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ORIGINAL CONTRIBUTION

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Objective evaluation of an occlusive overnight intensive patch containing onion extract and allantoin for hypertrophic scars

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Abstract

Background: Patients suffering from hypertrophic scars often describe esthetic, functional, and psychological impairments. While current guidelines for the treatment of pathologic scarring recommend the use of onion extract containing gels and sheets, hard evidence for its efficacy remains scarce due to inconsistent data. Onion extract and allantoin containing occlusive overnight intensive patches (OIP) were introduced as a recent option for noninvasive scar management. However, objective data demonstrating their efficacy are missing.

Aims: This study is the first to objectively evaluate the benefit and safety of an OIP for hypertrophic scars using a three-dimensional imaging device and a standardized scar scale.

Methods: Twelve patients with untreated, three to twelve months old hypertrophic scars received an OIP for 3 months. The assessment was performed using PRIMOS®*pico*, a three-dimensional imaging device and POSAS, a standardized scar questionnaire at baseline, one and 3 months after the last treatment.

Results: Objective evaluation at three months follow-up (FU) showed a significant decrease in scar height of 28.8% (baseline mean: 2.08 ± 0.68 mm, three months FU mean: 1.48 ± 0.52 mm) and a reduction in scar volume of 31.9% (baseline mean: 454.33 ± 265.53 mm3, 3 months FU mean: 309.58 ± 224.28 mm3). Pain and pruritus subsided under treatment. There were no negative side effects.

Conclusion: Overnight intensive patches is a convenient, painless, safe, affordable and effective prevention and treatment option for hypertrophic scars. Treatment should be performed at least for 3 months for visible effects.

KEYWORDS

hypertrophic scar, overnight intensive patches, onion extract, overnight intensive patch, scar therapy

1 | INTRODUCTION

Physiological wound healing is a complex cascade including three phases: inflammation, proliferation, and remodeling. In addition to a prolonged inflammatory phase, an increased liberation of transforming growth factor isoenzymes (TGF-β1/β2) is held responsible for the excessive tissue formation in pathologic scarring.[1,2] Scar formation is the result of an injury of the dermis followed by an imbalanced regeneration of the dermal tissue.[3] Hypertrophic scars can develop six to eight weeks after an injury and form within the margins of the original wound.[4] They can cause pain and pruritus and oftentimes have a serious psychosocial impact on affected patients.[5] Over time, up to 70% of hypertrophic scars show signs of regression.[4] However, prevention of scar formation by optimal wound care in early stages has proven to be crucial and easier than scar treatment.[4,6]

Onion extract *(Extractum cepae)*, with its potent flavonoid component quercetin, has been used for decades for scar management. It is known for its anti-inflammatory, anti-microbial, and anti-proliferating effects by regulating TGF-ß1/ß2.[7-9] Furthermore, studies have shown that quercetin reduces fibroblasts´ proliferation, thus induces the expression of matrix-metallo-proteinase-1, which leads to the remodeling of extracellular matrix (ECM) and ultimately results in an improved scar structure.[10,11]

Current German and international guidelines for the management of pathological scarring include a rather weak recommendation for onion extract containing gels.[4,12,13] Available data on the efficacy of extractum cepae for the prevention and treatment of hypertrophic scars are largely inconsistent and mostly based on subjective means of evaluation.[7-10,14,15] So far, the effectiveness of the novel application in form of an overnight intensive patch (OIP) has been examined in one multicenter clinical trial. However, evaluation was based predominantly on subjective parameters.[16] OIP suggests superior results for hypertrophic scars through occlusion and continuous drug delivery overnight. The occlusive effect leads to an accumulation of moisture in the skin and facilitates the penetration of the active components for six to ten hours.[16] Here, we examined OIP that contains onion extract and allantoin. Allantoin, a degradation product of uric acid, promotes epithelialization and skin elasticity with its keratolytic, moisturizing, and soothing effects.[17]

To evaluate this novel treatment regime and examine its viability for the treatment of hypertrophic scars, we employed a three-dimensional objective imaging device (*Phase shift Rapid* In-vivo *Measurement of Skin* (PRIMOS®pico)) and a standardized questionnaire (*Patient and Observer Scar Assessment Scale* (POSAS)).

