Evaluation of the literature on collagen induction therapy (microneedling) with

"Dermaroller MC“

„eDermastamp with eDermastamp Needle Module“

as of March 2017

This study summary gives an overview of the literature dealing with the effectiveness of the above microneedling devices according to their intended medical purpose as well as with their clinical safety.

The products "Dermaroller MC" and "eDermastamp" / "eDermastamp needle module" are manufactured and tested according to the state of the art, taking into account the applicable harmonized standards.

The devices' intended medical purpose is the minimally invasive perforation of the dermis (microneedling) with the following indications

Treatment of atrophic and hypotrophic scars, e.g. acne scars, mature hypertrophic scars, burn scars, and striae distensae

Numerous relevant evidence of the effectiveness of the Dermaroller MC / eDermastamp in the above-mentioned fields of application as well as of the devices' safety have been found in the evaluation of the relevant literature.

Conclusion:

Microneedling applying the Dermaroller / eDermastamp results in a clinical improvement of the treated skin area, in particular a reduction of scar depth and a normalization of skin structure. Using original Dermaroller® products and observing the instructions for use, the method is free of side effects, except for a slight temporary redness and swelling of the treated skin. The risk of hyperpigmentation is low, as is the risk of skin infections.

The evaluated literature and its essential aspects are summarized below.

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Basic studies on the therapeutic efficacy of microneedling

Orentreich & Orentreich in **1995** published a pioneering report on a new method to treat atrophic scars and wrinkles, the so-called 'subscision'. They showed that repeated piercing of a scar with a needle activates the wound healing process. A similar approach was chosen by **Camirand & Doucet (1997),** who used a tattoo gun (without pigment) to treat scars. These are the first publications that point towards the potential of 'needling' to treat scars and wrinkles. They also formed the basis for investigations regarding the effect of the Dermaroller on the induction of body-own collagen.

The first publications on the successful use of **microneedles** for the treatment of scars and wrinkles are from **Fernandes (2002)**. In this and two other papers **(Fernandes, 2005; Fernandes & Signorini, 2008)** the effectiveness of the collagen induction method, its indications, advantages and shortcomings are described in general. Fernandes did not use the original Dermaroller®, but the Medical Roll-CIT of Environ, South Africa. This microneedle roller resembles the Dermaroller® as regards the general principle of function, the cylindrical needle arrangement, and the materials used, so that the results can be incorporate into this literature evaluation. Environ, however, uses significantly longer needles (up to 3mm), which partly explains the differences in observed side effects (see "Safety and side effects").

Fernandes (2005) describes in the physiological basis of collagen induction by means of microneedle treatment. The microinjury induces the wound healing cascade and thus leads to the release of a number of different growth factors which induce cell proliferation. Collagen and elastin are formed as well as new capillaries (angiogenesis). In the final remodeling phase, collagen III is converted into collagen I, resulting in an increased firmness of the tissue. The author reports on the successful application of collagen induction therapy in the treatment of wrinkles, scars (esp. acne and burn scars), and stretch marks, but gives neither case numbers nor success rates. Advantages of the method are the constructive instead of destructive nature of the method, the possibility of using it repeatedly on all body parts, and the short healing phase. Disadvantages are bleedings during and shortly after the treatment as well as swelling and redness of the skin that can last for a few days.

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Indication: atrophic acne scars and scars of other etiology*

* Burn scars are covered in a separate section

A retrospective analysis of 480 patients from Germany and South Africa who had undergone collagen induction with the Environ Medical Roll-CIT (needle length 1-3 mm) was published by **Aust *et al.* (2008)**. The treatments were carried out in the years 1997 to 2006 (also refer to the aforementioned publications by Fernandes). Indications were wrinkles (350/480), lax skin (58), scars and stretch marks (72). Before and 6 months after treatment, biopsies were taken from 20 patients to compare pre- and postoperative collagen and elastin. Different staining methods were used for this purpose. Evaluation of the biopsies showed a significant increase of the amount of collagen and elastin 6 months after treatment. The collagen formed showed a normal lattice pattern and not the parallel pattern typical of scar tissue. The *stratum corneum* was normal, the epidermis had thickened by 40%.

