

*Research Article*

## Therapeutic Efficacy and Tolerability of 30% Versus 70% Concentrations of Topical Trichloroacetic Acid in Patients with Xanthelasma Palpebrarum: A Randomized Clinical Trial

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### Abstract

**Background:** Xanthelasma palpebrarum (XP) is the most common cutaneous xanthoma. It is a benign lesion that appears as yellowish plaque near the inner canthus of the eyelid. There is still paucity of strong evidence for the single best effective treatment of XP. **Objective:** The aim of this study was to assess the clinical efficacy and tolerability of once application of two concentrations of topical trichloroacetic acid (TCA) (30% versus 70%) in treatment of patients with XP. **Methods:** This randomized clinical trial was conducted on patients presenting to Oculoplastic Clinic at Tanta University Eye Hospital. Patients with Soft and semisolid xanthelasma lesion at upper or lower eyelids were included. Forty patients were randomly distributed into 2 groups: Group 1 treated by once application of 30% TCA and Group 2 treated by once application of 70% TCA. **Results:** There was a statistically significant ( $p < 0.001$ ) improvement in group 2 compared to group 1. Excellent results where the skin of the lesion returned normal as the rest of the surrounding skin were significantly higher in group 2 (94.1%) than group 1 (14.7%). Group 2 showed absence of significant ( $p > 0.05$ ) association between the clinical outcome and the number, type, or size of the lesion. There was a statistically significant ( $p < 0.001$ ) increase in lid erythema in group 2 compared to group 1 (45.0% versus 0.0%, respectively). **Conclusion:** A single session peeling with TCA 70% was highly effective than TCA 30% in the treatment of xanthelasma palpebrarum patients whatever the number, type, or size of lesion. The only significantly reported side effect was lid erythema.

**Keywords:** xanthelasma palpebrarum; trichloroacetic acid; chemical cauterization; randomized clinical trial.

### Introduction

Xanthelasma palpebrarum (XP) is the most common cutaneous xanthoma. It is a common benign lesion that appears as yellowish plaque near the inner canthus of the eyelid. Lesions are usually evenly distributed, and may be single or multiple, nodular or flat and soft, semisolid or calcareous<sup>(1)</sup>. Prevalence of XP peaks in the 4<sup>th</sup> and 5<sup>th</sup> decades of life, and it is characteristically more prevalent in women (1.1%) than in men (0.3%), which may be linked to the hormonal factors<sup>(2)</sup>.

Xanthelasma palpebrarum results from the infiltration of the superficial reticular dermis by lipid-laden macrophages (foam cells), followed by inflammation and fibrosis. This commonly affects the medial area of the eyelids and may extend laterally, with a higher frequency in the upper lids<sup>(3)</sup>.

The exact cause is unclear. However, the appearance of xanthelasma has been linked to

certain medical conditions, including hyperlipidemia, diabetes mellitus, cardiovascular

diseases, and thyroid dysfunctions<sup>(4, 5)</sup>. There are conflicting opinions regarding its relation to hyperlipidemia. Elevation in the mean cholesterol or low-density lipoprotein cholesterol levels has been reported in approximately half of XP patients<sup>(6)</sup>. Though, it might be seen in patients with normal cholesterol and triglyceride levels<sup>(7)</sup>.

Xanthelasma persists once it is developed and does not spontaneously disappear. Rarely it causes functional problems, and most patients seek medical consultation for cosmetic concerns. Different modalities of treatment are currently available such as surgical excision, cryotherapy, chemical peeling with trichloroacetic acid (TCA) or bichloroacetic acid, radiofrequency, and laser ablation<sup>(8-10)</sup>. However, each of these methods has certain limitations and complications such as scarring,

skin discoloration or loss, besides failure of treatment with persistence of the lesions. So, there is still paucity of strong evidence for the single best effective treatment of XP<sup>(11)</sup>.

Therefore, the aim of this study was to assess the clinical efficacy and tolerability of once application of two concentrations of topical trichloroacetic acid (30% versus 70%) in treatment of patients with xanthelasma palpebrarum.

