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When Testosterone Needs to be Contrasted: A Preliminary Study of Scar Prevention in Transmen Top Surgery with an Innovative Galenic Preparation

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Abstract

Background Transmen are individuals who live a marked incongruence between the assigned gender and the experienced gender. Crucial and life-changing steps in their transition are testosterone treatment and mastectomy to remove the stigma of feminine identity. After surgery, patients' attention turns to the scars, often not aesthetically pleasant. We thus created an innovative galenic preparation for scar treatment after surgery composed by spironolactone, alfa bisabolol and silicone gel. Functional outcomes, side effects and satisfaction were assessed.

Methods For the present prospective randomized controlled study, 30 patients with similar demographic characteristics who underwent double incision mastectomy with NA grafts between February 2014 and June 2019 were selected. The treatment Group A (n = 15) was treated for 12 months with "Top Surgery Scar go," the control Group B (n = 15) with silicon gel. Statistical analysis including Wilcoxon test and Kruskal–Wallis test per variable was performed. To assess satisfaction, a second Wilcoxon test was applied.

Results The differences between Group A and Group B were statistically significant, especially at T12 with very low p values. Satisfaction was greater in Group A (p value = 3e−4). No major side effects were noticed in Group A.

Conclusions TSSgo scar innovative treatment showed long-term efficacy in comparison with silicon gel in terms of improved scar tissue texture, pigmentation, pliability and height. It is easy to set up, cost-effective and safe. Further studies are necessary to better assess efficacy and validity of TSSgo, but it appears to be promising as the new treatment of reference for scar management after top surgery in transmen.

Level of Evidence IV This journal requires that authors assign a level of evidence to each article. For a full description of these Evidence-Based Medicine ratings, please refer to the Table of Contents or the online Instructions to Authors www.springer.com/00266.

Keywords Transmen · Top surgery · Scar · Scar treatment · Scar prevention · Testosterone · Silicon gel

Introduction

Transmen are individuals assigned female at birth who later in life identify themselves and live as men. Crucial steps in their transition are medical treatment with testosterone to induce body masculinization and mastectomy to remove breast stigma of feminine identity. The goal of top surgery is to achieve an aesthetically pleasing male chest. With the removal of breast tissue and skin excess, the reduction and repositioning of nipple and areola (NA) and the obliteration of the inframammary fold performed during the surgical procedure, it is possible to remove the female contour and the typical aspects of the female breast as to create a masculine chest-wall contour [1–3]. Patients who seek top surgery know that over the skin surgical incisions, there will be a scar after surgery [4–8]. Depending on the selected surgical technique, the scars

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may have different characteristics and position, but they will be always present.

As soon as the problem of the presence of the breast itself vanishes, the patient's attention turns markedly to the scars, an indelible stigma of surgery. If not aesthetically pleasant, a scar creates not only a significant cosmetic problem, but, especially when associated with pain and itch, it may dramatically affect patient's physical and psychological quality of life [8]. Assuming this, scar management for the prevention of hypertrophic scar tissue is becoming in time more and more important. For this reason, once we refined our surgical technique, more specifically the double incision mastectomy with NA graft [1–3], we focused on planning and creating an innovative galenic preparation called "*Top Surgery Scar go*" (TSSg) for scar management after top surgery in transmen.

The idea behind TSSgo was born from the integration between clinical and biological evidence. On the one side, satisfaction with the mammary scar is lower in transmen compared to that of the patients biologically female who underwent mastectomy, and on the other side the anabolic effects of testosterone.

The key ingredient of this formulation is spironolactone used as a local anti-androgen, since it inhibits testosterone's effect on the scar process without blocking the hormonal desired systemic effects.

The aim of this study is to illustrate the effectiveness of our formulation in preventing postoperative hypertrophic scars and keloids associated with double incision mastectomy with NA grafts in transmen.

Patients and Methods

The present perspective randomized controlled study was conducted between September 2018 and September 2019. Our group of patients consisted of thirty transmen who met preoperative selection criteria (characteristics of each patient before surgery), intraoperative selection criterium (the delta between the upper and lower incisions at the end of mastectomy) and postoperative selection criteria (patients' postoperative compliance).

