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Original Research Article

Botulinum Toxin Type A Effects on the Treatment of Keloid Lesions: Comparison of Intralesional Two Different Doses

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ABSTRACT

Background: Keloid is a lesion that creates from the excessive restoration of the scar and has beauty and functional complications for patient and changes their quality of life. Today, varieties of methods are used but because of lesion recurrence, patients' problems last. In this study, the two different doses of botulinum toxin type A, impact on the treatment of keloid lesion has been investigated.

Methods: In this double blind clinical trial, 43 patients with keloid lesions were interfered from August 2014 to May 2016. Patients were randomly divided into two groups. Each patient received BTX-A with concentration 200 units per ml and dose of 10 or 20 units per cubic centimeter lesion in a part of the lesion. In another part of the lesion, normal saline was injected with the same volume. Injections have been done monthly to three times. Patients were evaluated 9 months after the last injection, according to the Vancouver scar scales and Results were analyzed in both groups.

Results: The average Index of pigmentation in the first intervention group reduced to 0.64 and in the second intervention group, it reduced to 0.74 (P <0.01). Pliability of lesions had a statistical significant reduction than before in both groups of intervention, but, but there was no significant difference in height index of lesion (P = 0.72).

Conclusion: Injection of botulinum toxin type A in keloid lesions, not as a stand-alone method, but in ancillary of other therapy procedures such as surgery, can be useful in the management of symptoms caused by keloid lesions.

Keywords: Botulinum Toxin Type A, Keloid, Vancouver Scar Scales.

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INTRODUCTION

Keloid lesions and hypertrophic scars are the skin repair complications and they are resulting from an increase in Fibroblasts activity in improving skin lesions.[1] They may create pain, itching, and burning sensation. Hypertrophic scar had less size than one centimeter while larger lesions that are usually out of the wound edges, are called keloids. Genetically, it has an autosomal dominant trait with incomplete penetrance.[2] These lesions may occur from surgery, burns, acne, shingles, scratches, Tattoo, ear piercing or even spontaneously. Some body parts such as ears, the front of the sternum and upper back, are more prone to it.

In terms of histology, increased epidermal thickness and the absence of rete ridge occurs. The collagen deposition and glycoproteins will increase.[3] In keloid, fibers are connected loose to each other, their direction to the epithelium was random, and collagen fibers are larger and thicker than normal. The fibroblasts have normal proliferation, but their ability to produce collagen is twenty times more than the normal fibroblasts. These cells react to lower concentrations of transforming growth factor beta type (TGFβ).[2,3] Wound healing consists of four steps: 1-hemostasis 2-Inflammation 3- proliferation 4- maturation.[4] The first cell that enters into a wound is the platelets. After tissue damage, vessels are ruptured and blood enters the environment and with clots, it leads to activation of the coagulation system and the formation of fibrinogen and ultimately fibrin.[5] The second phase, inflammation begins from the moment of injury and continues up to 3 days. 24 hours later, monocytes entered into the wound and turned into macrophages and by secreting cytokines and growth factors, they perform the wound cleansing action.[6] The third stage proliferation starts from the fourth day. New blood vessel formation, cell proliferation and the formation of granulation tissue and collagen production are at this stage. From the fourth day, fibroblasts start to produce collagens that evolve to fibrous strings outside of cells and give power and strength to tissues.

We have 18 types of collagen in the body that the most common type is Type I. Type III secreted in a wound first and then gives its place to type I.[7] During the 6 to 12 months later, the amount of collagen will not change and they just become regular. After 6 weeks, the wound strength approached to 80% of normal tissue and after 12 months, the wound power reached its maximum level, but it will not reach the healthy skin before in terms of the healing power. During this period, the maturation of wound occur which means collagen will become regular shape and scars get soft.

Keloid lesions have unpleasant appearance and concern the patients. Therefore, treatment goals include relief of symptoms, restore function to the damaged area and prevent relapse. Today, many treatments used to these aims. Massage, pressure garments, intralesional corticosteroid injections, surgery, topical retinoid, injection of interferon and 5-fluorouracil in the lesion are used alone or with corticosteroids and bleomycin injection.[8-10] Triamcinolone acetonide is commonly used,[11] but this method has side effects such as hypopigmentation, skin atrophy and telangiectasia.[12] However, since the underlying causative mechanisms are not fully understood, treatment is not associated with high success.