In 50 patients (15 with scars / stretch marks, 35 with wrinkles), patient satisfaction was evaluated before and 12 month after treatment. In this, the patients rated their appearance on a visual scale from 0 (=completely dissatisfied) to 10 (= completely satisfied). In the group with wrinkles, satisfaction increased significantly ($p \leq 0{,}05$) from 4.5 to 8.5. In the group with scars, satisfaction increased also significantly from 3.0 to 7.5. In this group, two additional objective methods for assessing scars were used: ‚Vancouver Scar Scale, VSS' and ‚Patient and Observer Scar Assessment Scale, POSAS'. Both of these scales demonstrated a significant success of the treatment. None of the patients reported on scarring, hyper- or hypopigmentation or photosensitivity after the treatment. Two patients developed a *herpes simplex* infection that could be successfully treated.

In summary, the authors judge collagen induction **a safe and fast method for the treatment of wrinkles and scars, which leaves the epidermis intact instead of damaging it**.

A study regarding the efficiency of the original Dermaroller® to treat acne scars was published by **Fabbrocini *et al.* (2009)**. In this, 32 patients with acne scars received two treatments with Dermaroller model MS4 (needle length 1.5mm). The interval between treatments was 8 weeks. Before first treatment, scar severity was scored by a dermatologist on a visual 1-10 scale. Afterwards patients were divided into three groups: severe, moderate, and mild scars. Additionally, ≥ 3 photos were taken of each patient and evaluated digitally. These steps (scoring, photos) were repeated before and 8 weeks after the second treatment. For 5 of

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the patients, also a microrelief impression of the skin surface was made that was evaluated by image processing and also served as an objective measure of treatment success.

Eight weeks after the second treatment, a significant treatment success was evident. **Scar depth was significantly reduced**, irrespective of the initial scar grading. Scar severity was significantly reduced, too. The microrelief impressions showed a reduction of skin irregularities and a great reduction of scar severity. There were **neither (negative) signs of the treatment nor hyperpigmentation**. Patients reported redness and swelling after the treatment, but stated that these disappeared within 2-3 days.

Majid (2009) treated 36 patients having atrophic facial scars caused mainly by acne, but also by chicken pox. The instrument used is very likely the original Dermaroller®, even if this is not explicitely stated in the publication. The needle length used was 1.5mm. Patients were treated three or four times with a treatment interval of 4 weeks. Final evaluation was carried out 8 weeks after the last treatment. Also in this study, scar severity was scored on a visual scale (Goodman & Baron; grade 1 - grade 4 = severe) and photos were evaluated by image processing. Only patients with scars of grade 2-4 were included in the study. In the final evaluation, an improvement of scarring by two grades or more was labelled as 'excellent' response, improvement by one grade as 'good', and no improvement as 'poor'. The patients themselves rated their improvement on a 1-10 scale. In this, rating above 6 was graded as 'excellent' response, 4-6 as 'good' and <4 as 'poor'. Adverse effects were also noted down.

The objective assessment showed that **Dermaroller treatment resulted in an excellent response in 72% of the patients treated** (26 of 36). Especially scars of grade 2 and 3 showed mainly excellent response; severe scars showed a somewhat lower response. Of the scar types mainly 'rolling' and 'boxcar' types showed good to excellent response. Also the patients labelled the treatment response predominantly as excellent (80%). The treatment was well tolerated by all patients. **No adverse effects were observed except for a temporary erythema.** Hyperpigmentation was observed in one patient. All patients were able to attend their daily duties on the same day or the day after the treatment.

The results of the treatment of 31 Thai patients suffering from atrophic acne scars were reported by **Polnikorn (2009)**. All patients were medium to dark skin types (Fitzpatrick-scale III - V) and showed medium to severe acne scarring. The

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management of acne scars is generally more difficult in darker than in light skin types due to hyperpigmentation problems. The original Dermaroller® (needle length 1.5 mm) was used. One to four treatments were carried out with a treatment interval of one month. Clinical evaluation was done by two independent experts comparing standard photographs using a 0-6 (6 = severe) scarring scale. Six months after the last treatment, average scar severity had declined from 4.24 to 2.33. A reduction > 50% was observed in more than two thirds of the patients. The author concludes that the **Dermaroller treatment is an efficient and safe method for the treatment of atrophic acne scars in darker skin types**.

