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Safety and Efficacy of Local Administration of Contractubex® to Hypertrophic Scars in Comparison to Corticosteroid Treatment. Results of a Multicenter, Comparative Epidemiological Cohort Study in Germany

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Abstract. *Objectives: To investigate the safety and efficacy of Contractubex® administration to hypertrophic scars in routine out-patient practice and to compare it to corticosteroid treatment. Patients and Methods: This was a multicenter, retrospective cohort study, based on 38 randomly selected practices representatively distributed in Germany, including dermatologists and general practitioners. Data from 859 patients fulfilling the inclusion criteria were assessed and analyzed. Of these, 771 patients were eligible for the per protocol treatment with Contractubex® (n=555) and corticosteroid (n=216). The safety and efficacy of local administration of Contractubex® to hypertrophic scars was compared to corticosteroid treatment. Results: At the end of defined treatment periods (minimum 28 days for local therapy with 1 intralesional corticosteroid application), normalization of the pre-treatment pathological parameters (erythema, pruritus, consistency) of hypertrophic scars was more frequent (42.5%) after Contractubex® per protocol treatment as compared to corticosteroid per protocol treatment (22.2%). After adjusting imbalances of baseline characterisics between the treatment groups by the propensity score, the odds ratio was 2.274, demonstrating a significant superiority (p<0.001) of Contractubex® treatment as compared to corticosteroid treatment. The time to normalization of erythema, pruritus and consistency was significantly (p=0.034) shorter with Contractubex® treatment (median 344 days) than with corticosteroids (median 507 days). No unexpected or severe adverse events occurred in the Contractubex®-treated patients. Apart from moderate pruritus (10% Contractubex® vs. 1% corticosteroids), adverse events were significantly (p<0.001) more frequent in corticosteroid-treated patients (teleangiectasias 15% vs. 7% Contractubex®; cutaneous atrophy of scars 10% vs. 2% Contractubex®; cutaneous atrophy of scar surrounding skin tissue 11% vs. 1% Contractubex®). Conclusion: For the primary aim of this study (assessment of normalization of erythema, pruritus, and consistency of hypertrophic scars) and for time to normalization, local administration of Contractubex® was significantly more effective than corticosteroid treatment. Concerning safety, Contractubex® treatment was associated with significantly less adverse events (e.g. teleangiectasias, cutaneous atrophy of scars and surrounding skin tissue) than topical corticosteroid application.*

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Hypertrophic scars develop as the result of a proliferation of dermal tissue following skin injury. They are confined to the original injury and increase in size by pushing outward and not by invasion (1). Pathophysiologically, hypertrophic scars are characterized by exaggerated extracellular matrix deposition resulting in increased skin tension (2-4). Clinically, they present as elevated plaques or nodules associated with erythema, pruritus and pain and can be complicated by secondary infections and contractions, which can result in cosmetic disfigurement (1, 5). The therapeutic management of hypertrophic scars is a problem that has not yet been satisfactorily solved and includes, *e.g.,* compression therapy, topical/intralesional corticosteroid application, excision, radiation, cryotherapy, laser therapy, interferon therapy, and other therapies directed at a reduction of

collagen synthesis (1, 4, 6). All those treatment strategies are associated with a high rate of adverse events (*e.g.*, induction of basal cell carcinoma after radiation; dis-/hyperpigmentation after corticosteroid application). Accordingly, less harmful but safe and efficient treatment strategies for hypertrophic scars are urgently required.

Treatment with Contractubex® is reported to be of special value in hypertrophic scars (7-10). This preparation contains cepae extract, heparin and allantoin and has been in widespread use for more than 30 years. It is experimentally and clinically well evaluated and its scar-relevant anti-proliferative effect on fibroblasts and its effect on glycosaminoglycan synthesis have been proved (11). However, as hypertrophic scars have a very individual history and appear in various different forms, it is almost impossible to perform a randomized controlled trial (doubleblind, placebo-controlled) in which the initial values of the various scar parameters would be comparable between the groups.

Epidemiological cohort studies are based on representative samples of patients treated routinely in clinics or general practices, with rigid inclusion and exclusion criteria and treatment allocation prior to study initiation enabling valid comparisons of the safety and efficacy of treatments (12, 13). The dependence of treatment allocation on baseline conditions and other characteristics can be quantified by the propensity score, a proven tool for making adjustments for preferences and characteristics (14). Data acquisition can be done prospectively with newly treated patients or retrospectively by using the data from patients' files. In this study, the retrospective design was used. Cohort studies allow assessment of whether the beneficial effects of therapeutic treatments observed in controlled, prospective clinical trials occur in daily practice, thereby providing valuable information on the effectiveness and safety of such treatments in broad patient populations (15-17).