2 | MATERIALS AND METHODS

2.1 | Patients and study algorithm

A total of 12 patients with untreated hypertrophic scars, Fitzpatrick skin type I-III, consulting our outpatient clinic for pathologic scarring (eight females, four males) aged 18-61 years (34.6 ± 13.4 years) were included in this prospective, single-center, open-label study after receiving approval by the Ethics Committee of the university hospital of the Ludwig-Maximilian-University in Munich. A negative control group was not allowed in this pilot study. Written informed consent was obtained from each patient before initiating the treatment. Patients had to be of full age, healthy, with hypertrophic scars existing at least for three months but no longer than one year at the beginning of the study (mean age of hypertrophic scars was 10 months). Scars were located on the forehead (n = 1), shoulder (n = 1), abdomen (n = 2), neck (n = 2), knee (n = 2), and arm (n = 4) and resulted from surgery (n = 9; fractures, cesarean section, thyroidectomy) as well as from accidents (n = 3; bike, dog bite, burn).

Exclusion criteria were pregnancy and breastfeeding, malignant, infectious, or immunosuppressive diseases as well as a known type IV hypersensitivity to any OIP ingredient.

The patients were instructed to apply *Contractubex® Overnight Intensive Patch* (Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany) every night (at least 6 hours, up to 10 hours), for 3 months onto the scar. The patch was cut to the appropriate scar size so that all margins were covered. At baseline (visit 1) as well as one month (visit 2) and three months after the treatment period (visit 3), data were obtained using PRIMOS®pico for objective evaluation and a standardized questionnaire (POSAS) for subjective evaluation by both the examiner and the patient. Adverse events related to the OIP application were recorded by the investigator at each visit. Subjects were instructed to strictly restrain from any other scar treatment during the study period (Figure 1).

2.2 | PRIMOS

PRIMOS®pico (Lite Device, GFMesstechnik GmbH) is a computer-assisted surface measuring system which provides three-dimensional, high-resolution images of skin. It is most commonly applied to measure wrinkles,[18] but has been successfully used for evaluating volumes and dimensions of pathologic scarring throughout recent years.[19-21] Using a handheld camera device, a pattern of parallel stripes is projected onto the skin. Irregularities of the skin surface result in a deflection of the stripe pattern which can then be used to calculate surface roughness parameters, such as the highest peak of the scars in mm (S_{max}). Based on height-coded images of scars, the volume was calculated in mm^3. As the PRIMOS®pico allows examiners to overlay previous captures via its build-in projector, it greatly facilitates follow-up documentation.

2.3 | POSAS

The Patient and Observer Scar Assessment Scale is the most established questionnaire for evaluating pathologic scarring. The *patient* rates symptoms such as pain and itching of scars, as well as characteristic features like color, stiffness, thickness, irregularity, and overall opinion compared to normal skin. The *observer*, a specialist