Fabbrocini et al. (2014) presented results of a study on the treatment of acne scars in 60 patients representing skin types I (white) to VI (afor-carribean). The subjects received three treatments with a treatment interval of 4-12 weeks. Results were scored on the basis of digital photographs. In a selected group of patients, scar depth was measured before and three month after the third treatment using Visioscan. The aesthetic improvement of all patients was assessed using the Global Aesthetic Improvement Scale, GAIS. In most patients, the treatment reduced scar severity and improved the overall appearance of the skin. Aesthetic improvements were significant. Side effects like hyper- or hypopigmentation were not observed. The authors condlude that **'skin needling is a simple and safe method to treat acne scars in all skin types from I to VI'**.

In several review articles on acne scarring (**Fabbrocini et al. 2010, 2012b**) the authors draw the conclusion that "skin needling can be safely used in all skin colors and skin types; the risk of postinflammatory hyperpigmentation is lower than in other methods like dermabrasion, chemical peelings, and laser treatments."

Schwarz und Laaff (2011) treated ten patients with posttraumatic or acne scars using the original Dermaroller® (needle length 1.5 mm). Before and 6-8 weeks after the treatment, small skin samples were punched out, stained and fixated in paraffin. Evaluation was carried out in a blind study by an independent dermatologist / pathologist. Histological findings showed a **significant increase in the amount of elastic fibers in the treated biopsies**. Skin thickness had increased, too. The treatment was well tolerated and all the patients were content with the treatment results. Adverse effects were not observed except for a transient slight redness of the skin and occasionally slight hematoma. All patients could go to work or take part in social life normally.

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The effectiveness of microneedling for treating atrophic acne scars was confirmed by **Leheta et al. 2011** in a study comparing the so called "TCA CROSS technique", a chemical scar reconstruction method using trichloric acetic acid (TCA), with microneedling. 30 subjects with skin phototypes II – IV were split randomly between two groups. Group 1 was treated four times with the original Dermaroller® (1.5 mm needle length) every four weeks. Group 2 received four TCA treatments in the same rhythm. After treatment, all patients showed an **improvement of 68%** and 73% in group 1 resp. group 2. The difference between the groups was statistically not significant.

El-Dawela et al. (2013) studied clinical and histological effects of treatment with Dermaroller (1.5 mm needle length). After seven treatments every three weeks all 12 subjects showed significant improvements according to ECCA (clinical evaluation scale for acne scarring), with values down from 123.3±24.5 to 74.16±16.49. The histopathological evaluation presented a distinct increase in collagen production and deposition. Adverse reactions were only transient slight pain, swelling and redness in the treated area. None of the patients showed any signs of postoperative hyperpigmentation. The authors´ conclusion was: "**Microneedling is a safe minimally invasive treatment method with fast healing, short down time and minimal risk of hypo- or hyperpigmentation"**.

Lofti et al. (2013) also report good results for acne scar treatment. 30 patients of skin phototypes II and IV with "rolling", "boxcar" and "icepick" acne scars were treated five times (four weeks apart) with the Dermaroller (1.5 mm). The histopathological evaluation used different dyes. In addition, the patients gave a feedback and self-evaluation. According to this patient evaluation, rolling and boxcar acne scars had in 20% excellent and 70% good clinical results. Icepick acne scars could not be improved much. Side effects were not reported, apart from one case of transient redness. **The histopathological evaluation presented a significant increase of collagen (+50%) and elastic fibres (+65%). Both fibre types demonstrated an improved directionality. The epidermis showed a thickening of +50%.**

A further study for the evaluation of saftey and effectiveness of treating atrophic acne scars with Dermaroller expecially in Asian skin types (type IV and V) was performed by **Dogra et al. (2014)**. It could not be confirmed that the original Dermaroller had been used. 36 patients with atrophic acne scars were treated five times (four weeks apart). 30 patients finished the study. Before and after each treatment session the acne scars were classified by comparing them to

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photographs with a quartile scale. After conclusion of the treatment the patients were asked to do a self-assessment on a 10-point scale. The results demonstrated a statistically significant improvement of the scar depth, from 11.73±3.12 down to 6.5±2.71 after five treatments. The self-assessment of the patients resulted in "good success" in 22 patients (73%) and "excellent result" in 4 patients (13%).