The preoperative selection criteria were very narrow: Western patients; age ranged 20–23 years old; normal body mass indexes (BMIs 25–29.9 kg/m^2); Fitzpatrick skin type II–III; no history of smoking, important weight lost, pathologic scars, chronic medical illnesses or pharmacological treatments that might affect wound healing; no reported hypersensitivity/allergy to any medication used in the study.

In addition, all of them must have been on testosterone therapy for at least a year at the moment of surgery (max. for 2 years), being finally considered a suitable candidate for double incision mastectomy with NA grafts only if, in the standing position, the upper margin of the incision falls at or below the inferior margin of the pectoralis major muscle, regardless of breast size.

We excluded only the patients with small breast size and good skin elasticity, thus ideal for periareolar mastectomy.

The same procedure, in terms of preoperative marks, mastectomy and wound closure, was performed always by the same surgeon. All patients were informed about the study and provided written consent.

The intraoperative selection criterium was only one; we excluded the patients in which the distance between the upper and the lower skin incisions was greater than 5 cm at the end of mastectomy in the supine position (in order to eliminate the well-known "tension factor" on scar outcome) (Fig. 1).

After confirming normal epithelialization and wound healing on the incision site at the 14th postoperative day, patients who met the previous selection criteria were randomized to either the treatment group or control group. The initial thought behind our study was applying *TSSgo* on the one side and standard silicone gel on the scars on the other side of the same patient, in order to better evaluate the differences of scar process related to the two treatments while excluding the subjective variables.

Unfortunately, we did not easily obtain written informed consent by the patients fearing different esthetic results of the scars on the two sides of the thorax. We thus modified

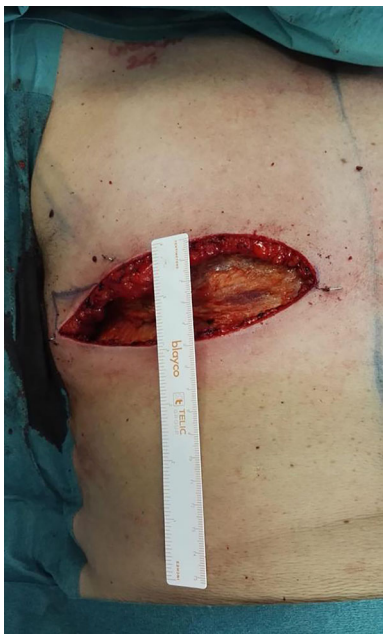

Fig. 1 Intraoperative image of the distance between the upper and the lower skin incisions at the end of mastectomy in supine position. We excluded patients in which the distance between the upper and the lower skin incisions was greater than 5 cm

the study design as follows. Treatment Group A (n = 15 patients) was treated for 12 months with *TSSgo*, the control Group B (n = 15 patients) with standard silicone gel (the same silicone gel of the *TSSgo*).

TSSgo is a galenic preparation composed of spironolactone (1.5 g), alfa bisabolol (1.5 g) and silicon gel (27 g).

The formulation, available in a tube, is applied as a thin layer right to the surgical scars twice per day, rubbing until it dries. When it dries, the *TSSgo* forms a thin, transparent, flexible, water-impermeable sheet that adheres to the skin and improves scarring.

Three blinded plastic surgeons performed the follow-up examinations before treatment (T0 = 14th postoperative day) after 3 months (T3) and 12 months (T12 = at the end of the treatment). All patients were analyzed at the end of the 12-month follow-up.

Scar assessment was performed using the modified Vancouver Scar Scale (MVSS) by evaluating scar pigmentation (0 = normal color, 1 = hypopigmentation, 2 = hyperpigmentation), vascularity (0 = normal color, 1 = pink, 2 = pink to red, 3 = red, 4 = red to purple, 5 = purple), pliability (0 = normal, 1 = supple, 2 = yielding, 3 = firm, 4 = banding-rope tissue, 5 = contracture) and height (0 = normal/flat, 1 $\leq$ 2 mm, 2 = 2–5 mm, 3 $\geq$ 5 mm) for each patient at the same side [9, 10].