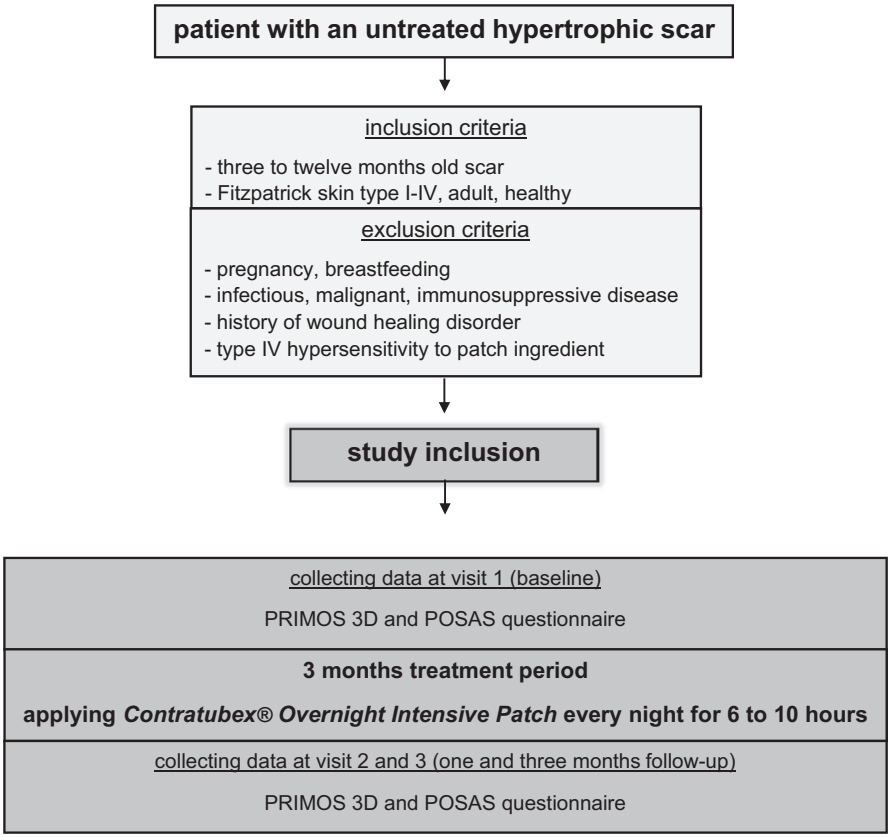


FIGURE 1 Study algorithm: Twelve patients with untreated hypertrophic scars were enrolled in the study. An onion extract and allantoin containing patch was applied every night for three months onto the scar. Data were collected at baseline (visit 1) and at one month and three months follow-up (visit 2 and visit 3) using PRIMOS 3D objective analysis and POSAS questionnaire

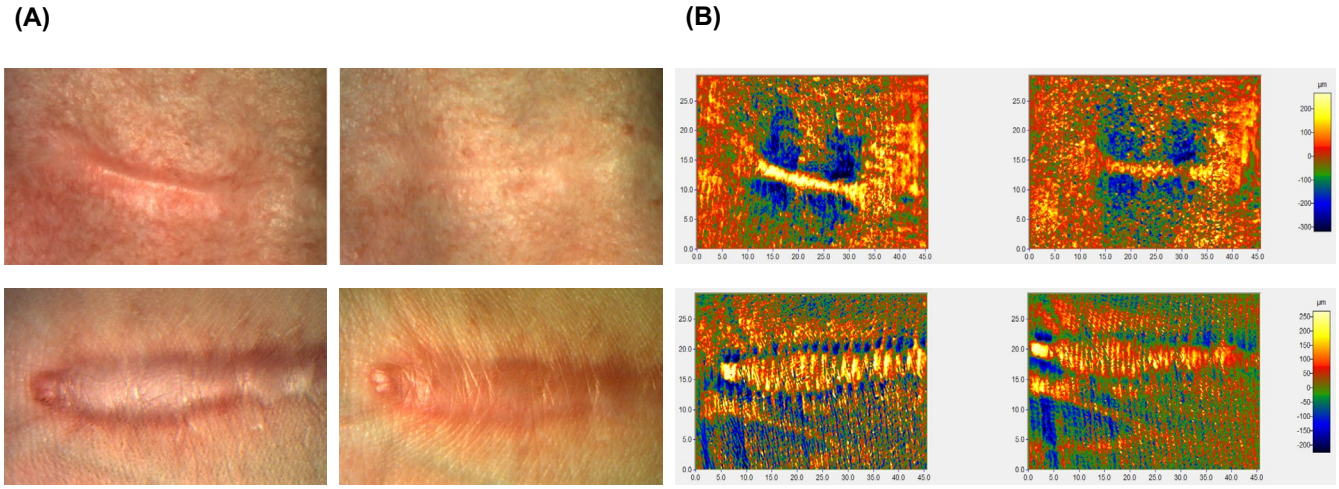


FIGURE 2 PRIMOS shows a clinical comparison of two cases in digital pictures (A) as well as in height-coded pictures (B) at visit 1 (left) and visit 3 (right), respectively

in scar prevention and scar therapy, evaluates vascularity of scars as well as pigmentation, thickness, relief, pliability, surface area and also states an overall opinion. Every category is scored from 1 to 10 (least severe to most severe).[22]