In contrast to the other studies, this study described a number of adverse reactions. Although the treatment was tolerated well by the majority of patients, the authors reported "postinflammatory hyperpigmentation" in five patients, as well as "tram track" marks in two patients. These adverse reactions and their possible causes will be discussed in the section "Side effects. In their conclusion the authors nevertheless recommend microneedling with the Dermaroller as a **"simple, cost effective treatment option with little down time and satisfactory results".**

Indication: Burn scars

A further focus for Dermaroller use is the treatment of burn scars. **Aust *et al.* (2009, 2010a)** report on a study on 16 patients suffering from burn scars after 2nd degree burnings. Patients were treated with the Environ Medical Roll-CIT with 3mm long needles. Also in this study, patient satisfaction was evaluated and histological examinations carried out (compare Aust *et al.* 2008). Twelve months after treatment, patients rated the improvement as, on average, 80% better than before the treatment. Histological examination demonstrated a considerable normalisation of the extracellular collagen-elastin matrix, a significant increase in collagen deposition, and thickened epidermis (*stratum granulosum* +45%). However, a complete restoration of the skin structure as in normal, healthy skin could not be achieved. Pigmentation problems that are often seen with ablative methods were not observed after collagen induction. Also the number of melanocytes was found to be normal. In summary, **medical needling is seen as very promising for the improvement of burn scars**.

The management of hypertrophic burn scars with the Dermastamp® is reported by **Kim *et al.* (2009)**. 51 patients were treated and the results evaluated using the Vancouver Scar Scale, VSS, and in one group also histological examinations. The clinical improvement of scar severity was 1-6 points on the VSS. Scar depth was reduced by 0.8 to 3.6 mm. Histological examination showed an increase of collagen and a more normal orientation of the collagen fibers. A disadvantage of

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this study is the extremely short treatment interval of 1-2 weeks. An interval of 4-6 weeks is recommended so that the newly formed collagen can 'mature'.

Impressive successes in the treatment of burn scars with the Dermaroller are also reported by **Safonov (2011).** The treatment with the original Dermaroller® (1.5 – 2.5 mm needle length) achieved the following effects: Reduction of existing erythema, better matching skin relief and skin color, creation of normally arranged collagen fibers in lieu of the old scar tissue. The particular advantages of the method are the **little side effects and short social or occupational downtime as well as cost efficiency**.

Indication: Stretch marks (*Striae distensae*)

Another field of application for the Dermaroller is the treatment of stretch. Literature findings for this field are not yet as numerous as for other applications, though.

The study of **Aust et al. (2008)** comprised 72 patients with scars / stretch marks (see above). Patient satisfaction was rated before and 12 month after microneedle treatment by a subgroup of 15 of these patients on a visual scale ranging from 0 (= completely dissatisfied) to 10 (= completely satisfied). Patient satisfaction in this group increased significantly from 3.0 to 7.5. The **significant improvement** resulting from the treatment was also confirmed by two objective measurements.

Fernandes & Signorini (2008) also recommend microneedling for the treatment of stretch marks. They advise to use 1-3 mm long needles, depending on the severity of the marks.

In a short communication, **Aust et al. 2010 b** report on a study on 22 female patients suffering from stretch marks who were treated once with a microneedle roller. Six months after treatment, the authors observed an **improvement of the skin structure, a tightening of the skin, and a formation of new blood vessels without a change of pigmentation**. Biopsies revealed an increase of collagen I and elastin.

Significant improvements in 5 out of 6 stretch mark patients were also achieved by **Rezai (2009)** after multiple treatments with the original Dermaroller® (1.5 mm needle length).

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A study of 16 Korean patients showing striae distensae was performed by **Park et al. (2012)**. In this study, the DTS microneedling system was employed, which is not fully comparable to the Dermaroller device. Treatments were applied at intervals of 4 weeks. After 3 sessions **very good to excellent achievements could be seen in 7 patients (44%),** minimal to moderate success in the other nine. No significant side effects were observed.

