vitamin E, tocopherol, tocotrienol, treatment, topical, topical administration, and topical use. Additional studies were identified and selected by searching reference lists from the selected articles. No limits were applied for year of publication or publication status.

Study Selection Criteria

We evaluated all types of studies reporting the treatment of scars using topical vitamin E. There were no limitations on the type of studies or the year of publication. The articles were published between 1951 and 2016. There was a limit for language; only articles in English, German, Dutch, Turkish, and Polish were included. In the grey literature search, we did not find any articles that could be included in this review. All the search terms were used as a medical subject heading (MeSH) term, except “topical,” because it is not a valid MeSH term. Two reviewers screened the identified records from the search for eligibility in an unblinded standardized manner. After the initial search, there was a result of 70 hits. The initial inclusion was based on the title and abstract. Articles that were excluded were reviews on scar treatment (7), review on scars caused by burns (1), therapy other than vitamin E for scars (10), animal studies (9), effect of vitamin E on events other than scarring the skin (23), letter to the editor (1), questionnaire (1), and articles not in English, German, Dutch, Turkish, or Polish language (9). Nine articles were found eligible after the initial inclusion. The reviewers read each of these nine articles to confirm that they met the inclusion criteria for this review.

Because of the limited number of articles published about vitamin E, we included all studies with topical application of vitamin E, whether used as monotherapy or combination therapy, in relation to wound healing or scar management. In the end, a total of six articles were included in this review after excluding articles without scientific value. We used two independent investigators to minimize the possibility of rejecting relevant studies. Any disputes in data extraction were resolved by a third independent reviewer.

Presentation of Data

This review was written using the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) statement, which is a checklist of items to include when reporting a systematic review.

Methodological Quality Assessment

The level of evidence of the extracted studies was graded according to the American Society of Plastic Surgeons (ASPS) Evidence Rating Scales. This classification assigns each article to a corresponding level of evidence ranging from I (highest) to V (lowest). Besides this classification, a practice recommendation was provided according to the ASPS Grade Recommendation Scale.

RESULTS

Study Characteristics

Our research yielded a total of 70 studies in the Cochrane, Medline, and PubMed databases. Of these 70 studies, 61 were excluded after reviewing the title and abstract. Studies were excluded either because of the use of vitamin E as a non-topical treatment, or if they were conducted for purposes other than scar treatment or other treatment modalities. Ultimately, after screening the full article, we could only include six studies for review (Figure 1). These included studies were conducted in a prospective manner using topical vitamin E, either in monotherapy or combination therapy, and had a level of evidence of type II, according to the ASPS Evidence Rating Scale for Therapeutic Studies.¹³

The length of follow-up in each of the six studies was quite different, ranging from 8 weeks to 1 year after treatment. We have conducted a review of funding resources for the included studies and found that only Khoo et al's work was funded by the University Sains Malaysia ShortTerm Grant. The authors have no conflicts of interest to declare.

Fig. 2. PRISMA-P flowchart of included and excluded studies.

Patient Characteristics

The size of the study population (n) of the six included studies ranged from 15 to 428 patients with three times as many male than female participants. Only one study was conducted among children¹⁴, and the other five studies were conducted among adults. Inclusion and/or exclusion criteria were only mentioned in three out of the six studies.^{11,14,15} None of the studies used the Fitzpatrick scale to determine the skin type of investigated patients, and only two of the studies described the racial appearance of their study population (white children and Malaysians).^{14,15}

Treatment

In this review, we focus on vitamin E as a topical agent. The six selected studies described vitamin E as a monotherapy as a gel or cream or as combination therapy with a silicone sheet or hydrocortisone, or with silicone and vitamin E in collodion (a syrupy solution). Next to the difference in local application, each study used a different concentration of vitamin E (Table 1).

Table 1. Characteristics of the included studies

Study	Studytype	n	Gender (m/f)	Race	Age (yrs)	Area of interest	Dosage vitamin E	Use, frequency and duration	Follow-up	Assessment type	Results	LoE*
Zampieri et al. 2010 ¹⁴	Prospective Single-blinded	428	319/109	White	2-9	Incision for inguinal surgery	N/R	At least 15 days, twice a day, before surgery At least 30 days, twice a day, after surgery	Follow-up: 10 days after end of treatment and after 6 months	Subjective -VSS	Studygroup reported no keloids (p<0.05) or wound infection	II
Baumann et al. 1999 ²⁰	Prospective Double-blinded	15	N/R	White	N/R	Skin cancer removal surgery (Mohs)	320 IU/gm	Twice daily for 4 weeks	Follow-up at weeks 1, 4 and 12	Subjective -Evaluation of appearance by physician and patient -photographs	Topically applied vitamin E does not help improve cosmetic appearance	II
Jenkins et al. 1986 ²¹	Prospective Double-blinded	111	N/R	White	3-20	Operative procedure for postburn contractures	200 units/gram	Three times a day with a massage of three minutes continued for 120 days	Follow-up at 1 month, 4 months and 1 year	Subjective -Evaluation by research nurse -Photographs	No significant difference of scar thickness	II
Khoo et al. 2011 ¹⁵	Prospective Double-blinded	85	75/10	Malaysian (88,4%) Other (11,6%)	16-59	Surgical scars	5% tocotrienol 71,7% deionised water	Twice a day for 6 weeks starting at 2 weeks after surgery	Follow-up at 0, 2, 6 and 16 weeks following the onset of topical application	Subjective -POSAS -VAS Objective - LDI	No significant effect on appearance and vascularity of scars	II
Palmieri et al. 1995 ¹¹	Prospective Single-blinded	80	N/R	White	18-63	Postsurgical / burn	Silicone gel sheets with vitamin E (3%, 5g/silicone sheet)	4 to 8 weeks	Follow-up at 4 and 8 weeks.	Subjective - Scott-Husskisson scale -Photographs	Vitamin E added to silicone sheets scored better results than simple silicone plate alone	II
Perez et al. 2010 ¹⁹	Prospective	30	N/R	White	>18	Keloids and hypertrophic scars	HSE (0.5% hydrocortisone, silicone and Vit E), Onion Extract	Duration of 16 weeks	Follow-up at 4, 8, 12 and 16 weeks.	Subjective -VAS Objective - MPR	HSE had a significant MPR in different fields.	II

