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SHORT REPORT

# Efficacy and safety of topical timolol 0.5% plus saline 0.9% versus each one alone in acne scar trichloroacetic acid-CROSS therapy: A blinded randomized controlled trial

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## Abstract

Trichloroacetic acid-CROSS (TCA-CROSS) or chemical reconstruction of scars is an approved method in the treatment of ICE-PICK scars. Timolol is a blocker of beta-adrenergic receptors that speeds up the healing of skin wounds. In this study, for the first time, the TCA-CROSS technique was combined with the use of saline injection and topical timolol to increase the effectiveness of treatment, and reduce the number of treatment sessions and complications, and thus improve the aesthetic result. In this parallel-group split-face randomized controlled assessor and analyst-blinded study, 45 patients with atrophic acne scars were randomly divided into 3 equal groups. TCA-CROSS treatment was performed on all facial scars of patients. In group 1, before TCA-CROSS, saline was injected under the scars on one side of the face, in group 2, after TCA-CROSS, 0.5% timolol eye drops were applied on the scars on one side, and in group 3, saline was injected before TCA-CROSS. After that, timolol eye drops were applied on the scars of the same side. In all groups, the choice of control side was random. The number of scars and patient and physician satisfaction were the main variables evaluating the effectiveness of the treatment. TCA-CROSS improved scars in both control and treatment sides of all 3 groups. Although the number of scars decreased on the treatment side of groups 2 and 3, the decrease was not statistically significant. In the saline + TCA group, the number of scars on the treatment side was slightly more than on the control side. In the group of patients who used timolol, the severity and duration of scar hyperpigmentation were significantly lower (group 2 $p = 0.016$, group 3 $p = 0.002$). No permanent complication was observed in the patients. Patients' satisfaction in groups 2 and 3 was higher in the treatment side than the control side. The combination of saline injection followed by TCA-CROSS is not recommended. Application of 0.5% timolol after TCA-CROSS caused a slight decrease in scar severity and a significant reduction of post-inflammatory

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hyperpigmentation (PIH) duration. So, the topical timolol makes a better result of TCA-CROSS for acne scar treatment.

**KEYWORDS**
acne, acne scars, atrophic scar, boxcar, ICE-PICK, normal saline, post-inflammatory hyperpigmentation, randomized controlled trial, rolling, trichloroacetic acid, trichloroacetic acid-CROSS, timolol

## 1 | INTRODUCTION

Acne is an infectious and inflammatory disease and one of the most common human diseases. Genetic factors, disease severity, and delay in treatment are the main factors causing acne scars.[1–3] Acne scars can be divided into three types: ICE-PICK, rolling, and boxcar. ICE-PICKs of scars account for about 60%–70% of scars. ICE-PICK scars can extend deep into the dermis and subcutaneous tissue and are the most difficult to treat.[4] Usually, treatment of acne scars requires a combination of different methods.[3,5] The treatment process is determined by the type of scar, so treatments such as laser resurfacing or dermabrasion are not suitable because they would not reach the deep parts of the ICE-PICK scars in addition to many probable pigmentary side effects long recovery period especially in people with dark skin.[4,6] Topical timolol has an acceptable safety profile; considering the effect of beta-adrenergic receptor blockers in improving and accelerating the healing process of superficial skin lesions and their different effects on keratinocytes, it seems that the use of these inhibitors, especially timolol after TCA-CROSS, accelerates wound healing, thus reducing scar complications.[7] Also, various studies have shown that injection of 0.9% saline stimulates fibroblasts, collagen production, and rearrangement of extracellular matrix, which disrupts the connection of collagen fibers of the upper dermis with the lower dermis and causes clots. As a result, bleeding due to this process causes swelling of the skin in the area of the scar and accelerates the healing of various atrophic scars caused by acne.[8] Therefore, this study aimed to determine the effect of simultaneous use of saline injection and topical timolol, in comparison with each alone, on atrophic acne scars of patients treated with TCA-CROSS in a parallel-group split-face randomized controlled assessor and analyst-blinded clinical trial.

## 2 | MATERIALS AND METHODS

The present study is a phase 2 clinical trial. In this assessor/analyst-blinded randomized controlled trial (RCT), 45 patients with atrophic acne scars were enrolled and randomly divided into three groups of 15 people. The treatment was performed on one side of their face, and the other side of their face was considered as control (split-face arms). In supplementary Table 1, you can see details of the method and materials. In supplementary Figure 1, the flow diagram of the study has been shown.