Use of the Dermaroller in combination with other methods

All studies presented so far are investigating and demonstrating the effect of the Dermaroller as the only therapeutic means for the treatment of scars, wrinkles and other skin changes. More recently, the effect of the Dermaroller has been increasingly studied in combination with other therapeutic means (mainly chemical peels, but also subscision and other methods). For the sake of completeness, the results of such studies are reported here, although the intended medical purpose does not provide for a combination of the Dermaroller with other methods and the effect as a single therapeutic means is adequately documented.

Enhancing the microneedling effect by a simultaneous injection of topically applied hyaluronic acid (HA) was examined by **Schwarz (2011)**. The aim was to increase the acceptance of collagen induction therapy in the patient by the immediately visible effect of HA application (such an effect is otherwise not present in the treatment because the newly induced collagen must mature for several weeks). After application of the HA, a Dermaroller treatment with 1.5 mm needles was performed. Even after the first appearance of petechiae the upholstery effect of the HA was clearly visible. In the further long-term course, HA is resorbed, but at the same time the body-specific collagen synthesis increases by the stimulation effect of the microneedling so that "*the combination method provides a faster and at the same time longer lasting result than the two methods alone*".

Sharad (2011) investigated a combination of Dermaroller treatment with a 35% GA peeling for treatment of acne scars in dark skin, which showed postinflammatory hyperpigmentation. 30 subjects each were treated exclusively with Dermaroller (group 1) or with a combination of Microneedling and 35% GA peeling (group 2). The evaluation of the treatment results showed a significant improvement for both groups on superficial and medium-deep scars (scar severity

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1-3 on the "Echelle d'Evaluation Clinique des cicatrices d'acne" scale). The combination with GA-Peel was more efficient in improving hyperpigmentation than the microneedling alone. Microneedling is judged as **a simple, low-cost method, which is also safe for use in Indian skin types (III-IV)**.

A combination with another peeling (20% TCA-Peel) was examined by **Leheta et al (2014a).** 24 patients were randomly divided into two groups. Group 1 received a deep peeling with phenol, the second group four sessions of a combination of Microneedling and 20% TCA peeling. The final evaluation took place 8 months after the end of treatment. The **severity of the scars was significantly improved by both treatment methods** (75% vs. 69%, methods not significantly different).

An alternate use of the Microneedling + 20% TCA method with a nonablative fractional laser treatment (1540nm) showed a further increase in efficiency versus the exclusive use of the respective method: Group 1 (Microneedling + TCA) and Group 2 (laser only) showed an improvement of 60% resp. 62% on average for the 13 patients in each group, while in group 3 (alternating use of the two methods) a 78% reduction was observed **(Leheta et al 2014b)**.

Gadkari & Nayak (2014) compared the method of subcision in combination with a Dermaroller or a Cryoroller for the treatment of acne scars. 30 patients were subjected to subcision three times at one month intervals, and then treated in a split-face approach with either a Cryoroller or a microneedle roller (2.5 mm length of needle, manufacturer unknown). An evaluation of the results 6 months after the end of treatment showed a significant improvement for both methods, the combination with the Cryoroller showing slightly better results (57% vs. 40% improvement). However, stronger side effects were also observed for the Cryoroller in the form of postinflammatory hyperpigmentation.

Garg & Baveja (2014) examined the combination of an alternating treatment with subscision, Microneedling and 15% TCA peeling for the treatment of atrophic acne scars. 50 patients were subjected to a total of 6 sessions each, and the severity of the scars was assessed before the treatment and one month after the end of treatment (Goodman and Baron Qualitative Scale and self-assessment of the patients). The alternating combination therapy showed very good results: of 16 patients with grades of severity 4, 10 (63%) patients had an improvement to severity 2, and in 6 (37%) patients to severity 3. Of 22 patients with grade 3 scars, 5 (23%) had no scars after treatment, 2 (10%) improved to severity 1 and 15 (67%) to severity 2. All 11 patients with severity grades 2 could complete the

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treatment without scars. Patient satisfaction was also high. Slight transient redness and swelling were noted as side-effects of the Dermaroller application.