HSE, hydrocortisone, silicone, and vitamin E lotion; LDI, laser Doppler imaging; LoE, level of evidence; MPR, mean percent reduction (volume, length, induration, erythema, pigmentation, tenderness, pain, and itching); N/R, not reported; POSAS, Patient and Observer Scar Assessment Scale; VAS, Visual Analogue Scale; VSS, Vancouver Scar Scale. * As determined by the authors using the ASPS Evidence Rating Scales.

Effectiveness and Recurrence

Each of the six included studies assessed the scars in a subjective manner using either the Vancouver Scar Scale (VSS),¹⁶ Patient and Observer Scar Assessment Scale (POSAS),¹⁷ Visual Analogue Scale (VAS),¹⁸ or the Scott-Huskisson Scale,¹¹ or simply by taking photographs. Only one study used a Laser Doppler Imager (LDI) as an objective evaluation.¹⁵

Of the six included studies, three reported a significant improvement in cosmetic appearance when using vitamin E. Of these three studies, only the study of Zampieri et al¹⁴ used topical vitamin E as monotherapy in a study

population consisting of white children ranging from 2 to 9 years of age. The two other studies demonstrated the effect of the use of vitamin E in combination therapy in an adult population: Palmieri et al¹¹ used vitamin E in combination therapy with silicone gel sheets, and Perez et al¹⁹ used vitamin E in combination with hydrocortisone and silicone sheets. These last two studies had no preventive interventions in the treatment of (hypertrophic) scars or keloids, compared with the study of Zampieri et al.¹⁴ Moreover, in the study of Zampieri et al, vitamin E was applied both in the preoperative and postoperative periods, whereas it was applied only in the postoperative period in all other studies. In demonstrating a positive effect of vitamin E on wound healing, these three studies all used a subjective method to assess the scars (either one or more from the VSS, VAS, Scott-Huskisson scale, or simply by taking photographs).

The three other selected studies among the six included in this review showed no beneficial effect when using topical vitamin E; there was no significant improvement in scar appearance. The subjective methods used to assess scar healing and appearance in these three studies were POSAS, VAS, and simply by taking photographs. No improvement could be detected at all: only one of these three studies, the study by Khoo et al,¹⁵ used an objective method to document scar improvement (LDI), and they did not find any objective change in the vascularity of the scars.

Complications

Two of the six included studies described adverse events of the application of topical vitamin E: the study by Baumann et al²⁰ described a contact dermatitis in up to 33% of the treated patients and the study by Jenkins et al²¹ mentioned an increased incidence of itching and rash. The other four included studies did not witness any adverse effect.^{11,14,15,19}

DISCUSSION

Topical vitamin E is a frequently prescribed topical agent in the treatment of scars, despite the lack of evidence of its presumed effect. In the study

of Curran et al,⁸ which evaluated the basic scientific knowledge of vitamin E among doctors, nurses, pharmacists, and students, nearly 68% of the patients had the opinion that vitamin E could improve the cosmetic appearance of scars and 25% would recommend vitamin E to patients to improve the cosmetic appearance of their scars. In addition, 22% of patients had used vitamin E themselves for scars. Based on our review, we conclude that there has not yet been sufficient evidence that monotherapy with topical vitamin E has a significant beneficial effect on scar appearance: only three out of our six selected studies reported some beneficial effect of vitamin E. In addition, the topical application of vitamin E might also result in side effects (itching, contact dermatitis, rash), making it detrimental on the final cosmetic outcome under certain circumstances.