## Methods

### Ethical considerations:

The study protocol obtained approval from the Ethics Committee of the Faculty of Medicine, Tanta University. An informed written consent was obtained from each patient. Confidentiality of the patients' data was maintained by assigning code numbers to patients that were known only by the researchers.

### Study design and setting:

This randomized clinical trial was conducted on patients presenting to Oculoplastic Clinic at Tanta University Eye Hospital during the period from April 2015 to December 2016.

### Eligibility criteria:

We included patients aged  $\geq 20$  years who had soft and semisolid xanthelasma lesions at the upper or lower eyelids. Patients with calcareous xanthelasma lesions, dermatochalasis, and those asking for blepharoplasty were excluded.

### Study design:

We enrolled 40 patients who were randomly divided into 2 groups: Group 1 treated by once application of 30% TCA and Group 2 treated by once application of 70% TCA.

All patients were subjected to full history taking including personal history, complaints, past history (of diseases e.g. diabetes mellitus, hypercholesterolemia, and hypertension or intake of drugs e.g. anticoagulants, aspirin, or NSAIDs, which may predispose to xanthelasma or affect wound healing), and family history.

We conducted physical examination for evaluation of the skin condition and for assessment of the xanthelasma lesions including size, site, and consistency.

Patients were subjected to laboratory estimation of plasma lipid levels and preoperative clinical photography to document the existing eyelid and periorbital anatomy. Patients with hypercholesterolemia were referred to internal medicine consultation.

### Technique:

The margin of the skin lesion was outlined with a pen before topical application of a local anesthetic (Emla® cream 5%, a mixture of lidocaine 2.5% and prilocaine 2.5%) over the lesion. The affected area was cleaned with spirit and the surrounding area was coated with petroleum jelly. Then, applying TCA (30% in group 1 or 70% in group 2) by painting very thin layers onto the xanthelasma with the pointed tip of a wooden applicator stick in circular fashion with greatest amount of TCA at the margin of lesion after light frosting of the skin. Then, washing with copious amounts of water to end the reaction.

All patients were given combined topical antibiotic/steroid skin creams (betamethasone/fusidic acid) (Fusicort®, Leo) for two weeks, besides applications of topical cream that stimulate healing for cosmetically disfiguring scars (B-sitosterol) (MEBO®, Julphar) for 4-6 weeks.

Photographic documentation of lesion before treatment, immediately afterwards, and at each of the successive checkup visits was done. The follow up period was 6 months.

Cosmetic outcome was evaluated subjectively and objectively by grading the results (rating from satisfactory to excellent: excellent = the skin of the lesion returned normal as the rest of the surrounding skin; very good = the skin of the lesion returned nearly normal as the rest of the surrounding skin; good = the skin of the lesion had acceptable color; and satisfactory = hardly seen scar).

### Statistics:

Statistical analysis and presentation of data was conducted using SPSS (Statistical Package for the Social Sciences) version 22 computer program. Categorical data were presented as numbers and percentages and Fisher's Exact test was applied to investigate the association between categorical variables. For continuous data, they were tested for normality by Shapiro-Wilk test. They were normally distributed and were expressed as mean  $\pm$  SD and Independent T test was used for comparison between the studied groups. Level of statistical significance was considered at  $P < 0.05$ .

### Results

In the present study, 53 patients were assessed for eligibility, out of whom 13 patients were

excluded; 9 declined participation and 4 did not meet the inclusion criteria (Figure 1).

The study included 40 patients with xanthelasma palpebrarum affecting upper or lower eye lids. Table (1) shows the baseline characters of the studied groups. There was no statistically significant difference between the two studied groups regarding age, sex, history of DM or family history of the disease. It was observed that 55.0% of all patients had high low-density lipoprotein levels with no significant difference between both groups (p=0.525). likewise, there was homogenous distribution of the number of lesions in both groups. Macular lesions were more common than nodular ones (less than 1 cm<sup>2</sup> represented 30.88%, while more than 1 cm<sup>2</sup> were 33.82%).