Durability of the positive effect of collagen induction therapy

An important question regards the durability of the positive effect after microneedle treatment of scars and wrinkles. Indirect statements towards this question can be found in the studied publications. First, it is noted that the positive effect will only be fully visible after about 6-12 months, since the induced collagen matures over a longer period of time (e.g., **Aust et al. 2008, Fabbrocini et al. 2009, Fabbrocini et al. 2012**). In addition, all publications emphasize that the collagen induction therapy stimulates the body's own wound healing cascade / collagen synthesis so that scars and wrinkles are thus repaired or padded 'from the inside'. This was e.g. shown by **Fabbrocini et al (2011)** in comparing ultrasound pictures before and 32 weeks after therapy, on which a marked thickening of the epidermis could be seen.

Due to this mechanism of action, the positive effects after collagen induction therapy are lasting. There is no 'rebound' effect. Treated skin is only subject to the normal aging process again afterwards. The findings are confirmed by experienced Dermaroller users (physicians).

Wrinkles, lax skin

Wrinkles and lax skin are no medical indications. However, treatment with the dermoller is effective for this skin condition, as e.g. the work of **Fernandes (2005), Aust et al. (2008) and Fernandes and Signorini (2008)** show, and thus the results will be presented here.

Treatment of upper lip wrinkles was examined by **Fabbrocini et al. (2012)** in a study with ten participants between the ages of 50 and 65 years. Before the start of the treatment, severity of the wrinkles was assessed by means of digital photographs using the Wrinkle Severity Rating Scale (WSRS), as well as microrelief casts of the upper lip. Then two treatments with the original Dermaroller (needle length 1.5 mm) were carried out at intervals of 8 weeks. Prior to the second treatment, the assessment of the wrinkle severity and the preparation of microrelief casts were repeated. Digital photographs and microreliefs were analyzed by image analysis and statistical methods. In addition, the improvement was assessed subjectively with the Global Aesthetic

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Improvement Scale 'GAIS'. The last assessment was made 30 weeks after the second treatment. The results showed a significant improvement after two treatments: on average, the wrinkle severity after WSRS had decreased by a factor of 2.3. There was also a marked improvement in GAIS. Apart from a transient slight swelling and redness of the treated skin areas no side effects were observed.

Compared to other treatment methods such as filler injections, "**microneedling stimulates a new production of body's-own collagen and can therefore counteract the time- and light-induced aging of the skin ".**

The effect of microneedling on lax skin was examined by **Fabbrocini et al (2011)** treating the "aging neck" of 8 patients (5 female, 3 male) between 45-65 years. After 2 treatments with the original Dermaroller, a significant improvement of the skin condition was achieved in 90% of the patients (verified by evaluation of the degree of wrinkle severity, surface microrelief and ultrasound examinations before and after treatment). Above all the epidermis was markedly thickened after the treatment (average 0.45 mm 32 weeks after the last treatment).

Safety and side effects of Microneedling treatment

Potential side effects of a microneedling treatment include pain, transient or prolonged swelling (edema) or redness (erythema) of the treated skin, and skin infections. Moreover, special attention is paid to pigmentation disorders (dis-, hypo- or hyperpigmentation), which are commonly observed following ablative skin treatments like laser, deep peelings or dermabrasion, especially in darker skin types. The occurrence of such side effects reported in the literature evaluated is summarized in the following.

Basic studies on the safety of microneedles

The safety of microneedling is the explicit topic of a study by **Bal *et al.* (2008)**. In particular, the authors studied pain and the occurrence of skin irritations (redness, bleeding) in 18 human volunteers. Two types of microneedles were used for this study: solid and hollow needles. The solid needles are similar to the Dermaroller needles with respect to material (stainless steel), diameter (200 µm) and needle length (200 - 400 µm). The Dermaroller needles are much sharper, though, and more uniform (tapered), their diameter is a bit smaller (150-200 µm at the basis). Another difference is the needle arrangement: cylindrical for the Dermaroller

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compared to flat 4x4 in the study, resulting in higer penetration forces for the latter. Still, the results are transferable to the Dermaroller.

Microneedle treatment was carried out on the inside of the forearms. It was described as painless by the majority of the volunteers. Pain scores for the solid microneedles ranged from 0-4 with an average of 1 on a 1-10 scale, regardless of microneedle length. Skin irritations were minimal and did not last longer than about two hours.
The results were confirmed in other studies of the authors (**Bal et al. 2010 a, b**): microneedle treatment was felt to be painless, there was no bleeding.