When vitamin E is used in combination therapy, there seems to be a positive effect on scar healing. In two selected articles in our review, vitamin E was used as combination therapy and reported an improvement in cosmetic appearance: Perez et al¹⁹ used vitamin E in a combination therapy with hydrocortisone and silicone, and Palmieri et al¹¹ used vitamin E in a combination therapy with silicone sheets containing vitamin E. However, whether vitamin E has a significant role in this positive effect is not quite clear from these studies, because both additional components (hydrocortisone and silicone sheets) are known to have a beneficial effect in scar healing and appearance.^{22,23} To date, evidence is limited for the use of topical steroids for scar management, but there is a broad consensus that the use of intralesional corticosteroids is efficacious. The use of intralesional corticosteroids is first-line therapy for the treatment of keloids and second-line therapy for the treatment of hypertrophic scars if other easier treatments have not been efficacious.²⁴

According to two systematic reviews about silicone gel therapy, there is weak evidence of a benefit of silicone gel sheeting to prevent abnormal scarring in high-risk individuals.²⁵ However, in burn wounds, the efficacy of silicone gel showed significant improvements.²⁶ Therefore, it seems that steroids and/or silicon therapy have some effect on scar healing, and the improved scar healing that was observed in the articles of Perez et al¹⁹ and Palmieri et al¹¹, cannot be solely ascribed to vitamin E.

Zampieri et al¹⁴ provided significant results regarding the prevention of scar formation. Topical vitamin E was applied both preoperatively and postopera-

tively, resulting in a significant beneficial effect and improved wound healing on the final cosmetic appearance of the scars using the VSS scale. However, the exact composition of their commercially available product containing vitamin E is unknown. Despite the observed positive effect in this study, it is questionable whether these results can also be obtained in a general population. The study population of Zampieri et al¹⁴ consisted of white children, a race less prone to develop hypertrophic scars or keloids, and it is known that keloids tend to develop more often in people with a darker skin and that they are never seen in people without skin pigmentation (albinos).^{27,28} Moreover, the age of the study population of Zampieri et al¹⁴ varied between 2 and 9 years of age, although people between the ages of 10 and 30 are more prone to develop keloids.^{29,30}

Unfortunately none of the six included studies used in our review used the Fitzpatrick skin scale or a similar skin scale to assess the skin type of their study population. This would have given a better objective impression of the effects of topical vitamin E in patients with an increased risk for hypertrophic scars and keloids.

An underexposed part of scar treatment is the use of scar massage. This could happen consciously by a therapist or with massage tips given to patients or unconsciously when you apply an emollient or moisturizing agent to a scar. Scar massage may have positive benefits on scars, leading to increased scar pliability, decreased scar banding, and some relief of swelling and induration.^{24,31} In a review conducted by Shin et al³² concerning the role of massage in scar management of 144 patients who underwent scar massage therapy, 65 patients (45.1%) experienced improvement in one or more of the following: POSAS, VSS, mood, range of motion, pruritis, pain, depression, and anxiety.^{32,33} Additionally, massage could also have a positive effect on anxiety levels, depression, and the overall mood of patients.^{31,32,34} Adverse effects of scar massage therapy have also been reported: it could lead to a break in the epidermis, bleeding, infections, wound dehiscence, graft failure, irritation from friction, and dermatitis caused by hypersensitivity to the used emollient.^{24,32,34} Early massage of the scar should also be avoided according to evidence in a mouse model, in which massage of the scar in the early phases of wound healing promoted hypertrophic scarring.^{32,35} Although there is no clear evidence that

the topical application of vitamin E may cause significant harm, several side effects of topical vitamin E have been reported since its introduction, such as contact dermatitis,³⁶⁻³⁸ erythema-multiforme-like eruptions^{37,39} and urticarial eruptions.³⁷ In our review, only two out of the six selected studies reported adverse events: Baumann et al²⁰ described contact dermatitis after the topical use of vitamin E in 33% of the patient population, and Jenkins et al²¹ reported an increased incidence of itching and rash. In the Jenkins study, the incidence of these side effects is not known, because the authors excluded all patients in their study who developed adverse effects. Widgerow et al⁴⁰ found that the early use of vitamin E to treat scars can result in a reduction of the tensile strength of the wound, which could lead to broad and stretched scars.

In recent decades, several scar assessment scales have been developed. However, none of them has completely met the clinimetric requirements. Although many authors consider the POSAS to be most suitable for scar assessment, a solid gold standard for objective scar assessments is still lacking⁴¹ and actually wanted. All selected studies in our review used subjective methods to measure scar changes, with the exception of Khoo et al¹⁵, which used an objective method (LDI) to measure scar changes.

Limitations of this review include the small number of studies published on this topic, the quality and level of evidence of the collected studies, the lack of standardized outcome measures, and the variation in the study population (children vs adults).

Vitamin E, or tocopherol, is a substance often found in scar creams and also recommended by medical personnel in hospitals or by general practitioners. The general consensus about the application of a vitamin E-based cream or emollient is that it would lead to beneficial scar healing. Doing research on this topic eventually leads us to the idea that there was no comprehensive review performed on the scientific evaluation of the use of vitamin E on scar treatment. Therefore this literature review on the effects of vitamin E on scar treatment is, to our knowledge, the only review conducted to date that concentrates solely on the topical administration of Vitamin E on scars.