This epidemiological cohort study was performed to evaluate the safety and efficacy of Contractubex® on hypertrophic scars and compare it to corticosteroid administration, which currently represents the "gold standard" treatment for this indication.

Patients and Methods

Study design. This was a multicenter, retrospective cohort study in patients suffering from hypertrophic scars from 38 practices in Germany. Extensive descriptions on the design and validity of this type of cohort study are published elsewhere (12-14, 15-17).

Investigation sites. Practices were chosen at random from a comprehensive public address database of doctors. The practices included general practitioners and dermatologists and were representatively distributed all over Germany.

Study population. From the randomly chosen practices, the case reports of all patients treated for hypertrophic scars from January 1995 until December 2003 were checked for inclusion/exclusion criteria to assure representativity of the selected patients within the study. Inclusion criteria: Patients suffering from hypertrophic scars, 6 – 65 years old, were locally treated with Contractubex® (study group) or corticosteroids (control group) for at least 28 days with 1 intralesional corticosteroid application. Exclusion criteria: Patients simultaneously treated with Contractubex® and corticosteroids or with other indication-relevant medications. Patients' data were transferred into the case report forms anonymously and in accordance with data safety regulations, including standard demographic data, disease history (*e.g.*, date and basis for scar development, disturbances of primary wound healing, inflammation), state of scars at the beginning and at the end of therapy (Vancouver Scar Scale), covariants influencing scar development and medications administered (*e.g.*, date of start and end of therapy, concomitant diseases and additional medications). The physicians' opinions on efficacy and safety of the therapies were documented.

Study protocol. The study comprised at least two visits by the patients, one at the start, the other at the end of treatment (minimum 28 days for topical Contractubex® or corticosteroid application; 1 intralesional corticosteroid injection). Scar development was clinically investigated. Erythema, pruritus, consistency (primary aims) and pigmentation, pain, height and duration of symptoms (secondary aims) were evaluated by scoring. The Vancouver Scar Scale (18) was applied for further validation and for international comparability of the data. The patient details were transferred to case report forms, and strict standard operation procedures and close monitoring of data acquisition were implemented to ensure good data quality. The patient and physician characteristics were recorded. Independent monitors verified the accuracy of the data by a special interview technique. The interviews were conducted together with the physician.

Study outcomes. The primary outcome was the normalization of erythema, pruritus and consistency of hypertrophic scars after appropriate treatment (minimum 28 days for topical administration of Contractubex® or corticosteroid; 1 intralesional corticosteroid injection). The secondary outcome was the validation of pigmentation and pain. The duration of erythema, pruritus, and the consistency of hypertrophic scars until normalization was calculated.

Statistical analysis. It was estimated that a sample size of 500 patients was required in the selected cohort with a probability 95% of at least one case with seldom events (probability 0.6% in the population). The per protocol sample (patients who met all inclusion criteria and had none of the exclusion criteria) were used for analyses. To adjust for imbalances in baseline variables between both treatment groups, the propensity score (probability for treatment with Contractubex® as function of individual baseline variables) was estimated by logistic regression from the cohort data. The effect sizes (log-odds-ratio, hazard ratio) were adjusted to a propensity score of 0.5 presenting equal chances for each treatment group.

For the primary efficacy criterion (normalization of erythema, pruritus and consistency of hypertrophic scars) the unadjusted normalization rates were compared between the treatment groups

with the Chi^2-test. Logistic regression analysis was used to analyze the influence of treatments and baseline characteristics (quantified by the propensity score) to normalization of scars, and to test the differences in adjusted changes between the treatment groups. The unadjusted distributions of time to normalization were estimated for each treatment group using the Kaplan-Meier technique and the difference between groups was tested with the log rank test. Adjustment of the hazard ratio to baseline conditions (constant propensity score 0.5) was performed with Cox regression. Statistical analysis was done with SPPS+ for Windows, version 12.0.

Results

Study population. Data from the medical records of 859 patients with hypertrophic scars were documented from 38 centers/practices. Of these, 771 patients were eligible for the per protocol treatment, 555 of whom were treated with Contractubex® and 216 with corticosteroid. The reasons for excluding 88 patients comprised: duration of local treatment less than 28 days (n=82), no pathological parameters (erythema, pruritus, consistency) before treatment (n=3), age <6 or >65 years (n=3).