2.4 | Data analysis

GraphPad Prism® Software (GraphPad Software Inc) was used to perform statistical analyses. D´Agostino and Pearson omnibus normality test was used to test for Gaussian distribution. Then, the repeated measures ANOVA was applied to calculate statistical significance of our results, which were displayed as mean ± standard deviation. To compare the results of each visit in detail, we used Bonferroni's multiple comparison test. The significance level was set *P*-values of $^{*}P = <.05$. The primary endpoint was defined as the change in the height of scars between the visits. Secondary endpoints were the change in volume of scars and the absolute change in the observer- and patient-evaluated POSAS scores between the visits.

3 | RESULTS

3.1 | Safety and comfort

All patients completed the study and were very satisfied with the practical handling of the patches. Two females paused the application for one night while reporting a slight erythema of the skin in the patch area. Besides that, no adverse events were observed.

3.2 | PRIMOS

PRIMOS®pico enabled a pre/postanalysis of scars showing the effect of the OIP through digital and color-coded pictures. (Figure 2) Objective evaluation showed that the highest peak of the hypertrophic scars (S_{max}) as well as the volume of the scars improved over the course of the study.

S_{max}, the primary endpoint, presented with a mean score of 2.08 ± 0.68 mm at visit 1. After treatment, we found a significant reduction down to 1.72 ± 0.54 mm at visit 2 and 1.48 ± 0.52 mm at visit 3 ($P < .05$). Hence, this translated into a relative improvement in the scar's height of 17.3% when comparing visit 1 and visit 2 and 28.8% when comparing visit 1 and visit 3.

On average, the scar's volume at visit 1 was 454.33 ± 265.53 mm^3. Measurements showed a reduction down to 393.17 ± 234,84 mm^3 at visit 2 and 309.58 ± 224.28 mm^3 at visit 3, thus, resulting in a relative improvement of 13.5% between visit 1 and visit 2, and of 31.9% between visit 1 and visit 3 ($P > .05$) (Figure 3).

3.3 | POSAS

Significant improvements were seen in the observer-evaluated POSAS scales comparing visit 1 to visit 3 in categories of vascularity, pigmentation, thickness, relief, pliability, and surface area comparing hypertrophic scars to normal skin. We observed an absolute reduction from 3.2 ± 1.1 points at visit 1 to 1.7 ± 1.0 points at visit 3 in the overall opinion score. Evaluation of the patient-evaluated POSAS also revealed significant improvements in scar characteristics between visit 1 and visit 3 regarding pain, itching, color difference, stiffness, thickness, and irregularity of scars. The overall opinion score dropped from 7.8 ± 1.6 points at visit 1 to 4.7 ± 2.5 points at visit 3 (Figures 4, 5).

4 | DISCUSSION

This pilot study confirmed the efficacy and safety of an OIP containing onion extract and allantoin for the treatment of hypertrophic scars. Compared to previous clinical trials, this study provides objective data on this subject, even though investigating a small case number.[7,14,16,23]

The study met its primary objective by showing a significant decrease in scar height after only three months of treatment. Importantly, we found a long-lasting positive effect of OIP application with further improvements of investigated parameters after visit 2 and 3. It remains to be seen whether these improvements were caused by the treatment or through natural regression of the scars, as hypertrophic scars frequently show significant involution without treatment before they have matured. Future studies should include an untreated control group or split-phase design to further elucidate this issue.

PRIMOS measurements of scar volume—the secondary endpoint—showed improvements between post-treatment visits, however, without significant differences. Possibly, the variance in scar lengths could have contributed to volume deviation. Use of B-mode ultrasound or optical coherence tomography could provide more precise information in this regard in future studies, especially when considering, that PRIMOS only measures scar volume above the skin surface. Subcutaneous scar tissue and its development unfortunately cannot be assessed using PRIMOS technology.

Confirmation of the efficacy was further supported by comparison of POSAS scores. Significant differences were detected in all categories while comparing the scars to normal skin before and three months after the treatment period.