CONCLUSIONS

Although the practice of prescribing vitamin E after surgery is widespread, there is a paucity of evidence that vitamin E has any beneficial effect. This systematic review regarding the effectiveness of topical vitamin E on scars and wound healing resulted in a limited series of six studies fulfilling the criteria of evaluating the effectiveness of vitamin E in a prospective manner. Based on this review, we conclude that there is not yet sufficient evidence that monotherapy with topical vitamin E has a significant beneficial effect on scar appearance to justify its widespread use. Only one of the six selected studies found improved scar appearance/ healing when using vitamin as monotherapy, and two studies found efficacy when using vitamin E in combination therapy. Further prospective studies regarding vitamin E monotherapy and/or combination therapy are therefore warranted to draw better conclusions regarding the value of vitamin E in the management of scar healing.

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CHAPTER 8

General discussion and future perspectives

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

The management of scars remains a challenge for both plastic surgeons and patients. Many treatments for improving scar quality have been proposed.

Negative pressure wound therapy

A preventive modality for problem scar treatment is negative pressure wound therapy (NPWT). In a multicenter study conducted across USA, France, South Africa and the Netherlands (Chapter 2) we showed that significantly fewer healing complications were noted in NPWT-treated patients following reduction mammoplasty. NPWT also resulted in a significantly lower incidence of dehiscence compared to standard care by day 21 post-surgery. Generally, one of the most important factors for preventing dehiscence is to avoid tension over the closed incisions. It is suggested that one of the key mechanisms of action of NPWT is minimizing tension and increasing breaking strengths of wounds, which was demonstrated using computer modelling, in vitro measurements^{1,2} and animal studies.^{3,4} Other potential mechanisms are enhanced tissue perfusion and reduction of incisional edema. All these findings support the growing evidence that post-incisional NPWT use may reduce wound complications^{5,6}. In another study (Chapter 3), we showed that at day 42 and 90, the incision sites treated with NPWT resulted in a statistically significant better quality of scarring and aesthetic appearance, as measured by POSAS and VAS scales, compared to the sites treated with fixation strips. The mechanisms by which NPWT improves quality of scar formation is not understood. Proposed mechanisms are enhancement of skin hydration, reduction of inflammation and edema, which emerged from studies using silicone sheeting.⁷ Further actions influencing quality of scarring are optimized wound healing, enhanced local pressure on the incision and reduction of traction.^{8,9}

To verify long-term results of these studies, we have performed a study (Chapter 4) in our center with a follow-up of 1 year. We found similar re-

sults, such as the number of wound complications was significantly lower for the NPWT treated sites compared to fixation strips. POSAS and VAS scores at 42 and 90 days revealed a significantly better quality of scarring in the NPWT treatment breasts than fixation strips. At 180 days follow up there was a significant improvement in total VAS scores. No consistent significant improvement in scar quality was demonstrated at 360 days. This could be due to the maturation phase of the scar, indicating that the end result of scarring will be similar. No significant improvement was noted using scar assessment tools, such as hydration, trans-epidermal water loss and viscoelasticity. This could be due to measurements being performed with different probes and other external factors influencing results. Even after standardizing measurement locations it proved difficult to exactly measure the same section of scar/skin during follow-up. Moreover, some patients had thin scars and the probe was relatively big so it overlapped onto normal skin. Despite our best efforts to minimize environmental factors, by keeping the room temperature and air humidity stable, it was practically impossible in the out-patient clinic, where the measurements were performed. During the follow-up period, seasons changed making scar measurements even more difficult. Some patients were stressed because they were late or had put on body lotion when they were not supposed to.

Custom-molded pressure ear-clips

For the treatment of keloids, the application of mechanical pressure by compression devices has gained popularity. Nowadays, pressure earrings are widely used as an adjunct to surgery in the treatment of auricular keloids. In two studies (Chapter 5 and 6) we have demonstrated successful outcomes in 71% of the patients who used our custom-molded pressure clips. Of the treated patients 29% had a recurrence. These findings are similar to those patients who were treated with other compression devices, where recurrence ranged from 10-20%^{10,11}. The slightly higher recurrence rate in our study may suggest that our method is less effective. However keloid recurrence can occur as late as after 3 years. In our study, the mean follow-up was 8,5 years, compared to a maximum of 2 years follow-up in other studies. Therefore, long term, the success rate of the 2 years follow-up study may in fact be lower. Other findings of our study showed significant differences

in the Fitzpatrick scale between the recurrence and no recurrence group. Darker-skinned patients were more prone to keloid recurrence than those with a lighter-skin color. These findings are in line with current research showing a higher incidence of keloids for those with a higher Fitzpatrick skin type score.¹²

Furthermore, treatment with our custom-molded pressure ear-clip resulted in a statistically significant improvement of all the item scores of the PO-SAS. This confirms the efficacy of our custom-molded device. In addition, patients were in general satisfied with the ear-clip, but disliked the appearance. In comparison to other ear-clips our device is more visible and unattractive. Often other devices lack the ability to adjust the pressure and to treat retro-auricular keloids^{11,13,14}, which are unique features of our device. A limitation of our study was the lack of a control group. However, since our specialized scar center treats very complex cases, it was not ethically acceptable to exclude patients from treatment.