The baseline characteristics and patient data of the study and control groups were generally similar, although small but statistically significant differences were noted for gender (p=0.002; surplus female patients in both groups) and age (p=0.051). These differences might reflect the tendency of female and elderly patients to prefer less aggressive treatment options, although extended in time. The mean duration of local treatment was 242 days for Contractubex® and 170 days for corticosteroids, respectively. The corticosteroids administered were Triamcinolon (28% intralesional, 18% local application), Clobetasol (11% local application) and Betamethason (7% local application). Data concerning the patients' history and covariables that could have influenced the treatment assignment are presented in Tables I and Table II.

Study outcomes. The percentage of patients with normal symptoms of erythema, pruritus, consistency, pigmentation, pain and height of the scar is shown in Figure 1 (start of therapy) and Figure 2 (end of therapy). Obviously, normalization of the symptoms at the end of therapy was more pronounced in patients treated with Contractubex®. The difference between both groups was statistically significant for erythema (p=0.024), consistency (p<0.001) and height (p<0.001). The normalization rate of the primary study aims (erythema, pruritus, consistency) was 42.5% for the Contractubex® application and 22.2% for treatment with corticosteroids (Figure 3). The difference was highly significant (p<0.001). The unadjusted odds ratio was 2.589 (95% confidence interval: 1.802 – 3.720). Imbalances in baseline variables between both treatment groups were quantified by the propensity score, *i.e.*, the probability for treatment with Contractubex® as a function of the individual baseline variables age, gender, wound healing, sum score of erythema, pruritus and consistency at start of therapy, ethnic background, type of skin and concomitant diseases. Significant imbalances were found for wound healing, sum score at start and type of skin. After adjustment with logistic regression using the propensity score, the odds ratio was 2.274 (95% confidence interval: 1.560 – 3.316). This demonstrated a significant superiority of the Contractubex® treatment compared to corticosteroid treatment. The Kaplan-Meier curves for time to normalization of erythema, pruritus and consistency for both groups are shown in Figure 4. The median time to normalization was 344 days for the Contractubex® group and 507 days for the corticosteroid group. The difference was statistically significant (p=0.034; log rank test). The unadjusted hazard ratio for normalization between Contractubex®- and corticosteroid-treated patients was 1.397 (95% confidence interval: 1.024 – 1.906). After adjusting for all imbalances by Cox regression using the propensity score, the hazard ratio was 1.594 (95% confidence interval: 1.158 – 2.195; p=0.0004).

To evaluate the safety of Contractubex® in the treatment of hypertrophic scars, all adverse events were documented and validated. Moderate pruritus was significantly (p<0.001) more frequent in Contractubex®-treated patients (10%) as compared to corticosteroid-treated patients (1%). However, the antipruritugenic activity of the corticosteroids is well documented and the obvious reason for this finding. Other adverse events, *e.g.*, teleangiectasias, cutaneous atrophy of scars of surrounding tissue were significantly more frequent (p<0.001) in corticosteroid-treated patients, whereas pigmentation, pain and other adverse events were comparable. Accordingly, the expected adverse events of the treatment of hypertrophic scars occurred predominantly in the corticosteroid-treated patients, while severe or unexpected adverse events could not be detected.

Discussion

Hypertrophic scars develop as the result of a proliferation of dermal tissue following skin injury. It is generally thought that tension plays a major pathophysiological role (5, 19). Hypertrophic scars are proliferative scars and they are clinically characterized by limitation to the original wound, spontaneous regression, onset within 3 months after injury, occurrence at any anatomical site and unclear genetic background (1, 3).

Although plenty of treatment recommendations exist for hypertrophic scars, no single treatment has been particularly successful, the results being moderately successful at best. All treatment protocols are individualized, but the standard approach to hypertrophic scars usually begins with