One of the new treatments is injecting Botulinum toxin type A (BTX-A) in the lesion. This toxin will be produced by Clostridium botulinum that is anaerobic gram-positive bacterium.[13] For the first time, a German poet and physician called Justinus Kerner (1786-1862), suggested the idea to the therapeutic use of the toxin. In those days, they called it "sausage poison" because first this poisoning was caused by consumption of infected sausages.[14] BTX is divided into seven types from A to G that have a similar structure, but different in terms of antigen and antibody. American Food and Drug Administration (FDA) in 2002 confirmed the use of Botox called Cosmetic Botox for the temporary improvement in the appearance of moderate to severe frown lines in people 18 to 65 years of age.[15] After the injection of this toxin, it deploys at the end of the nerves or synapses and prevents the release of chemical mediators Acetylcholine which is responsible for muscle contraction and in fact, some temporary muscle paralysis will happen that last 3 to 6 months.[16]

In recent years, BTX-A has been used in the treatment of hypertrophic scars and keloid and the results of these studies indicate its relative effects on improving symptoms and preventing recurrence of the lesions.[17,18] Due to the limited number of studies available, this study has reviewed the effects of BTX-A in the treatment or improvement of keloid lesions symptoms based on Vancouver Scar Scales.

PATIENTS AND METHODS

This study is a prospective randomized controlled trial with human samples. 43 patients with keloid lesion of plastic surgery clinic of our hospital were studied from the August 2014 to May 2016. Patients were randomly assigned to one of two groups, first (23 patients) or second (20 patients). The lesion was randomly divided into two portions in each patient. In one part (the first group), the BTX-A (Disport made in England, the manufacturer company IPSEN) at a concentration of 200 units per ml and a dose of 10 units per cubic centimeter lesion for the and a dose of 20 units per cubic centimeter lesion for the second group injected and on the other side of the lesion (control group), normal saline injection was carried out with the same volume. Randomization based on quaternary numbers blocking was done by computer software. The injectable solution (normal saline or BTX-A) was prepared in the same syringe by the supervisor. One part code lesion was given to each syringe that only supervisor aware of it and the researcher and patient did not aware of syringe content. The injection was repeated every one month and up to three times. The patients were evaluated according to Vancouver Scar Scales (VSS), 9 months after the last injection by three plastic surgeons who did not know the type of injection. In VSS, pigmentation index was rated from 0 to 2, vascularity from zero to 3, the height from 0 to 3 and the pliability index from 0 to 5 points. Zero shows normal state and the higher number show more distance than normal state.

The study variables included patient age, sex, lesion location, the time it develops and the four criteria of Vancouver. Inclusion criteria for the study: patients with keloid, older than 12 years, patients consent to participate in the study with knowledge of the conditions and its implications.

Exclusion criteria for the study: lack of patient satisfaction in doing a research intervention, sensitivity to BTX-A, pregnant and breastfeeding women, patients with neuromuscular diseases and any contraindications to the use of BTX-A (such as local infection). In this study, patients' identity and secrets were preserved, and in the case of photography, their identity was not revealed. Consent to participate in the study was obtained from patients or their guardians.

Photographs and other steps of intervention and research was done free of charge for patients. This study has the confirmation code of the ethics committee at University of Medical Sciences. The results and findings were analyzed in terms of the relationship between the control group and control with the study variables, with SPSS software and the significant level of $P < 0.05$ was considered.

RESULTS

The first group findings

In the first group, 23 patients with keloid were entered into the study. The mean age of patients was 24.5±6.5 years (age range 18-35 years). In this group, there were 10 male patients (43.5%) and 13 female patients (56.5%).

Table 1 shows the patients' demographic data and variable. Average time of lesion formation was 28.08 months and the average time of last treatment intervention in patients receiving other interventions was 9.5 months. No significant relationship was observed between the causative reason of lesion with the response therapy in both control and experimental groups ($P = 0.9$).

Also, there was no significant relation between the location of keloid and level of improving symptoms ($P = 0.7$). Vancouver quartet features were evaluated in both groups of intervention and control. The average pigmentation index in the first intervention group reduced from 1.78 to 1.14 (reduction of 0.64 points and $0.01 > P$) (Fig. 1).The average vascularity index of the group one, decreased 0.90 ($0.01 > P$). There was a statistically significant decrease in the pliability index than before, but in the height of lesions, no significant change occurred ($P = 0.32$). These variables in the first control group had no significant difference before and after the study. The data are shown in table 2.