Topical vitamin E

A much prescribed topical agent in the treatment of scars is vitamin E, despite the lack of evidence of its presumed effect. A significant proportion of medical professionals as well as patients believe that treatment of scars with topical vitamin E can help to improve cosmetic outcome of a scar¹⁵. In our systematic review, we have found only six studies which met the inclusion criteria. Of these six studies, three showed no significant improvement in scar appearance when using topical vitamin E as monotherapy. The other three reported a significant improvement in cosmetic appearance, but two of the studies used combination therapy. One of the studies used vitamin E in combination with hydrocortisone and silicone¹⁶ and the other used it combined with silicone sheets.¹⁷ Conclusions from these studies whether vitamin E has a significant effect on scar improvement cannot be drawn. Both additional components hydrocortisone and silicone are known to have a beneficial effect in scar treatment.^{18,19} While the evidence for topical steroids for scar therapy is limited, there is consensus about the efficacy of intralesional corticosteroids. To date, evidence is limited for use of topical steroids for scar management, but there is a broad consensus that intralesional corticosteroids is efficacious.¹⁹

There is also evidence supporting significant improvements in scar quality when using topical silicone therapy.²⁰ In conclusion, it seems that both steroids and silicon therapy may have some effect on quality of scarring and that the observed improvement in scar quality cannot be attributed solely to vitamin E. In our systematic review, there was only one study which showed evidence that monotherapy with topical vitamin E had a significant beneficial effect on scar appearance.²¹ It is important to note the limitations of this study when comparing the cosmetic results of the scars in this study with the general population. The patients in this study were Caucasian children aged from 2 to 9 years. Both factors have to be taken into account: Caucasians are less prone to develop hypertrophic scars than darker skinned people. Similarly, prepubescent children have less common keloid formation than those aged 10 -30 years.^{22,23}

Although there is no conclusive evidence that topical application of vitamin E may cause significant harm, two of the six included studies reported adverse events such as contact dermatitis²⁴ and a combination of itching and rash.²⁵

Future perspectives

In this thesis, we have discussed innovative non-invasive preventive and therapeutic treatment modalities for problem scars.

We have shown with the single use NPWT treatment its beneficial effect on scar appearance. Despite the fact that the device is well tolerated by the patients, it is more cumbersome for the patient than a fixation strip. It comes with an external device that is to be carried, with the tubes attached to the dressing. Much more convenient would be to have a dressing with a self-vacuum pulling effect or to combine dressings with topical agents which increase vascularization, skin hydration and reduce edema of the wound bed.

Regarding the earclip treatment, we have developed our own novel pressure device consisting of a custom-molded silicone inner liner with a separate adjustable pressure splint. The device has the advantage of being molded to match the patient's ear shape and can therefore evenly distribute pres-

sure to the postsurgical site. Furthermore, the device also makes it possible to treat retro-auricular keloids. The downside however is the aesthetic appearance; therefore, focus is on improving the appearance of the ear-clip. This will enable better acceptance and compliance and therefore efficacy of the treatment. Regarding the pressure clips, nowadays we are adjusting these clips manually according to the blanching of the keloid. It would be preferable, to implement electronic pressure sensors in the ear-clip, so we can choose a pre-set pressure to the keloid, whereby increasing its efficacy and minimizing complications like pressure ulcers or necrosis.

As discussed in our systematic review, even though vitamin E has mostly anti-oxidative properties, it may be an option to develop other topical products for combination therapy, preferably with beneficial wound healing properties. A recently developed topical scar treatment modality in this regard is a double layer adhesive silicone dressing as a potential dermal drug delivery film²⁶. Another promising topical agent is nicotine. Despite the fact that it is proven that smoking has a negative effect on wound healing²⁷, several studies show that nicotine has, in contrary to its reputation, angiogenetic and wound healing properties^{28,29}. A possible explanation for this is that nicotine is one of the 4000 chemical constituents of cigarettes and therefore the physiological effects may be different. Topical application of nicotine has shown its beneficial effects on wound healing in animal models³⁰, however more research is needed to further explore this compound. As long as the etiology and development of hypertrophic scar and keloid formation has not yet been fully scientifically clarified, it is our opinion that a combination strategy of preventive measures and multimodal follow-up treatments are necessary to achieve optimal results. In spite of the many guidelines that have been published recently, there is still a long road to go to achieve even more uniform golden standards.

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CHAPTER 9

Summary & Nederlandse samenvatting
(Dutch summary)

SUMMARY & NEDERLANDSE SAMENVATTING (DUTCH SUMMARY)

Summary

Scar treatment has always been and still is an important topic for plastic surgeons. Further research is to be performed on development of scarring, its prevention and treatment, in order to develop effective treatments.

In Chapter 2, 3 and 4 we discussed that the application of NPWT to closed incisions in mammoplasty reduction offered statistically significant and clinically important benefits to patients compared to standard postoperative dressings.

In Chapter 2 we presented a sufficiently powered prospective, randomized, within-patient, controlled, multicenter study and demonstrated a statistically significant reduction in wound healing complications specifically dehiscence compared to standard care. This translates into significant clinical benefits, when placed in context of the large number of breast-reduction procedures performed each year globally, providing evidence supporting utilization of incisional NPWT. Regarding improvement of scarring we discussed in Chapter 3, the results of this multicenter trial, demonstrating that NPWT, using a portable system on closed incisions post-surgery, effectively supported wound healing, promoting optimal scar formation, offering benefits over standard care.