Table I. *Primary history of hypertrophic scar development.*

		Therapy					
		Study group (Contractubex®)		Control group (corticosteroid)		Total	
		n	%	n	%	n	%
Age of scar	up to 4 weeks	81	15.5%	30	14.4%	111	15.2%
	4 weeks - 1 year	281	53.7%	106	51.0%	387	52.9%
	1- 5 years	109	20.8%	54	26.0%	163	22.3%
	more than 5 years	52	9.9%	18	8.7%	70	9.6%
	total (p=0.506)	523	100.0%	208	100.0%	731	100.0%
hypertrophic scar	yes	555	100.0%	216	100.0%	771	100.0%
	total	555	100.0%	216	100.0%	771	100.0%
wound healing	primary	402	74.3%	147	71.0%	549	73.4%
	secondary	139	25.7%	60	29.0%	199	26.6%
	total (p=0.362)	541	100.0%	207	100.0%	748	100.0%
inflammation of the wound	moderate	165	33.5%	67	35.4%	232	34.1%
	strong	76	15.4%	27	14.3%	103	15.1%
	none	251	51.0%	95	50.3%	346	50.8%
	total (p=0.284)	492	100.0%	189	100.0%	681	100.0%

Table II. *Baseline variables which may influence the outcome.*

		Therapy					
		Study group (Contractubex®)		Control group (corticosteroid)		Total	
		n	%	n	%	n	%
Ethnic background	caucasian	536	96.6%	185	85.6%	721	93.5%
	other	19	3.4%	31	14.4%	50	6.5%
	total (p<0.001)	555	100.0%	216	100.0%	771	100.0%
type of skin	I or II	288	52.3%	119	55.6%	407	53.2%
	III - VI	263	47.7%	95	44.4%	358	46.8%
	total (p=0.406)	551	100.0%	214	100.0%	765	100.0%
smoker	yes	133	27.7%	36	22.8%	169	26.5%
	no	347	72.3%	122	77.2%	469	73.5%
	total (p=0.224)	480	100.0%	158	100.0%	638	100.0%
diabetes mellitus	yes	19	3.6%	4	2.2%	23	3.2%
	no	512	96.4%	178	97.8%	690	96.8%
	total (p=0.363)	531	100.0%	182	100.0%	713	100.0%
pregnancy	yes	10	1.8%	3	1.4%	13	1.7%
	no	541	98.2%	207	98.6%	748	98.3%
	total (p=0.713)	551	100.0%	210	100.0%	761	100.0%
familiar disposition	yes	19	3.6%	6	3.2%	25	3.5%
	no	507	96.4%	181	96.8%	688	96.5%
	total (p=0.797)	526	100.0%	187	100.0%	713	100.0%

corticosteroid injection followed by surgical excision and pressure dressings (1, 20).

Contractubex® gel contains the ingredients cepae extract, heparin and allantoin and its value in the local treatment of hypertrophic scars has been well established for decades. After the evaluation of the experimental efficacy and pharmacokinetics of each active ingredient and their combination (21-23), clinical studies were performed to