## 3 | RESULTS

Therefore, the demographic and clinical characteristics of patients were homogeneous between the three treatment groups (supplementary Table 2).

### 3.1 | Effectiveness

The average number of scars was not significantly different between the treatment area and the control area of three groups (supplementary Table 3) ($p > 0.05$), and the average number of scars after the intervention was significantly lower than the average of this variable before the intervention in all three groups and in both sides of each group (supplementary Table 4), which at a significance level of 0.05, all $p$ values are significant ($p < 0.05$). It means that in a trial with homogeneity of variables, TCA as control and TCA in combination with other methods as intervention are significantly effective in reducing acne scars number.

To evaluate the efficacy of the treatment (before and after the intervention) in comparison with the control group (control), the Generalized Estimated Equations (GEE) method was used. First, this method was performed separately for the treatment groups, and in the next stage, the treatment groups were entered into the GEE model as a variable, and the efficacy of the treatments was compared with the control groups (Table 1). The intra-group comparisons showed that the effect of treatment in each group was not significant at the significance level of 0.05. In the saline + TCA group, the mean number of scars in the facial treatment area was more than that of the control area; however, the effect of time (measurement of scars before and after the intervention) was significant, which means that the number of facial scars would be reduced during study irrespective of intervention or control arm. The evaluation of the efficacy of the type of treatment and time showed that none of the studied treatments had a significant effect on the number of scars compared to the control group, meaning that the efficacy of new treatments was not significantly different from the control treatment, which was TCA-CROSS.

### 3.2 | Satisfaction

The patient's opinions about satisfaction with treatment, in the first and the second groups showed a significant difference compared to

**TABLE 1** Comparison of the number of scars by treatment groups using the GEE method

| Variables<br>TCA + saline | Effect size ± SD (B ± SD) | 95% confidence interval | P |
|---|---|---|---|
| Facial area | | | |
| Control area | – | – | – |
| Treatment area | 6.37 ± 3.71 | (−0.90, 13.64) | 0.086 |
| Time | | | |
| Before intervention | – | – | – |
| After intervention | −4.97 ± 0.94 | (−6.81, −3.13) | <0.001 |
| Treatment area*Time | **0.73 ± 0.43** | (−0.10, 1.57) | 0.086 |
| **TCA + timolol** | | | |
| Facial area | | | |
| Control area | – | – | – |
| Treatment area | 2.20 ± 1.89 | (−1.51, 5.91) | 0.246 |
| Time | | | |
| Before intervention | – | – | |
| After intervention | −5.73 ± 0.92 | (−7.53, −3.93) | <0.001 |
| Treatment area*Time | −2.53 ± 0.52 | (−3.56, −1.51) | <0.001 |
| **TCA + saline + timolol** | | | |
| Facial area | | | |
| Control area | – | – | – |
| Treatment area | 5 ± 3.45 | (−1.75, 11.75) | 0.147 |
| Time | | | |
| Before intervention | – | – | – |
| After intervention | −7.20 ± 2.50 | (−12.08, −2.32) | 0.004 |
| Treatment area*Time | −2.20 ± 0.52 | (−3.21, −1.18) | <0.001 |

*Note*: *Interaction of the treatment area and time.

**TABLE 2** Comparison of the patients' satisfaction and physician's satisfaction using the GEE method

| Type of treatment | Effect size ± SD (B ± SD) | 95% confidence interval | *p* |
|---|---|---|---|
| Patients' satisfaction | | | |
| TCA | – | – | – |
| TCA + saline | −4.33 ± 2.55 | (−9.34, 0.67) | <0.001 |
| TCA + timolol | 8.33 ± 2.66 | (3.13, 13.54) | 0.002 |
| TCA + saline + timolol | 9.67 ± 2.18 | (5.39, 13.94) | 0.09 |
| Physician's satisfaction | | | |
| TCA | – | – | – |
| TCA + saline | −2.67 ± 2.12 | (−6.82, 1.49) | <0.001 |
| TCA + timolol | 8 ± 2.39 | (3.32, 12.68) | 0.001 |
| TCA + saline + timolol | 8 ± 2.17 | (3.74, 12.25) | 0.208 |

*Note*: Table numbers are reported in percentage.

the control group. In the saline + TCA group, the patients were more satisfied with the TCA treatment, which was the control therapy, but in the TCA + timolol group, the patients were more satisfied with the new treatment compared to the control (TCA). There was no significant difference in patients' satisfaction with the two studied treatments in the group of patients who received saline + TCA + timolol. It was also observed that the results of physician satisfaction with the areas of the treatment and control were not different from the results of patients' satisfaction. Only in the treatment group that received TCA + timolol, the physician's satisfaction was significantly higher compared to the control treatment. The physician satisfaction with saline + TCA therapy was lower than the control treatment (Table 2).