In Chapter 4 we presented a single center study with a follow-up of 1 year, which showed less wound healing complications and a significant improvement in quality of scarring in the earlier stage of scar healing in favor of the NPWT treated sites. The results indicated NPWT to be an attractive option for these patients.

We developed a custom molded pressure ear clip to treat postsurgical scars after keloid excision. In Chapter 5 we presented the advantages of our device as a retro-auricular treatment option, delivering adjustable pressure while minimizing complications. A disadvantage of the device is its

unattractive appearance. The results of adjuvant pressure therapy with our ear clips are comparable with the recurrence rates of other devices presented in recently published studies. Although the custom molded pressure ear clip study had a long follow-up period, the included patient group size was moderate. We therefore performed a further extended study with a larger patient group, which is presented in Chapter 6. This study showed similar results to previous studies, suggesting that our ear-clip can be an effective device for the prevention of ear keloid recurrence. Moreover patient satisfaction with this treatment was shown to be high. Therefore the device seems an interesting option as an adjuvant therapy combined with surgical keloid excision.

Although practice of prescribing vitamin E after surgery is widespread, scientific evidence that vitamin E has beneficial effects is scarce. In Chapter 7, we presented a systematic review exploring the effectiveness of topical vitamin E on scars and wound healing. Based on this review, we concluded that evidence on monotherapy with topical vitamin E is lacking and that its widespread use for improving scar appearance cannot be justified on the basis of evidence. Further prospective studies regarding vitamin E monotherapy and/or combination therapy are to be performed to explore value and role of topical vitamin E in the management of scarring.

Nederlandse samenvatting

Littekenbehandeling is en blijft altijd een belangrijk thema voor plastisch chirurgen. Het is uitermate belangrijk dat we verder onderzoek blijven doen naar dit onderwerp, zodat er nieuwe ontwikkelingen blijven bestaan zowel op het gebied van preventie als behandelingen van probleemlittekens.

In hoofdstuk 2, 3 en 4 hebben we aangetoond dat de toepassing van NPWT op gesloten incisies bij borstverkleining statistisch significante en klinisch belangrijke voordelen biedt voor patiënten in vergelijking met standaard postoperatieve verbanden.

In Hoofdstuk 2 hebben we de eerste grote prospectieve, gerandomiseerde, intra-patiënt, gecontroleerde, multicentrische studie uitgevoerd en hebben we een statistisch significante vermindering van dehiscenties aangetoond.

Dit biedt significante klinische voordelen met name door het grote aantal borstverkleiningsprocedures dat elk jaar wereldwijd wordt uitgevoerd en de bewezen toepasbaarheid van NPWT bij patiënten met onderliggend lijden.

In hoofdstuk 3 hebben we een soortgelijke studie uitgevoerd echter in dit geval met betrekking tot littekenverbetering. We hebben hier aangetoond dat de toepassing van NPWT met het PICO™ apparaat voordelen geeft ten opzichte van standaardzorg bij chirurgische ingrepen met betrekking tot wondgenezing en de hierdoor resulterende verbetering van littekens.

In Hoofdstuk 4 hebben we in een soortgelijke studie dezelfde conclusies bevestigd maar dan in een single center verband met een follow-up van 1 jaar. Ook hier werden minder complicaties voor wondgenezing en een significante verbetering in de kwaliteit van de littekens gezien in de vroege fase van de littekenheling. Deze resultaten geven aan dat NPWT een effectieve behandeling is.

Een van onze eigen ontwikkelde behandelingen is onze op maat gemaakte oorclip. In hoofdstuk 5 hebben we aangetoond dat de voordelen van ons apparaat veelzijdig zijn: o.a. de retro-auriculaire behandelingsmogelijkheden, de individuele instelbare drukken en de minimale kans op ernstige complicaties. Het grootste nadeel is het onaantrekkelijke design. De resultaten van onze studie zijn vergelijkbaar met de recidiepercentages van recent gepubliceerde studies. De kracht van deze studie is de lange follow-up, maar de patiëntenpopulatie is van een middelmatige grootte. Daarom hebben we (hoofdstuk 6) een nieuwe uitgebreide studie uitgevoerd met een grotere patiëntengroep. Ook in deze studie hebben we vergelijkbare resultaten bereikt en bewezen dat onze oorclip een effectief hulpmiddel is met een hoge patiënttevredenheid bij het voorkómen van een oorkeloïd recidief. Daarom wordt onze oorclip aanbevolen als een adjuvante therapie na chirurgische excisie.

Het voorschrijven van vitamine E na een operatie wordt veelzijdig wereldwijd toegepast. Echter is er tot op heden niet veel wetenschappelijk bewijs dat vitamine E een gunstig effect heeft op littekengenezing. In hoofdstuk 7 hebben we een systematische review uitgevoerd met betrekking tot de effectiviteit van topicale vitamine E op littekens en wondgenezing. Op basis van deze beoordelingen kunnen we concluderen dat er nog onvoldoende

bewijs is dat monotherapie met lokale vitamine E een significant gunstig effect heeft op littekenvorming om het wijdverspreide gebruik ervan te kunnen rechtvaardigen. Verdere prospectieve studies met betrekking tot vitamine E-monotherapie en/of combinatietherapie zijn daarom nodig om betere conclusies te kunnen trekken met betrekking tot de waarde van vitamine E bij de behandeling van littekens.