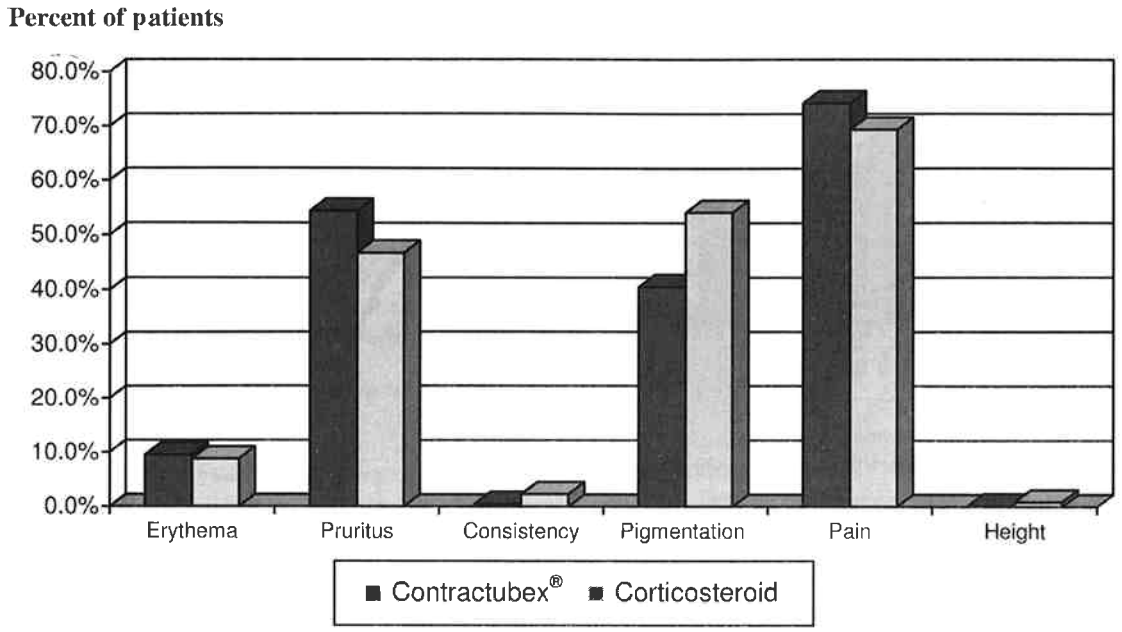

Figure 1. *Frequency of normal parameters before the start of the treatment.*

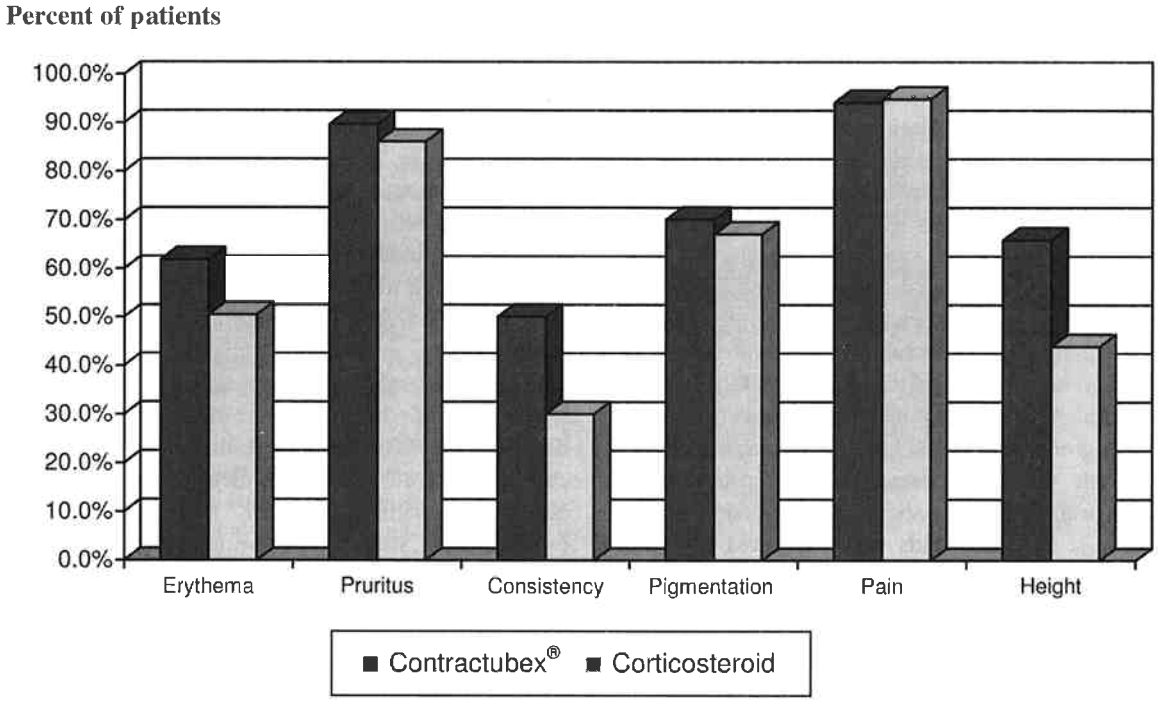

Figure 2. *Frequency of normal parameters at the end of the treatment.*

prove its safety and efficacy. The efficacy of Contractubex® in minimizing the severity of hypertrophic scar formation, in reducing scar size and in promoting the paling of scar erythema could be shown in clinical investigations (7-10).

This retrospective cohort study was performed to evaluate the safety and efficacy of Contractubex® in routine out-patient practice. This study type was chosen since it immediately reflects the out-patient situation. Further on, it

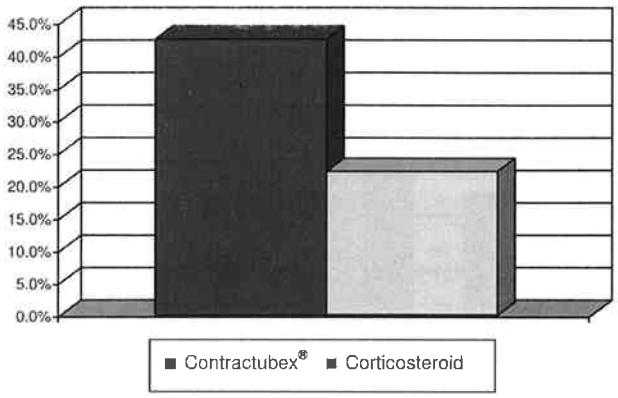

Figure 3. *Frequency of normalization of erythema, pruritus and consistency at the end of per protocol therapy. Adjusted odds ratio 2.274 (95%CI: 1.560–3.316).*