The treatment unit was used twice per day for 12 months. The side effects experienced by the patients were assessed every 2 months. After 12 months, the patients were asked to rate their satisfaction using a four-point grading scale (1 = unsatisfied, 2 = slightly satisfied, 3 = satisfied, 4 = very satisfied) for each group.

The postoperative selection criteria included: 12-month regular follow-up; total compliance to the treatments, adhesion to all the postsurgical indications (compressive thoracic band of 18 cm 24/24 h during the first 4 weeks, 12/24 h during the subsequent 4 weeks; abstention from physical activity for the first month, avoiding excessive effort and weightlifting; and avoidance of sun exposure).

For each group, the distribution was studied calculating mean, standard deviation and median. The comparison between two or more groups was assessed with Wilcoxon test and Kruskal–Wallis test, respectively. The efficacy of the treatment on each parameter was compared via mean of the scores. In particular, the Wilcoxon test was used to compare the efficacy of the treatment in the two groups under investigation. The Kruskal–Wallis test was performed to check the differences between the four variables at different tested time points and the potential bias coming from the three different surgeons' scores. To assess patient satisfaction, a second Wilcoxon test was performed. For all statistical tests, a significance threshold of $p < 0.05$ was considered.

Results

In the present perspective study, our innovative *TSSgo* formulation was compared with the conventional silicone gel treatment in terms of efficacy of preventing hypertrophy scars after mastectomy in transmen. The efficacy of the two treatments over time and the different outcomes between them were statistically significant. We found that each single evaluated parameter of MVSS responded differently to the two treatments (Fig. 2). Regarding the scar height, no significant difference at T0 was found. At T3, the difference is slightly significant (p 0.034) but a strong difference was noticed at T12 as observed from the mean score between Group A and Group B (Fig. 2, Table 1). Concerning the pliability, at T0 there was a significant difference between the two groups and Group B was better than A, at T3 means are almost identical and the difference between the groups is not significant, while at T12 a significant difference was again observed (Fig. 2, Table 1). Although at T0 individual/personal characteristics of the patients can play a role in scar tissue formation, the decrease in pliability of Group A patients was very important over time in comparison with those of Group B that showed almost constant mean score over the 12 months (Fig. 2, Table 1). For scar pigmentation at all the time points, the difference was statistically significant increasing notably over time (Fig. 2, Table 1). Finally, the vascularity was the fourth parameter analyzed; while at the beginning and at the end of the treatment the difference between the groups was significant, at T3 the p value was slightly below the threshold although the mean value of Group B is higher than Group A. (Fig. 2, Table 1).

A Kruskal–Wallis test for each variable was performed to check if the scores given by different surgeons could have had some bias on the comparison of the two groups. There was no bias coming from surgeons' score.

To evaluate the patient's satisfaction, a Wilcoxon test was performed and the two groups were significantly different showing a greater satisfaction of Group A patients (p value = 3e−4; Fig. 3). The patients self-reported a high degree of therapy compliance, with 98% of them usually or always applying the gel as prescribed. No major side effects were noticed in Group A. The clinical results are reported in Figs. 4 and 5.

Discussion

A cutaneous scar is an area of dermal fibrous replacement tissue, the physiological result of the wound healing process [11]. When injured, the skin must consistently and rapidly repair itself.