CHAPTER 10

Valorization Addendum;
Acknowledgements (dankwoord);
Curriculum Vitae;
List of Publications

10

VALORIZATION ADDENDUM

This paragraph intends to discuss the social and economic value of the results described in this thesis. Numerous scar treatment strategies have been developed and recommended and no single therapy has been accepted universally as the standard care. The primary focus of this thesis has been on scar treatment to investigate three innovative interventions that offer plastic surgeons viable treatment options: one preventive and two therapeutic treatment modalities to better manage the clinical treatment of scars.

In Chapter 2, 3 and 4 we discussed that the application of Negative Pressure Wound Therapy (NPWT) to closed incisions in mammoplasty reduction offered statistically significant and clinically important benefits to patients compared to standard postoperative dressings. In Chapter 2 we demonstrated a statistically significant reduction in wound healing complications specifically dehiscence compared to standard care. In Chapter 3 and 4 we have discussed the improvement of scarring. In summary, NPWT effectively supported wound healing, promoting optimal scar formation, offering benefits over standard care. In terms of socioeconomic value, less wound complications or problem scars can reduce health care costs by reducing consultations, hospital visits and/or hospital admissions. Other benefit is the less frequent dressing changes which will also have the added benefit of increasing the quality of life of the patients. Despite the fact that the device is well tolerated by the patients, it is more cumbersome for the patient than a fixation strip. It comes with an external device that is to be carried, with the tubes attached to the dressing. To further improve the quality of life, the development of a dressing without the need for an external device and tubes could be considered.

In Chapter 5 and 6, we demonstrated that our custom molded pressure ear clip can be an effective device for the prevention of ear keloid recurrence. Skin scarring is a clinical problem that may cause psychological and social difficulties which could result in decreased self-esteem and quality of life. This could be as the result of remembering the cause of the scarring, its clinical symptoms like itching or to the appearance of the scar itself. Thus, by preventing problem scars effectively this could have a positive impact on the quality of the life of the patient. We have also presented the advantages of our device which are the retro-auricular treatment option and delivering

adjustable pressure while minimizing complications. A disadvantage of the device is its unattractive appearance. So, by improving the appearance of the ear-clip, we could achieve even better acceptance and compliance and therefore efficacy of the treatment. Besides, we are adjusting these clips manually according to the blanching of the keloid. It would be preferable, to implement electronic pressure sensors in the ear clip, so we can choose a pre-set pressure to the keloid, whereby increasing its efficacy and minimizing complications like pressure ulcers or necrosis.

In Chapter 7, we concluded that evidence on monotherapy with topical vitamin E is lacking and that its widespread use for improving scar appearance cannot be justified on the basis of evidence.

It may be an option to improve topical Vitamin E products or to develop other topical products preferably with beneficial wound healing properties. It would be socio-economically beneficial to have an effective over-the-counter topical product for preventing problem scars without the need for hospital care. As long as the etiology and development of hypertrophic scar and keloid formation has not yet been fully scientifically clarified, it is our opinion that a combination strategy of preventive measures and multimodal follow-up treatments are necessary to achieve optimal results. In spite of the many guidelines that have been published recently, there is still a long road to go to achieve even more uniform golden standards.

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CURRICULUM VITAE

Volkan Tanaydin, M.D., PharmD.

PROFESSIONAL EXPERIENCE

FELLOWSHIP AESTHETIC PLASTIC SURGERY,

Ivo Pitanguy Institute, Rio de Janeiro, Brazil

2016 - 2017

Specialization with emphasis on practices of aesthetic/cosmetic surgery.

- Learnt techniques of Brazil's plastic surgeons including injectables, peelings, cellulite treatment, facelift and buttock augmentations.
- Mentored by Prof. dr. Henrique Cintra.

CO-FOUNDER, Aesthetic Center of Maastricht

University Medical Center, Maastricht, Netherlands

2016 -2017

Co-founding role within academic cosmetic center focused on injectables (Botox and fillers) laser and peelings.

- Mentored by dr. Peter Velthuis, founder of Velthuis clinics.

FOUNDER AND CO-OWNER, *Betan MediX*,

Maastricht, Netherlands

2015 - current

Founding position within cosmetic company with emphasis on development of new innovative high-quality skin care products.

- Developed skincare in collaboration with Prof. dr. Berend van der Lei
- Orchestrated complete development, testing, production and marketing

RESIDENT PLASTIC SURGERY, *Maastricht University*

Medical Centre, Maastricht, Netherlands

2014 - 2018

Training function concentrated on plastic surgery.

- Perform surgeries in multiple fields including micro surgery, hand and wrist surgery, breast reconstruction, burn wounds and cosmetic surgery.

RESIDENT GENERAL SURGERY, *Atrium Medical*

Center Heerlen, Heerlen, Netherlands

2012 - 2014

Mandatory part of plastic surgery training.