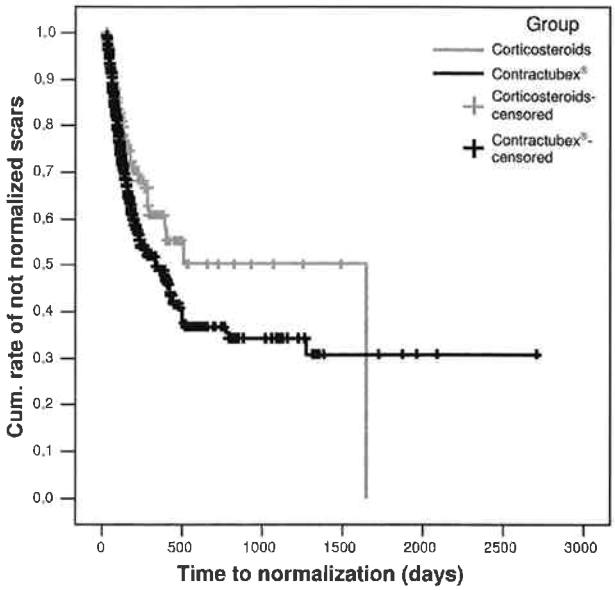

Figure 4. *Kaplan-Meier curves of time to normalization of erythema, pruritus and consistency. Adjusted hazard ratio: 1.594 (95%CI: 1.158–2.195).*

was shown that well-designed observational cohort studies do not systematically overestimate or underestimate the effect of treatment compared with randomized controlled trials investigating the same clinical topic, provided that a number of criteria similar to those in a randomized trial are fulfilled (24, 25).

Contractubex® treatment of hypertrophic scars in the routine clinical setting was compared to local/intralesional corticosteroid treatment. Altogether, 859 patients were enrolled into the "intention to treat" analysis (n=592 Contractubex®/study group; n=267 corticosteroid/control group). Eighty-eight patients did not fulfil the inclusion criteria, and 771 patients were treated per protocol (n=555 study group; n=216 control group) and evaluated. Imbalances of patients baseline conditions (*e.g.*, gender, duration of treatment, pre-treatment status) were quantified by propensity score and adjusted for preferences and characteristics. At the end of the per protocol treatment, 42.5% (study group) and 22.2% (control group), respectively, of the patients showed a normalization of pre-treatment pathological primary aims (erythema, pruritus, consistency of hypertrophic scars). The odds ratio, adjusted to similar baseline conditions for all patients, was 2.274 (95% confidence interval: 1.560 – 3.316) and confirmed the statistically significant superiority of the Contractubex® treatment as compared to corticosteroid treatment. The time to normalization was significantly lower for patients treated with Contractubex® than for patients treated with corticosteroids.

No severe or unexpected adverse events occurred during this study, however, teleangiectasias (15% control group *vs.* 7% study group), cutaneous atrophy of scars (10% control group *vs.* 2% study group) or surrounding tissue (11% control group *vs.* 1% study group) were significantly more frequent in the corticosteroid-treated patients as compared to the Contractubex®-treated patients. Due to its antipruritogenic effect, corticosteroid application presented with a significantly lower rate of moderate pruritus (1% control group *vs.* 10% study group).

A fear of biased results has often been associated with observational studies. However, recent evidence suggests that observational, retrospective trials can provide valid results that do not overestimate the treatment effect. In an evaluation of 53 observational studies and 83 randomized, controlled trials of 19 treatment comparisons, only 2 analyses showed that the combined magnitude of the effect in observational studies lay outside the 95% confidence limits of the randomized, controlled trials (26). Similarly, another study showed clear similarities between the findings of total observational studies and randomized, controlled trials upon analysis of 99 trials investigating 5 clinical topics (27). The results of this study confirmed the findings of previous investigations on the effects of Contractubex® application to hypertrophic scars (7-10).

In conclusion, this study demonstrated the validity of the retrospective study design to evaluate medical treatments in the routine outpatient practice and it provides further evidence for the safety and efficacy of Contractubex® and corticosteroid treatment of hypertrophic scars. However, Contractubex® application proved to be significantly superior to corticosteroid application in terms of safety and efficacy after a minimum 28 days of local treatment.

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