The noninvasive and painfree application of the OIP led to high patient satisfaction with this form of treatment. It was well tolerated throughout the study and proved cost-effective. Application was uncomplicated, and the patches could be worn overnight, while other gel-based solutions have to be renewed throughout the day.

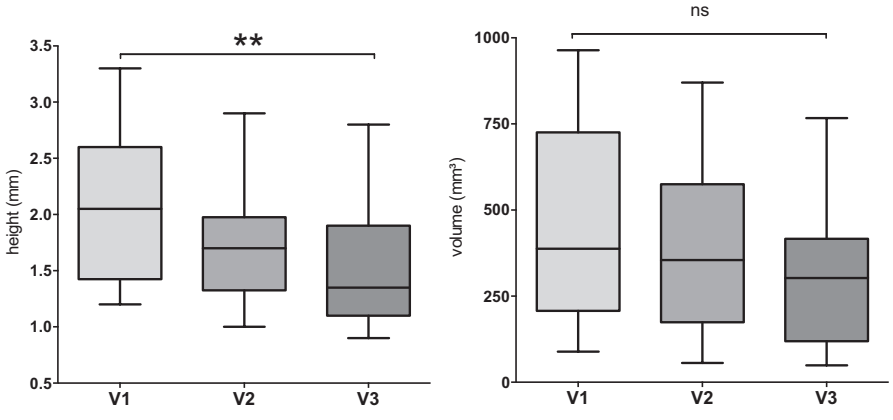


FIGURE 3 Absolute height (left) and absolute volume of hypertrophic scars (right) using PRIMOS for objective analysis. (n = *12*, *P*** = *.008*, *ns = nonsignificant*, *V = visit)*

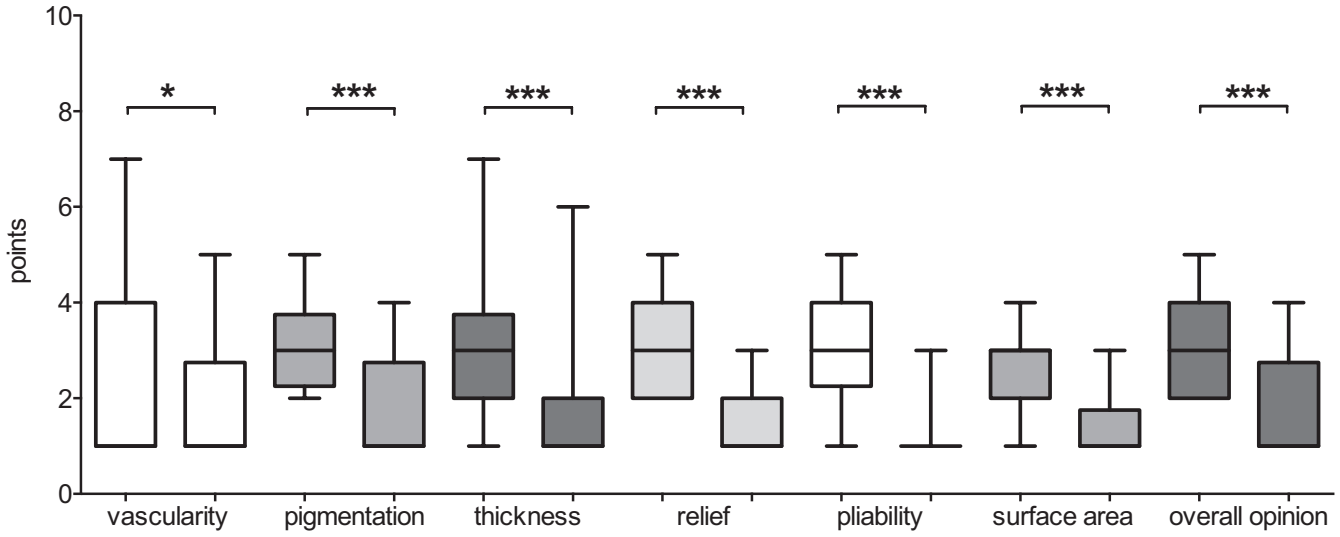
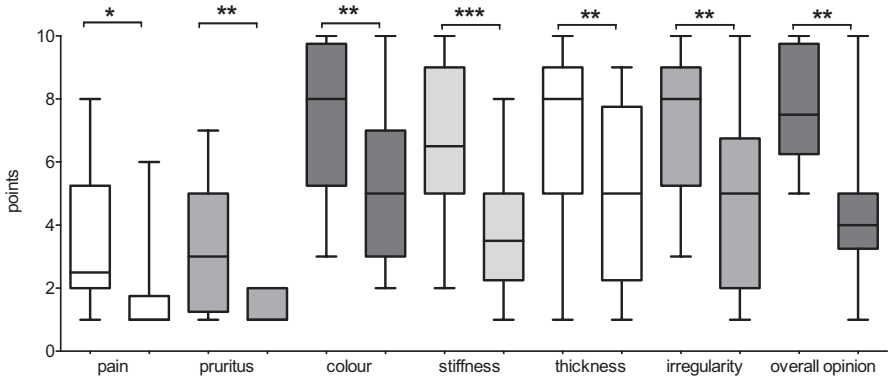