PHARMACIST, *Pharmacy Struytse Hoeck*,

Hellevoetsluis, Netherlands 2008

COURSE ASSISTANT, *University of Groningen*,

Groningen, Netherlands

2005 - 2006

Teaching role focused on lecturing Pharmaceutical Chemistry and Analysis to 80 – 100 students.

EDUCATION

Plastic and Reconstructive Surgery

- **Pre-registration Clerkship, *Chang Gung Memorial Hospital***, Taipei, Taiwan, supervisor: Prof. dr. Fu-Chan Wei, grant received from Groninger University Fund for Excellent Students, 2010 – 2011

- **Pre-registration Clerkship, *University Medical Center Groningen***, Groningen, Netherlands, supervisor: Prof. dr. Werker, 2010
- **Extracurricular internship, *Dr. Hoffmann's HPC Oldenburg***, Oldenburg, Germany, supervisor: Dr. Hoffmann, 2010

Medicine

- **Master Medicine, *University of Groningen***, Groningen, Netherlands, 2011
- **Bachelor in Medicine, *University of Groningen***, Groningen, Netherlands, accelerated one-year education for selected group of high performing students, 2007

Pharmacy

- **Master of Science in Pharmacy, *University of Groningen***, Groningen, Netherlands, comparable with Pharm D title in US, 2008
- **Bachelor in Pharmacy, *University of Groningen***, Groningen, Netherlands, 2004

SURGICAL TRAINING

- **EBOPRAS certification (European Board of Plastic Reconstructive Aesthetic Surgery)**, Bern, Switzerland, 2017
- **1:1 Hands-on Training Buttock Augmentation/BBL, *dr. Raul Gonzalez***, Ribeirao Preto (Sao Paolo), Brazil, 2017
- **Deep peel training, *Dermaclinics***, Zwolle, 2016
- **Injectables Training AMWC Congress**, Monaco, 2016
- **1:1 Hands on Aesthetic Training, *dr. Velthuis, MUMC+ Esthetisch Centrum***, 2016
- **AO Trauma Course, Basic Principles of Fracture Management**, Melbourne, Australia, 2014

- **Laparoscopic Surgical Skills, *European Association for Endoscopic Surgery (EAES)***, 2013
- **FCCS (Fundamental Critical Care Support)**, New York, US, 2013
- **ATLS (Advanced Trauma Life Support)**, Miami, US, 2013
- **ALS (Advanced Life Support) Atrium, *Heerlen***, 2012
- **Microsurgical training, *Chang Gung Memorial Hospital***, Taipei, Taiwan, 2011
- **TESSYS (Transforaminal Endoscopic Surgical System)**, 2010

LIST OF PUBLICATIONS

Published

- **“Randomized controlled study comparing disposable negative-pressure wound therapy with standard care in bilateral breast reduction mammoplasty evaluating surgical site complications and scar quality”**, V. Tanaydin, J. Beugels, A. Andriessen, J.H. Sawor, R.R.W.J. van der Hulst, *Aesthetic Plastic Surgery*, 2018
- **“Incisional Negative Pressure Wound Therapy for Prevention of Wound Healing Complications Following Reduction Mammoplasty”**, R. Galiano, D Hudson, R.R.W.J van der Hulst, V. Tanaydin, F. Duteille, R. Djohan, J. Shin, J. Cockwill, S. Megginson, E. Huddleston, *Plastic Reconstructive Surgery – Global Open*, 2018
- **“The role of topical vitamin E in scar management: a review of literature”**, V. Tanaydin, J. Conings, M. Malyar, R. van der Hulst, B. van der Lei, *Aesthetic Surgery Journal*, 2016
- **“Efficacy of custom-made pressure clips for ear keloid treatment after surgical excision”**, V.Tanaydin, J. Beugels, C. Colla, A. Piatkowski, E. van den Kerckhove, G. Hugenholtz, R. van der Hulst, *Journal of Plastic Reconstructive and Aesthetic Surgery*, 2015
- **“Management of ear keloids using custom molded pressure clips: a preliminary study”**, V.Tanaydin, C. Colla, A. Piatkowski, J. Beugels, E. van den Kerckhove, G. Hugenholtz, R. van der Hulst, *European Journal of Plastic Surgery*, 2014
- **“Clinical elective review at Chang Gung Memorial Hospital, Taiwan, under the supervision of prof. Dr. Fu-Chan Wei”**, V.Tanaydin, *Journal of Microsurgery*, 2011
- **“Gunshot wound: Reconstruction of a defect of the ankle in a 5-year-old child (Case report)”**, V. Tanaydin, H.A.H. Winters, W.R. Hogeboom, A.V.C.M. Zeegers, O.T. Zöphel, *Journal of Foot and Ankle Surgery*, 2011

Submission process

- **“An intra-patient, randomized, comparative, multi-center trial evaluating post-surgical scarring quality in patients undergoing reduction mammoplasty when using negative pressure wound therapy compared to standard care”** V.Tanaydin, R. Galiano, D. Hudson, J. Shin, R. Djohan, F. Duteille, J. Cockwill, A. Rossington, E. Huddleston, R.R.W.J van der Hulst, 2018