Some of the studies evaluated can provide clues with regard to the risk of skin infections.
Bal *et al.* (2010a) showed that without occlusion the micropores close after 10-15 minutes. For that reason the risk of skin infections after microneedling is considered very low. From studies of the transepidermal water loss (TEWL) **Badran *et al.* (2009)** concluded that micropores close after about 2 hrs *in vitro*. However, they emphasize that this very probably occurs more rapidly *in vivo*.

Penetration of microorganisms through microneedle lesions in contrast to lesions made by hypodermic needles *in vitro* was studied by **Donnelly et al. (2009)**. For this purpose, the authors used flat arrays of densely arranged silicon microneedles (280 µm high, 250 µm diameter at the basis). As models of the human skin, Silescol®-membranes were used as well as skin from newborn pigs. Results showed that significantly less microorganisms (*Candida albicans*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*) penetrated through the microneedle lesions than through the puncturing channels of a conventional 21-gauge needle. Furthermore, no microorganism could penetrate the living epidermis. The risk of infection by a microneedle treatment is thus to be classified as very low. However, further studies *in vivo* are needed to confirm the results in the opinion of the authors.

Side effects observed in studies using the original Dermaroller

Polnikorn (2009) observed **mild to moderate skin redness for a few days** after treatment with 1.5 mm needles. Post-op pain was described as 'generally minimal'. Treatment results were stated to be comparable to those of a CO2 laser treatment, but with 'better healing and significantly less post-op complications'.

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All 37 patients treated with 1.5 mm needles in the study of **Majid (2009)** tolerated the Dermaroller treatment well. Only a **temporary reddening** of the face was observed. One patient showed a transient post-inflammatory hyperpigmentation. All patients could resume their daily routine on the day of the treatment or the following day at the latest.

Fabbrocini et al. (2009, 2014) report that the treated skin area was reddended and swollen for 2-3 days after treatment. The authors point out that "the **risk of postinflammatory hyperpigmentation is less** than with other methods such as dermabrasion, chemical peels and laser application".

Schwarz und Laaff (2011) also report that the treatment "was well tolerated." Adverse side effects were not present, only a **slight reddening and occasional mild hematoma** were observed. All patients could go to work as usual.

Leheta et al. (2011) noted pain during the Dermaroller procedure despite a topical anesthetic, temporary redness and swelling and a downtime of about 3.8 days. In two patients, some acne lesions developped that were treated successfully with BPO. **In comparison to TCA CROSS technique, downtime was significantly lower and redness was much less pronounced.**

Also in the study of **El-Dawela et al. (2013)** for the treatment of acne scars, only **transient mild pain, swelling and redness** were observed in the treated area. None of the patients showed signs of postoperative hyperpigmentation. The authors conclude: "Microneedling is a **safe minimally invasive treatment method with fast healing, low downtime and minimal risk of hypo- or hyperpigmentation**."

Some studies show that treatment with the Dermaroller not only carries a low risk of hyperpigmentation, but that existing pigmentation disorders (hyper- and hypopigmentation) are even alleviated by the treatment. Already **Fernandes (2002)** pointed out that 'white' scars approach the surrounding skin color again after microneedling. The reason for this is a re-vascularisation and re-pigmentation, the exact causes of which have not yet been thoroughly investigated. An improvement in the color has also been reported in the treatment of burn scars (Safonov, pers. Mitt.). Furthermore, **Fernandes (2005)** reported an improvement in telangiectasia by a microneedle treatment, "probably because the fine blood vessels are punctured in so many places that they can not be repaired".

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Even after the treatment of burn scars with the Dermaroller (1.5 - 2.5 mm needle length) erythema and swelling was observed only for 24-48 h after treatment. Post-operative pain was low **(Safonov, 2011)**.

In contrast to most other works, the study of **Dogra et al. (2014)** on treatment of acne scars in Asian skin types reported more side effects. While the treatment was "well tolerated by most patients", the authors also report post inflammatory hyperpigmentation in five patients, as well as "tram track scars" (see below) in two patients. In conclusion, the authors still recommend microneedling with the Dermaroller as "a simple, cost-effective treatment option with less downtime and satisfactory results".
It is uncertain if in this study the original Dermaroller was used. Needle length and treatment protocol are not clear, since only the abstract is present, so a final assessment is difficult.