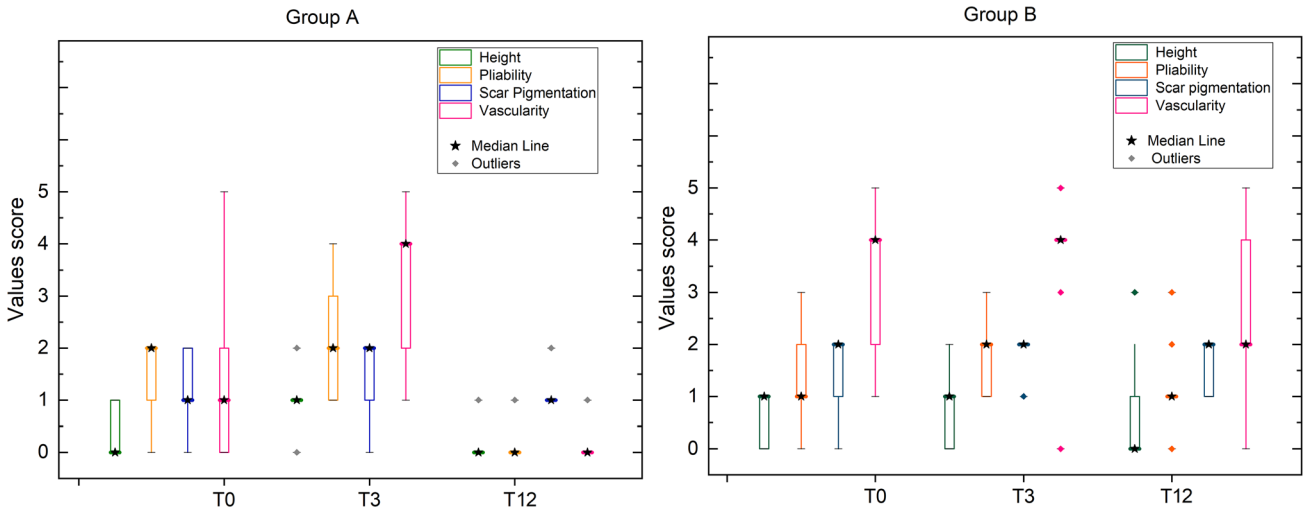

Fig. 2 Efficacy of treatment for each evaluated parameter. Each parameter shown in the graph with different color was plotted for Group A (left panel) and Group B (right panel) to observe the trend over time of the treatment. Stars represent median lines and diamonds are the outliers. Kruskal–Wallis was always $p < 0.05$

Table 1 Mean and standard deviation of each parameter considered for the comparison of the two treatments

Group	Features	T0	T3	T12
A	Height	0.5 ± 0.5	1.1 ± 0.6	0.1 ± 0.3
B	Height	0.6 ± 0.5	0.8 ± 0.6	0.5 ± 0.7
A	Pliability	1.6 ± 0.5	1.9 ± 0.9	0.2 ± 0.4
B	Pliability	1.2 ± 0.8	1.8 ± 0.6	1.0 ± 0.8
A	Scar pigmentation	1.2 ± 0.7	1.7 ± 0.6	1.0 ± 0.1
B	Scar pigmentation	1.7 ± 0.5	2.0 ± 0.2	1.5 ± 0.5
A	Vascularity	1.3 ± 1.3	3.2 ± 1.5	0.1 ± 0.3
B	Vascularity	3.4 ± 1.3	3.9 ± 1.1	2.5 ± 1.6
A	Satisfaction			3.9 ± 0.3
B	Satisfaction			2.9 ± 0.7

Group A is composed by patients treated with TSSgo; Group B is treated with conventional silicone gel. Numbers at each T point are presented as means ± SD

Rate and quality of scar tissue vary among individuals, and alterations in this process, whether extrinsically or intrinsically derived, give as outcome of the development of a chronic wound or an abnormal scar.

What a patient macroscopically sees at the site of the surgical incisions is the replacement of a "usual-appearing skin" having normal texture, elasticity and resilience with a lesser functional and textural substitute. When normal, it clinically appears as a normal red fine-line scar, raised line, which will gradually get paler and flatter over time. On the contrary, a pathological cutaneous scar is the result of a general failure of the normal wound healing process [7]. As well known, it consists of three predictable and overlapping phases (inflammatory, proliferative and remodeling phase). An alteration of one or more of these phases may result in greater or lesser scarring [11]. More specifically, pathological scars are usually characterized by a prolonged inflammation, excessive fibroblast proliferation and abnormal deposition of extracellular matrix proteins. The quality of scar tissue varies among individuals, and alterations in this process may result in the development of a chronic wound or an abnormal scar [7].