Table 1: Patient Characteristics

Characterstic	Group 1	Group 2
No. of Patients	23	20
Mean age (Year)	24.5 6.5	26 10
Sex (No/%)		
Male	10 (43.5)	6 (30)
Female	13 (56.5)	14 (70)
Mean Duration from Lesion Formation, Months	28.08 0.8	29.00
Cause of Lesion (No/%)		
Burn	6(26)	7(35)
Surgery	10(43.4)	9(45)
Infection	2(9)	3(15)
Trauma	5(21.6)	1(5)
Location		
Ear	5(21.73)	4(20)
Neck	2(8.7)	2(10)
Chest	6(26)	5(25)
Back	2(8.7)	3(15)
Upper Ext.	5(21.73)	3(15)
Lower Ext.	3(13)	1(5)
Inguinal	0(0)	2(10)
Previous Intervention		
Surgery	21(91.3)	17(85)
Silicon Therapy	3(13)	1(5)
Pressure Garment	5(21.7)	4(20)
Triamcinolone Inj.	21(91.3)	19(95)
Surgery+ Triamcinolone Inj.	15(65.2)	16(80)
Multiple	19(82.6)	13(65)

Table 2: Mean VSS scores in two groups

VSS PARAMETERS		BEFORE		AFTER		DIFFERENCES		P value	
		Case	Control	Case	Control	Case	Control	Case	Control
Pigmentation	**A***	1.78	1.78	1.14	1.77	0.64	0.18	0.01	0.20
	B*	2.00	2.00	1.26	1.89	0.74	0.11	0.01	0.06
Vascularity	**A**	2.53	2.53	1.68	2.3	0.90	0.17	0.01	0.23
	B	2.43	2.43	1.70	2.22	0.73	0.21	0.01	0.29
Pliability	**A**	3.66	3.66	2.73	3.44	0.93	0.22	0.01	0.24
	B	3.98	3.98	3.08	3.89	0.99	0.09	0.20	0.72
Height	**A**	2.13	2.13	2.04	2.09	0.09	0.04	0.34	0.55
	B	2.42	2.42	2.23	2.39	0.19	0.03	0.72	0.93

A*: The first group which received $10^{u/cm3}$ BTX-A, B*: The second group which received 20u/cm3 BTX-A
Control group: received normal saline.

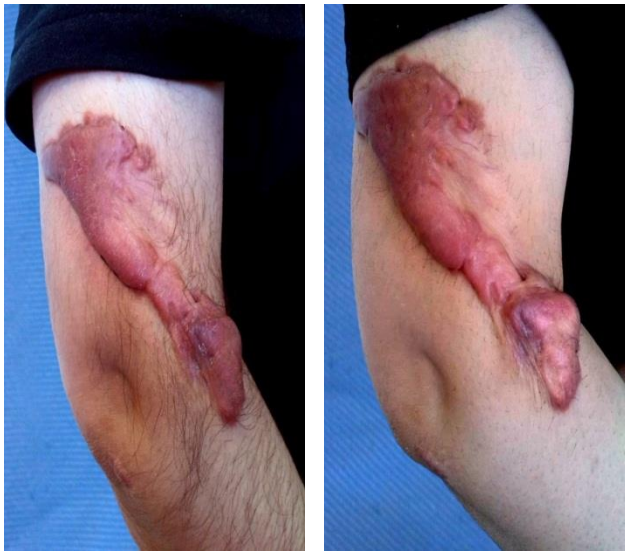

Fig 1: (Left) Keloid lesion on the lateral side of the right arm & elbow of 32-year-old woman who under gone injection of BTX-A $10^{U/Cm3}$ of lesion (group 1) in distal part of it. (Right) 9 months after last injection. Note hypopigmentation in distal part.

The second group findings

A total of 20 patients with keloids and a mean age of 26±10 years were studied. 65% of patients were under multiple interventions before the injection of BTX-A, but after a while, their lesion recurred. In this group (group II) average time of lesion formation was 29 months and the average time of last treatment intervention in patients was 10 months.

There was no relationship between the location of keloid and improvement of symptoms (P = 0.9). According to VSS, the average of the pigmentation index in the second intervention group decreased from 2 units to 1.26 units (a reduction of 0.74 units and 0.01> P) (Figs. 2 and 3).