### 3.3 | Side effects

In this study, 10 patients (66.7%) in the saline + TCA group, seven patients (46.7%) in the TCA + timolol group, and 12 patients (80%) in the saline + TCA + timolol group experienced hyperpigmentation of scars after treatment. The study showed that following the use of TCA + timolol or saline + TCA + timolol, the hyperpigmentation of the scars which remained on the patients' faces had a significant shorter period of time, in comparison to the patients that received saline + TCA treatment (supplementary Tables 5 and 6).

In Figure 1, you can see the effect of therapy in the salin or timolol group in comparison with TCA alone and significant healing effect of topical timolol on TCA-induced hyperpigmentation.

## 4 | DISCUSSION

In this study, in order to reduce the side effects of TCA and increase the final improvement, we implemented the TCA-CROSS method using 100% TCA in combination with topical timolol and saline injection for the treatment of atrophic acne scars, especially ICE-PICK types. Since timolol, as an inhibitor of beta-adrenergic receptors, can improve the aesthetic outcome and reduce the side effects of treatment by accelerating the wound healing process. The results of the study showed that in groups 2 (TCA + TIMOLOl) and 3 (TCA + SALINE + TIMOLOL) who received timolol after TCA treatment, post-inflammatory hyperpigmentation (PIH) was significantly less than the group 1 (TCA + SALINE), and it was also less than the control side. No stable complication was observed while all but five patients had skin types 3 and 4. Since the use of timolol in accelerating wound healing has received less attention, we, in a review article, reviewed the studies on this topic.[7] Moreover, we have studied the effects of various factors on the treatment of acne vulgaris and related scars and its complications.[5,7,9–15] In the present study, for the first time in a randomized clinical trial, the interaction of TCA-CROSS, topical timolol, and saline injection in the treatment of atrophic acne scars were evaluated.