There was a statistically significant improvement in group 2 than in group 1 (p<0.001). Excellent results with the skin of the lesion returned normal as the rest of the surrounding skin were significantly higher in group 2 (94.1%) than group 1 (14.7%). Whereas, less efficacy was observed in group 1; where satisfactory results with hardly seen scar and failure of treatment were found (23.5% and 8.8% respectively) (Table 2).

Table (3) shows absence of significant difference in clinical efficacy of treatment in patients with normal or high LDL levels in each of the studied groups (p>0.05). Additionally, Group 1 showed significant association between each of number, type, and size of lesion and the clinical outcome (p<0.05). Significantly higher percentage of excellent results were observed in single (80%), macular (100%), and in small (less than 1 cm<sup>2</sup>) lesions. Alternatively, Group 2 showed absence of significant association between the clinical outcome and the number, type, and size of lesion (p>0.05).

Concerning patient satisfaction, non-significantly higher percentage of patients in group 2 were satisfied than in group 1 (95.0% vs 70.0% respectively, p=0.154) as shown in table (4).

Table (5) shows ulcer healing time and tolerability of the treatment. The mean required time for healing of ulcers was 9.1±2.0 and 9.7±2.3 days in groups 1 and 2 respectively with no significant difference (0.359). There was a statistically significant increase in lid erythema in group 2 compared to group 1 (45.0% versus 0.0%, p <0.001). Mild lid edema was non-significantly higher in group 2 (45.0%) than in group 1 (35.0%).

**Table 1: Baseline characters of the studied patients.**

		Groups				P value
		Group 1 30% trichloroacetic acid		Group 2 70% trichloroacetic acid		
		N	%	N	%	
<b>Age (years) Mean±SD</b>		46.3±8.0		47.7±5.8		0.516
<b>Gender</b>	<b>Female</b>	14	70.0%	12	60.0%	0.507
	<b>Male</b>	6	30.0%	8	40.0%	
<b>Diabetes mellitus</b>	<b>No</b>	9	45.0%	8	40.0%	0.749
	<b>Yes</b>	11	55.0%	12	60.0%	
<b>Low density lipoprotein level</b>	<b>Normal</b>	10	50.0%	8	40.0%	0.525
	<b>High</b>	10	50.0%	12	60.0%	
<b>Family history</b>	<b>No</b>	8	40.0%	13	65.0%	0.113
	<b>Positive</b>	12	60.0%	7	35.0%	
<b>Number of lesions</b>	<b>1</b>	10	50.0%	10	50.0%	1.00
	<b>2</b>	7	35.0%	7	35.0%	
	<b>3</b>	2	10.0%	2	10.0%	
	<b>4</b>	1	5.0%	1	5.0%	

N: number, SD: standard deviation

**Table (2): Comparison of clinical efficacy in the two studied groups.**

		Groups				P value
		Group 1 30% trichloroacetic acid Number of lesions =34		Group 2 70% trichloroacetic acid Number of lesions =34		
		N	%	N	%	
Objective assessment of cosmetic outcome	Excellent	5	14.7%	32	94.1%	<0.001*
	very good	9	26.5%	1	2.9%	
	Good	9	26.5%	1	2.9%	
	Satisfactory	8	23.5%	0	0.0%	
	Failure	3	8.8%	0	0.0%	