Over the decades, several treatments and prophylactic approaches were thought and adopted for the management of hypertrophic scars and keloids, including conventional therapies such as radiation, pressure therapy, cryotherapy, topical silicone gel, intralesional injections of corticosteroids, laser treatment, surgical excision and various medications and adjuvant and emerging therapies including interferon, 5-fluorouracil, imiquimod, tacrolimus, sirolimus, bleomycin, doxorubicin, transforming growth factor-beta, epidermal growth factor, verapamil, retinoic acid, tamoxifen, botulinum toxin A, onion extract, hydrogel scaffold and skin tension offloading device [7, 8, 12–18]. To date, the aim is rather to prevent the formation of a pathological scar and get a normal line scar tissue with characteristics as much similar as possible to the normal replaced skin.

Our study comes up by the hypothesis that testosterone is involved in the scarring process. In the transmen group of patients, the surgical scars after double incision mastectomy with NA grafts appear quite good, but usually a trend toward hypertrophy occurs. This clinical evidence is corroborated by our experience with such operation and subsequent regular physical examinations during follow-up. In addition, compared to those of the biologically female patients who undergo simple mastectomy due to

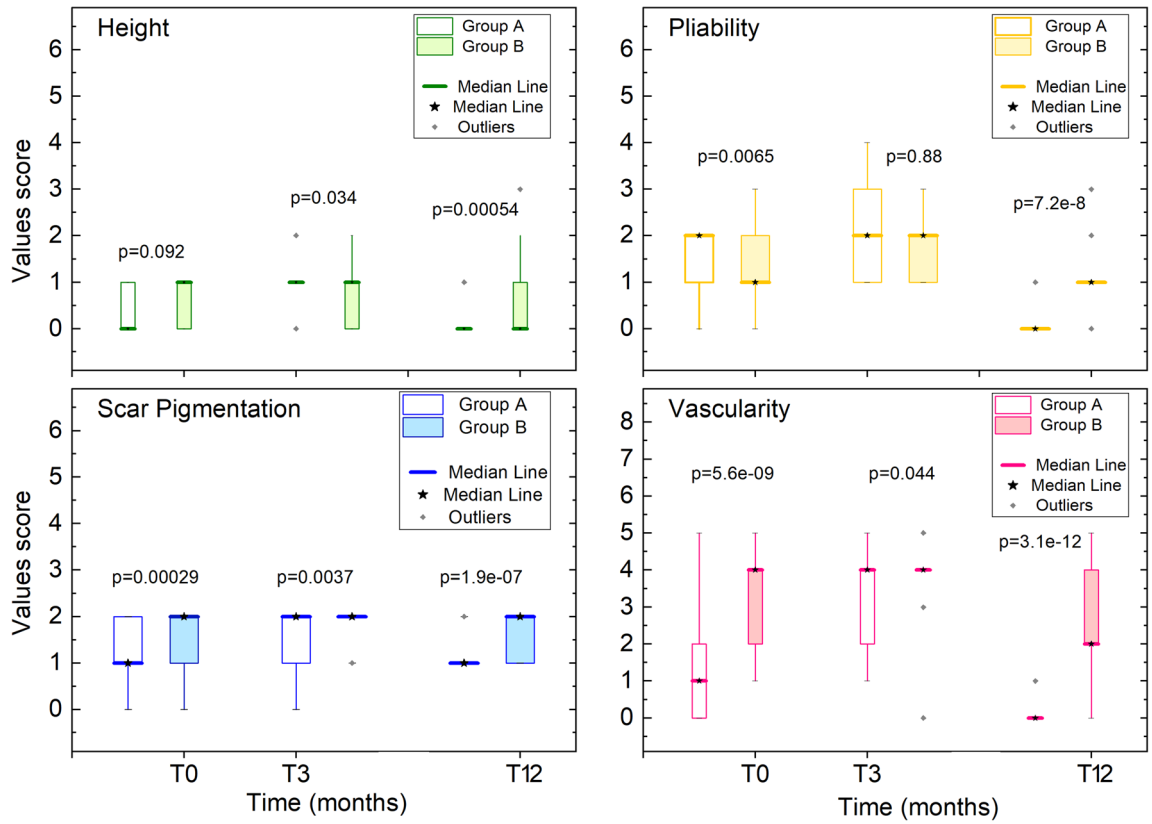

Fig. 3 Difference between the two treatments. Groups A and B analysis for all the variables/parameter tested during the treatment at different time points. The Wilcoxon test was applied with statistical significance $p < 0.05$

breast cancer, in our experience transmen' mammary scars are in general aesthetically less satisfactory.