FIGURE 4 Observer scar assessment scale rating characteristics of hypertrophic scars comparing visit 1 to visit 3, respectively. *(n = 12, P*** = <.0003, P* = <.05)*

FIGURE 5 Patient scar assessment scale rating characteristics of hypertrophic scars comparing visit 1 to visit 3, respectively. *(n = 12, P*** = <.0003, P** = <.005, P*=<0.05)*



Even in difficult anatomic locations like the knee or the head, patch adherence was maintained without complications.

Our results provide clinical data for the effective treatment of hypertrophic scars with occlusive OIP containing onion extract and allantoin. The efficacy of both these active ingredients has previously been evaluated by different study groups.[7-11] Based on the hypothesis that an imbalance of MMP activity and ECM synthesis leads to excessive accumulation of matrix and thus causes formation of hypertrophic scars, Cho et al were able to demonstrate that onion extract increased the expression of MMP-1, leading to a decrease in scar formation in an in vitro and in vivo setting.[11] For allantoin, Araújo et al showed that topical application of allantoin ameliorated scar tissue formation and fastened the reestablishment of vital, healthy skin in rodents.[17]

The greatest limitation of this study is the small number of cases. Furthermore, by using a ready-to-use medical device in contrast to the vehicle or the active ingredients alone, this study could not draw any conclusions about the contribution of each individual component with regard to the overall efficacy. In an experimental rat model, Sahin et al could demonstrate that Contratubex® gel with its active ingredients onion extract and allantoin was more effective than allantoin monotherapy in the treatment of scars.[24] Moreover, it would be interesting to see whether a continued OIP application would result in further improvement of scars. Not only the treatment period but also the follow-up time should be prolonged in further studies.

So far, the study by Prager et al is the only one examining the effectiveness of an onion extract and allantoin containing OIP in the treatment of hypertrophic scars. 125 patients were treated in an intra-individual randomized, controlled design.[16] The study showed that OIP promotes healing of postdermatologic surgery scars. There were no safety concerns, and the comfort of the application was emphasized. Our results deliver objective data to support these findings.

In accordance with many previous studies on onion extract and allantoin gel application, our current study demonstrates a safe and viable use of the novel OIP technique in the treatment of hypertrophic scars.[7,25] Undesirable effects were rare, bearing in mind that the ingredients of the patch could possibly lead to an allergic contact dermatitis. Patients with known allergies should be monitored closely.

5 | CONCLUSION

The beneficial effect of occlusive OIP containing onion extract and allantoin should be considered for prophylaxis and treatment of hypertrophic scars. Patch application should be performed for at least three months for visible effects. Especially, due to the increasing number of pharmaceutical and cosmetic skin products, objective evaluation on their efficacy is required more than ever.

CONFLICT OF INTEREST

GG serves as speaker and advisor for Merz Pharmaceuticals, and AG, HS, JP, and SS declare no conflicts of interest.

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