\*Significant at p<0.05

N: number

**Table (3): Relation of clinical efficacy to LDL levels, type, size, and number of lesions in the studied groups.**

			Groups										P1		P2	
			Group 1 30% trichloroacetic acid Number of lesions = 34					Group 2 70% trichloroacetic acid Number of lesions = 34								
			Excellent	Very good	Good	Satisfactory	Failure	Excellent	Very good	Good	Satisfactory	Failure				
Low density lipoprotein level	High	N	2	6	6	5	3	24	0	0	0	0	0.415	0.080		
		%	40.0	66.7	54.5	83.3	100.0	75.0	0.0	0.0	0.0	0.0				
	Normal	N	3	3	5	1	0	8	1	1	0	0	0.006*	0.588		
		%	60.0	33.3	45.5	16.7	0.0	25.0	100.0	100.0	0.0	0.0				
Number lesions	1.0	N	4	2	3	1	0	8	1	1	0	0	0.035*	0.727		
		%	80.0	22.2	27.3	16.7	0.0	25.0	100.0	100.0	0.0	0.0				
	2.0	N	0	5	7	0	2	14	0	0	0	0				
		%	0.0	55.6	63.6	0.0	66.7	43.8	0.0	0.0	0.0	0.0				
	3.0	N	0	2	1	2	1	6	0	0	0	0				
		%	0.0	22.2	9.1	33.3	33.3	18.8	0.0	0.0	0.0	0.0				
4.0	N	1	0	0	3	0	4	0	0	0	0					
	%	20.0	0.0	0.0	50.0	0.0	12.5	0.0	0.0	0.0	0.0					
Type of lesion	Macular	N	5	7	5	6	1	17	1	0	0	0	0.035*	0.727		
		%	100.0	77.8	45.5	100.0	33.3	53.1	100.0	0.0	0.0	0.0				
	Nodular	N	0	2	6	0	2	15	0	1	0	0				
		%	0.0	22.2	54.5	0.0	66.7	46.9	0.0	100.0	0.0	0.0				
Size of lesion	Less than 1 cm <sup>2</sup>	N	5	6	8	0	1	19	1	0	0	0	0.004*	0.661		
		%	100.0	66.7	72.7	0.0	33.3	59.4	100.0	0.0	0.0	0.0				
	More than 1 cm <sup>2</sup>	N	0	3	3	6	2	13	0	1	0	0				
		%	0.0	33.3	27.3	100.0	66.7	40.6	0.0	100.0	0.0	0.0				

\*Significant at p<0.05

N: number

**Table (4): Comparison of patient satisfaction in the two studied groups.**

			Groups		P value
			Group 1 30% trichloroacetic acid	Group 2 70% trichloroacetic acid	
Patient satisfaction	Average	N	3	1	0.154
		%	15.0%	5.0%	
	Not satisfied	N	3	0	
		%	15.0%	0.0%	
	Satisfied	N	14	19	
		%	70.0%	95.0%	

N: number; SD: standard deviation

**Table (5): Comparison between the studied groups regarding ulcer healing time and tolerability of the two trichloroacetic acid regimens.**

			Groups				P value
			Group 1 30% trichloroacetic acid		Group 2 70% trichloroacetic acid		
Ulcer healing time (days)	Minimum		4.0		7.0	0.359	
	Maximum		12.0		15.0		
	Mean		9.1		9.7		
	SD		2.0		2.3		
Tolerability		N	%	N	%	P value	
Erythema	No	20	100.0%	10	50.0%	<0.001*	
	Mild	0	0.0%	9	45.0%		
	Moderate	0	0.0%	1	5.0%		
Edema	No	13	65.0%	11	55.0%	0.519	
	Mild	7	35.0%	9	45.0%		

\*Significant at p<0.05

N: number; SD: standard deviation

**Discussion**

This study revealed significantly higher improvement in patients treated with 70% TCA compared to those treated with 30% TCA. The use of higher concentration of TCA showed high efficacy with excellent outcomes in most (94.1%) patients compared to only 14.7% of patients treated with 30% TCA. Furthermore, cosmetic outcomes were significantly related to the number, type, and size of lesion only in case of TCA 30% application. However, lid erythema was significantly more common with TCA 70% compared to TCA 30%.

Trichloroacetic acid is an analogue of acetic acid and is characterized by a wide range of skin penetration. It has gained great attention in chemical peeling for cosmetic purposes<sup>(12)</sup>. In this work, two concentrations of TCA 30% and

70% were used by single application to investigate their efficacy and tolerability.