The actual difference between these patients and cis-women is ultimately the medical treatment with testosterone, the milestone of hormonal gender affirming treatment in transmen [19].

The anabolic properties of testosterone were defined in the 1930s [20]. These, among all, include an increase in skin thickness, which has been also noted in hypogonadal men upon administration of testosterone. The reason for differences in skin thickness and texture is the testosterone/estrogen ratio in males and females [21]. For example, the male epidermis is 20% thicker than the female one containing more collagen and being able to bind a larger amount of moisture. This contributes to make male skin, at all ages, more dense and vigorous [22].

On the contrary, low testosterone levels lead to the thinning and weakness of the skin and impaired wound healing [21].

Schierle et al. [23] reported an increase in testosterone receptors in hypertrophic scars, which may explain the greater tendency for the development of pathological scars during adolescence. It is not a case that hypertrophic scarring often initiates at the onset of puberty or during pregnancy, this underlying the hormonal impact on wound healing process [24].

Elevated levels of androgen receptors in keloid tissue were also found by Ford et al. [25], who observed that keloids strongly bind dihydrotestosterone. They concluded that androgens have some trophic influence on keloid formation and that androgen inhibitors may have some effect on reducing scar tissue growth [23].

Integrating all this clinical and biological evidence, we have developed our idea on the management and prevention of the scars immediately after top surgery, giving birth to our galenic *TSSgo* composed of spironolactone and alfa bisabolol in addition to silicon gel.

Assuming testosterone's effects on scarring process, spironolactone is the key component of our formulation in its functioning as a local anti-androgen. It does not reach, indeed, the blood circulation when topically applied, thus preventing safely possible undesired systemic side effects [26].

Alfa bisabolol is a natural monocyclic sesquiterpene alcohol, with a weak sweet floral aroma. We introduced it as a second component of our unit since it is able to neutralize spironolactone's acrid smell [27]. Our product has thus a pleasurable smell.