Side effects observed in other studies on microneedling

Fernandes (2005) reports bleeding and swelling and redness of the skin after treatment with the Envrion Medical Roll CIT, which can last for several days. These side effects, which are more pronounced in comparison to a Dermaroller treatment, are partly due to the fact that Environ uses significantly longer needles (3 mm, relating to a penetration depth of 1.5-2 mm into the skin). In addition, Dr. Fernandes sees the cause of triggering the wound healing cascade in the exit of blood cells and serum into the surrounding tissue. Triggering of bleeding is therefore a desired effect and an 'energetic' rolling over the skin is recommended. In contrast, the manufacturer Dermaroller is convinced that even the penetration of the needles into the skin starts the wound healing process (**Liebl & Kloth 2013**). Blood leakage is not required. Consequently, treatment with the Dermaroller / eDermastamp is only performed with very light pressure. A uniform formation of small blood spots on the skin is a sufficient indication of a proper execution.

In 2012, a case of scarring after a microneedle treatment was described in a patient for the first time **(Pahwa et al. 2012).** It was called 'Tram Track Effect' ("railroad track" effect) by the authors. One month after her second, well going treatment, a 25-year-old female patient with hyperpigmented atrophic acne scars developed multiple papular scarrings on the forehead, the temples and above the cheekbone. These were regularly arranged like railroad tracks. The microneedle

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roller used came from the company Dermaindia (Chennai, India) and had a needle length of 2 mm. The second treatment was carried out more "aggressively" than the first. In addition to scarring, the patient had shown pain during treatment, temporary redness and swelling, as well as postinflammatory hyperpigmentation. The authors suspect the cause of this side effect to be "the use of longer needles and the greater pressure exercised during the second treatment." Both these conclusions support the view of Dermaroller GmbH, according to which the shortest possible needle length should always be chosen - especially close to the bone - and the treatment should always be carried out using gentle pressure.

The same type of side effect was later also observed by **Dogra et al. (2014)** in two patients (see above). Again it can not be excluded that too long needles were used and / or excessive pressure was applied during the treatment(s).

The possible adverse effects of using topical active ingredients and/or special vitamin preparations before and during microneedle treatment are described by **Soltani-Arabshahi et al. (2014)**. Thus it is "common dermatological practice" to apply 'Cosmeoceuticals', e.g. Vitamin C products, to the skin before microneedle treatment in order to improve treatment success. These are then introduced into the skin by the subsequent microneedle treatment. The authors report allergic reactions in three patients aged between 40 and 60 years. In two patients, "Vita C Serum" (Sanítas Skincare) had been applied before the treatment, the third patient had different products (at different sessions): "Boske Hydra Boost Gel" (Boske Dermaceuticals) and "Vital Pigment Stabilizer" (Dermapen LLC), and in a later session also "Vita C Serum". For microneedling, the Dermapen, an electrical microneedle device from the USA, was used in all cases. Some days to weeks after the treatment the patients developed severe local symptoms (erythema, pustules), in two cases systemic symptoms (joint pain, high fever, exhaustion). Treatment with topical and oral corticosteroids remained unsuccessful; therapy with doxycyline and minocycline hydrochloride was effective in one of the patients.

Biopsies revealed granulomatous foreign-body type reactions in all cases. The first two patients showed a positive reaction to "Vita C Serum" in an allergy test. According to the authors, the cause of the serious side effects is "an inadmissible use of topical products which have not been developed for the introduction into the skin" and point out that "only drugs permitted for intradermal injection are safe in the context of microneedle treatment ".

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Conclusion 'safety and side effects':

It is apparent from the studies that the severity of side effects increases as the length of the needle increases: the shorter the needles, the less painful the treatment and the smaller the tendency to bleeding, postoperative redness and swelling.

When using the original Dermaroller® / eDermastamp and observing the instructions for use, the method is free of side effects, except for a slight temporary redness and swelling of the treated skin. The risk of postinflammatory hyperpigmentation is low, as is the risk of skin infections.

No topical products that are not suitable and approved for intradermal application should be used in the context of microneedle treatment.

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