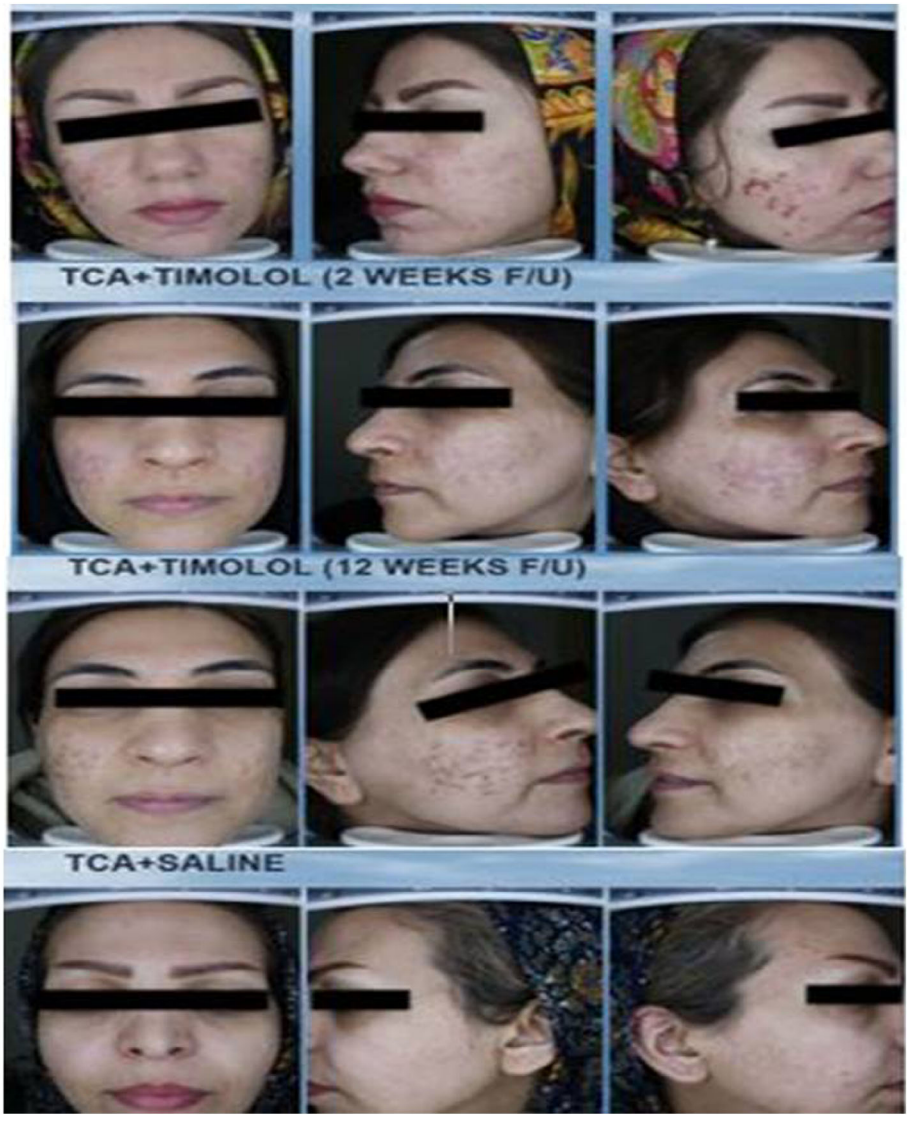


**FIGURE 1** Acne treatment process in patients treated with TCA + timolol (row 1 & 2) and saline + TCA (row 3 & 4), as shown, timolol resulted in significant decrease of final hyperpigmention that was obvious early after therapy (two weeks later) and either at the end

The limited use of trichloroacetic acid on ICE-PICK scars, known as the chemical reconstruction of skin scars (CROSS), was first described by Lee et al.[16] They reported better results after the use of 100% TCA compared to 65% TCA, because in the TCA 65% group there was an excellent improvement in scars after six sessions and in the TCA 100% group after three sessions.[16] Brodland et al. showed that the use of TCA in high concentrations causes protein precipitation, coagulation necrosis of epidermal cells, and collagen necrosis of papillary and reticular dermis.[17] TCA-CROSS is an affordable treatment for atrophic acne scars, especially ICE-PICK scars, which are among the most resistant types of acne scars.[16,18] Despite the undeniable effect of this treatment, which has been confirmed in various studies and the present study, the use of this method is still less considered among dermatologists which is mainly due to stress, caused by not controlling over the complications, including PIH.[19] Accordingly, the limited use of this method was one of the major concerns of the authors of this study when designing this RCT. Therefore, we decided to use the combination of TCA-CROSS for the first time along with a topical drug and saline injection so that we can increase the attention to the use of this method by improving the aesthetic results and reducing the side effects.

## 5 | CONCLUSION

TCA-CROSS has been previously presented in several studies as an effective and economical method in improving atrophic scars, especially ICE-PICK scars; the results of the present study also demonstrated the effectiveness of this treatment in improving this type of scars, so that the number of scars decreased significantly in all treatment groups and on both treatment and control sides ($p$ value <0.001). Also, according to the results of this study, injection of 0.9% saline before TCA-CROSS is not recommended as a treatment method, because in the first group of patients (TCA + Saline) this method did not reduce the side effects of the treatment and slightly reduced the efficacy of TCA-CROSS treatment; however, the results of groups 2 (TCA-CROSS + Timolol) and 3 (TCA-CROSS + Saline + Timolol) showed that the use of 0.5% topical timolol solution in combination with TCA-CROSS can be used as an effective and safe treatment since this method could cause a slight increase in scar improvement (which was not statistically significant), and it also significantly reduced the duration of PIH (group 2 P-value = 0.016; Group 3 $p$ value = 0.002).

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## CONFLICT OF INTEREST

All the authors declare that there is no conflict of interest for this project.

## AUTHOR CONTRIBUTION

Concept and design and drafting: Mohammadreza Ghassemi, Mohamad Hasan Shahverdi; Acquisition and analysis and interpretation of data: Elham Behrangi, Fatemeh Sadat Hosseini-Baharanchi, Azadeh Goodarzi; All authors contributed to drafting the article and approved the final version to be published.

## DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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