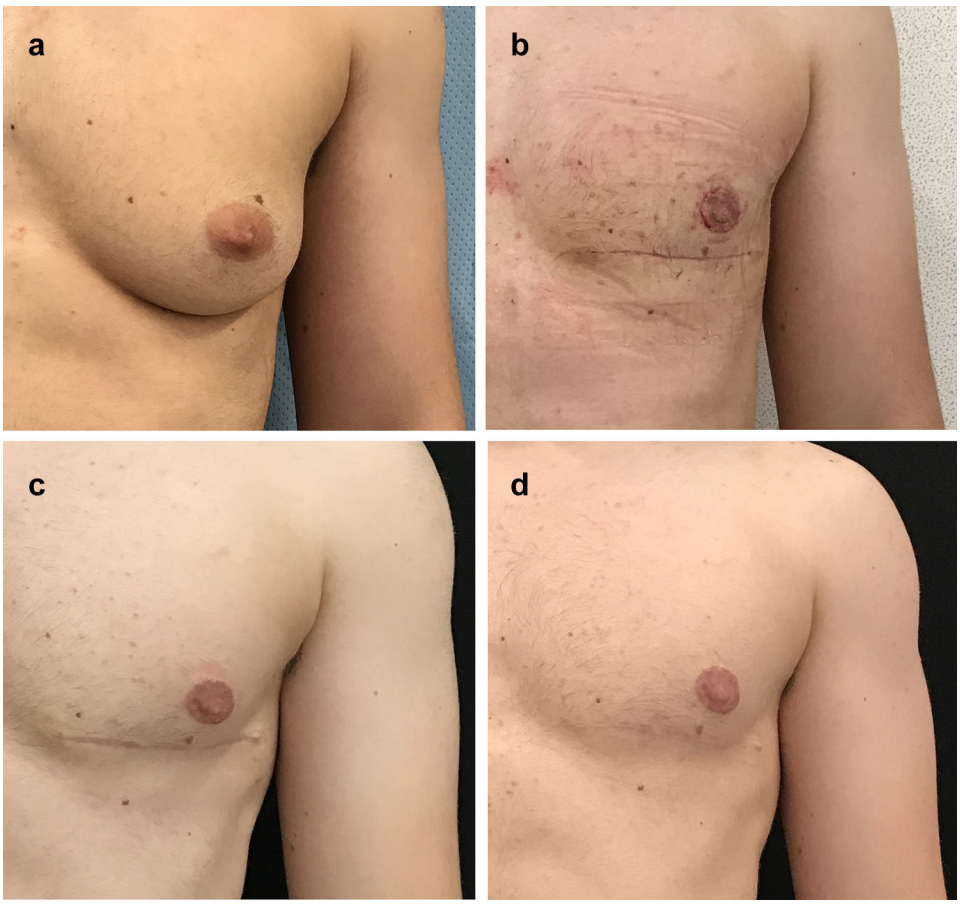

Fig. 4 This 22-year-old transmen patient is shown **a** preoperatively before double incision mastectomy with nipple areola graft. **b** Fourteen days after surgery (T0), right before starting *TSSgo* treatment (T0). **c** Three months after surgery (T3). Scar management was done by the application of *TSSgo*. **d** One year after surgery (T12), end of treatment with *TSSgo*

The third ingredient of *TSSgo* is the silicon gel, which has been demonstrated to increase occlusion and hydration of wounds while decreasing collagen deposition, resulting in an improvement in overall scar appearance [28].

In this preliminary prospected randomized study, we compared the efficacy of the use of the conventional topical silicone gel (control group of patients) with our *TSSgo* formulation (treatment group of patients), evaluating their long-term efficacy on preventing hypertrophic scar formation after top surgery. The selection criteria for transmen patients to be enrolled in this study were very restrictive in order to standardize the population as much as possible.

We found out that at T0, the only parameter of MVSS that did not show any significant difference is the height of the scar, confirming also that the initial variability is not marked and the difference at the subsequent time points (T3–T12) is more likely a consequence of the treatments. Regarding the other parameters, they appeared to be statistically different among the patients possibly due to the fact that, as it is well known, each individual responds differently to wounds. Wound healing is indeed a complex process, on which many subjective factors may play a role [29].

According to the performed statistical analysis, at T3 it was not possible to detect any significant statistical difference for each of the considered parameters of MVSS between Group A and Group B. Just scar pigmentation and pliability showed p values slightly below the threshold of $p > 0.05$.

Visual inspections confirmed that at T3, the scars presented similar characteristics in both groups, alike with T0 or slightly worsened (see Table 1). Our results are in accordance with the existing literature on the matter of tissue scarring [9, 14–16, 30]. As is well known, the proliferative phase of the scarring process starts early during the first week after injury and can last up to 8 weeks. With the up-regulation of vascular endothelial growth factors, angiogenesis is also initiated during this phase. Therefore, a physiological "worsening" of scar appearance can be expected within 3 postsurgical months. That would explain why any significant clinical improvement was noticed at T3 neither in Group A nor in Group B corroborated by the statistical analysis, which did not show statistical differences between the two groups analyzed [18]. At T3, *TSSgo* seemed thus to be as effective as standard silicone gel.

What we observed at T12, instead, was a general improvement in the quality of the surgical scars both in