In this study, single application of 70% TCA showed high efficacy with excellent outcomes in most (94.1%) patients. In comparison, TCA 30% revealed only 14.7% excellent results besides the presence of satisfactory results and failure of treatment in 23.5% and 8.8% of patients, respectively. Likewise, Mourad et al.,<sup>(13)</sup> investigated the efficacy and tolerability of 35%, 50%, and 70% concentrations of TCA in the treatment of patients with XP. They concluded significantly higher clinical efficacy for TCA 70% that was associated with the least required number of sessions in the treatment of XP. Additionally, a prospective analysis of XP patients treated with 70% TCA after 6 months of follow up exposed excellent results in 45.8%

and good results in 33.3% of patients with high patient satisfaction<sup>(14)</sup>. Furthermore, a comparative study of radiofrequency ablation versus TCA application in the treatment of XP concluded comparable results. However, radiofrequency needed fewer sessions for achieving more than 75% clearance of lesions<sup>(15)</sup>. Moreover, 70% TCA application achieved similar efficiency and rate of complications to erbium: YAG laser ablation when used to treat different XP lesions on the same patient<sup>(16)</sup>. A more recent study favored the use of TCA application to reduce the size of extensive XP lesions before surgical excision<sup>(8)</sup>. Actually, the use of TCA application in the treatment of XP has the advantage of being simple, very cost-effective, and is easily accessible with all practitioners<sup>(17)</sup>.

Trichloroacetic acid produces superficial coagulative necrosis of epidermis and upper papillary dermis. Then, over several days, sloughing of these necrotic layers occurs with skin re-epithelization, followed by epidermal and dermal reconstruction with new collagen deposition<sup>(18)</sup>. Pathologic evaluation of XP lesions by Mittelviehhaus et al.,<sup>(19)</sup> demonstrated a thickness that ranged from 502.9 to 4429.5  $\mu\text{m}$  with about half of the specimens showing infiltration of the entire dermis. Thus, the use of TCA 70% in our study might be associated with an increased depth of peel that allowed for deeper regenerative changes with better outcomes. An earlier study of the histologic changes of the eye lid skin after TCA peeling stated that increased strength of TCA produced more depth of necrosis that reached the papillary dermis<sup>(20)</sup>.

In this study, TCA 70% produced similar results whatever the number, type (macular or nodular), or the size of lesion, whereas 30% TCA had significantly higher percentage of excellent results in single (80%), macular (100%), and in small (less than 1  $\text{cm}^2$ ) lesions. Compared to this finding, Mourad et al.,<sup>(13)</sup> reported nonsignificant relation between therapeutic efficacy and type of xanthelasma lesions treated with different TCA concentrations. However, they reported that TCA 50% was more effective in the treatment of macular xanthelasma, and TCA 70% was particularly effective in the treatment of papular lesions. Likewise, Haque and Ramesh<sup>(21)</sup> highlighted the relation between TCA concentration the clinical

response. They concluded that TCA 50% was sufficient for macular xanthelasma, TCA 70% was very effective in flat plaques, whereas TCA 100% was the best in papulo-nodular lesions.

Concerning tolerability of the treatment in this study, the only noted side effect after single application of TCA 70% was a significantly increased rate of lid erythema compared to TCA 30% (45.0% versus 0.0%,  $p < 0.001$ ). In agreement with this finding, higher frequency of scarring and pigmentation were reported with radiofrequency ablation than with TCA use at 4 weeks of follow-up of XP patients<sup>(15)</sup>. The previously reported serious side effects of chemical peeling using TCA such as scarring, hypo or hyperpigmentation, ectropion, ulceration, or burns<sup>(13, 14, 22)</sup> were not recorded in our study. There is still a controversy regarding the relation between TCA concentration and the incidence of these complications<sup>(11)</sup>.

Xanthelasma was found to be associated with dyslipidemia, and it has been recommended that XP patients should check their lipid profile and receive diet control and lipid-lowering medications for better outcomes and to minimize recurrence of the lesions<sup>(23)</sup>. In this work, there was a nonsignificant relation of cosmetic outcomes to LDL levels. In contrast, Mourad et al.,<sup>(13)</sup> found a significant improvement in patients with normal lipid profile compared to those with lipid profile abnormalities. It has been suggested that extravasation of lipids to the surrounding tissue is aggravated by some factors such as increased heat, physical movement, and friction<sup>(24)</sup>.

## Conclusion

A single session peeling with 70% TCA was highly effective compared to 30% TCA in the treatment of xanthelasma palpebrarum patients whatever the number, type, or size of lesion. The only significantly reported side effect was lid erythema.

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