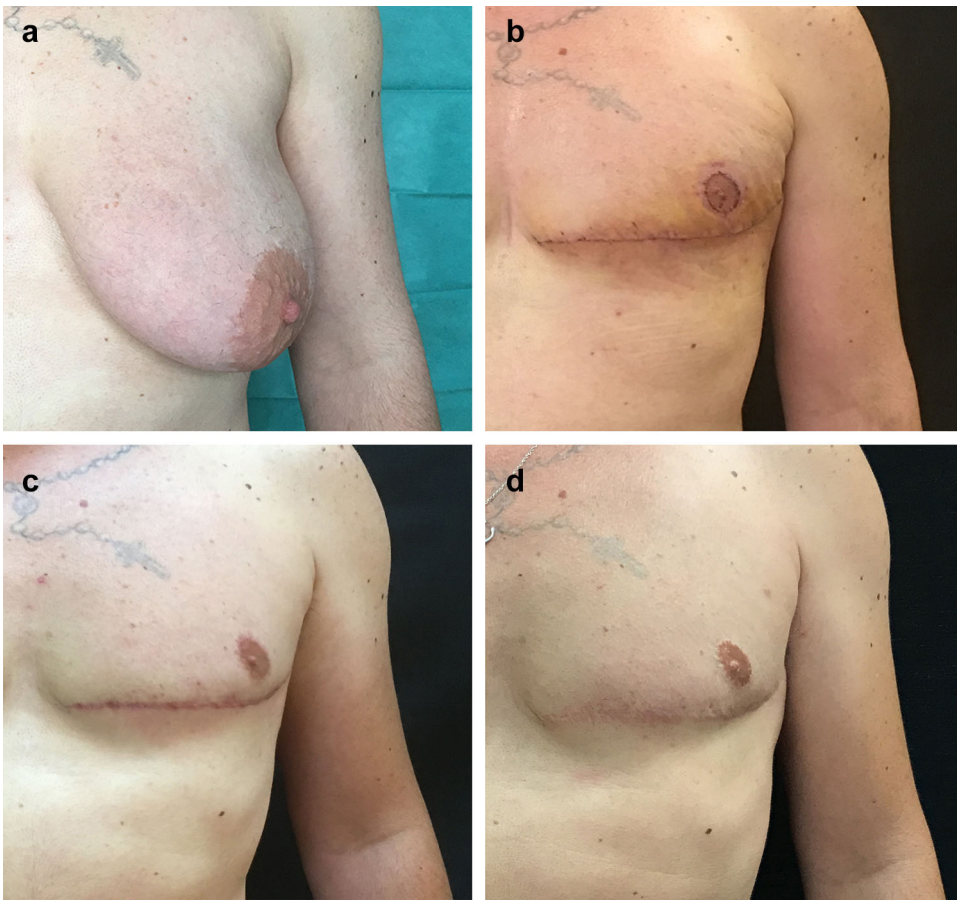

Fig. 5 This 22-year-old transmen patient is shown **a** preoperatively before double incision mastectomy with nipple areola graft. **b** Fourteen days after surgery (T0), right before silicone gel treatment (T0). **c** Three months after surgery (T3). Scar management was done by the application of silicone gel. **d** One year after surgery (T12), end of treatment with silicone gel

control and treatment groups, more pronounced in Group A treated with our galenic formulation (Table 1, mean and SD).

Indeed, all the variables evaluated showed significant differences between the two treatments ranked in descending order as follows: vascularity > flexibility > scarring pigmentation > height (Fig. 2, T12 and *p* values).

The effects of the use of our formulation on surgical scars appeared more visible on scar vascularity and elasticity. This led us to conclude that, to parity of silicone gel, this is probably due to the effects of the key component of our formulation, spironolactone, with its anti-angiogenic and anabolic properties of testosterone.

Our innovative *TSSgo* scar treatment showed finally long-term greater efficacy in comparison with silicone gel for all studied parameters. Although our sample groups were small, according to the encouraging results of this preliminary study, we believe that our formulation may be a valid alternative for hypertrophic scar prevention in transmen patients. Plastic surgeons should indeed emphasize more on the principle of prevention, in order to avoid further nonessential cosmetic surgeries.

Conclusions

This prospective randomized controlled study based on our clinical experience highlighted that *TSSgo* scar innovative treatment showed long-term efficacy in comparison with standard silicone gel in terms of improved scar tissue texture, pigmentation, pliability and height. *TSSgo is* furthermore easy to set up, cost-effective and safe. Although further studies and an increased group number are necessary to better assess the efficacy and validity of *TSSgo*, our product seemed to be a very promising new alternative treatment for scar management after top surgery in transmen.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest to disclose.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of

the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent All participants have given their informed consent in writing.

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