The average of vascularity index decreased 0.73 (0.01> P). Lesion pliability had a statistically significant reduction than before, but the height of the lesion had no significant difference (P = 0.72). The variables in the second control group had no statistically significant difference before and after the study. In other words, from four indices of Vancouver, three indices of lesions color, vascular status and its consistency to BTX-A injections had a significant response (Fig.4).

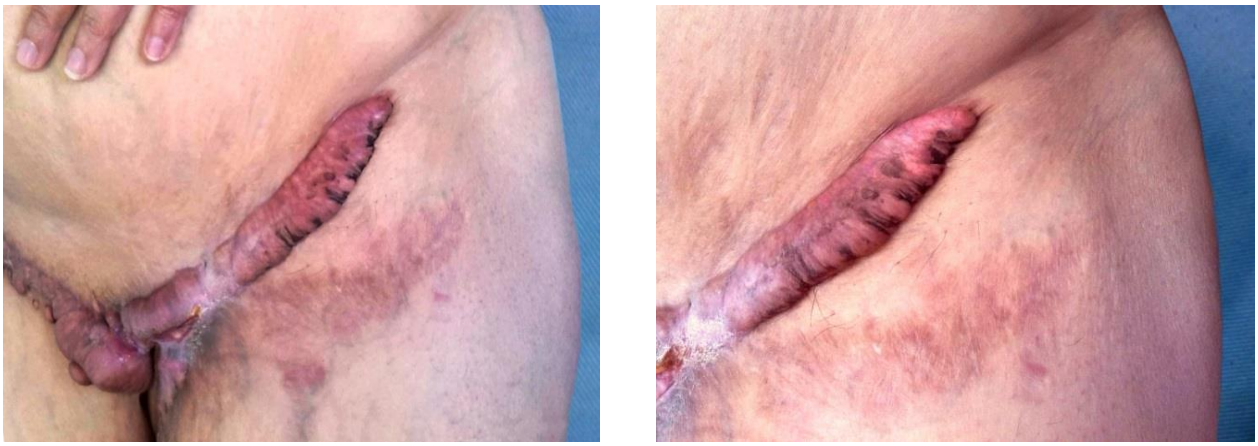

Fig 2: A 30-year-old woman before (left) and 9 months after (right) injection of 20 $^{U/Cm3}$ of BTX-A (group 2) in top of her inguinal keloid lesion. Some hypopigmentation and softening in top-left side of the lesion.

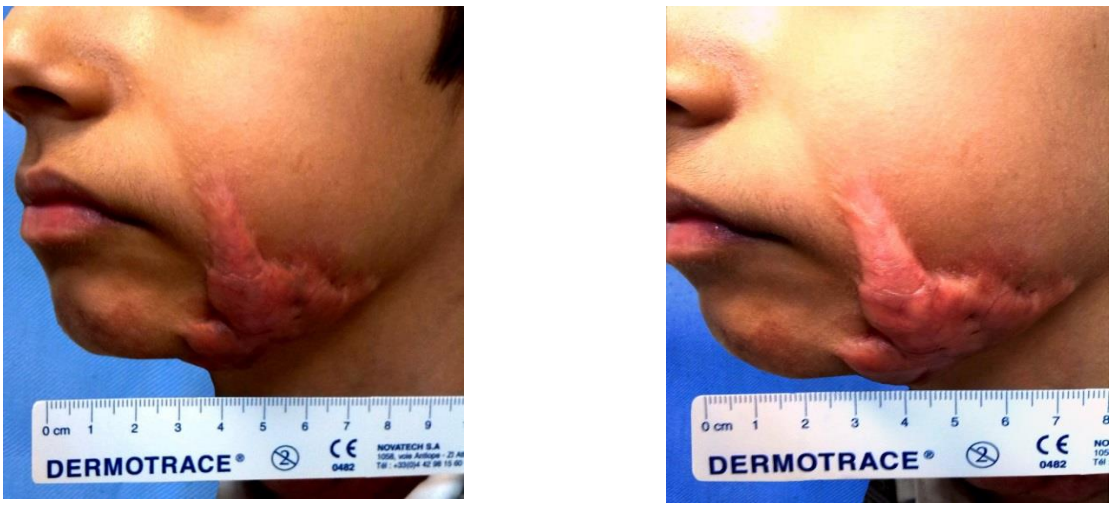

Fig 3: (Left) Keloid lesion on the left check of a 14-year-old boy before injection of BTX-A (group 2). (Right) Nine months later, hypopigmentation and softening of the top of the lesion were be detected.

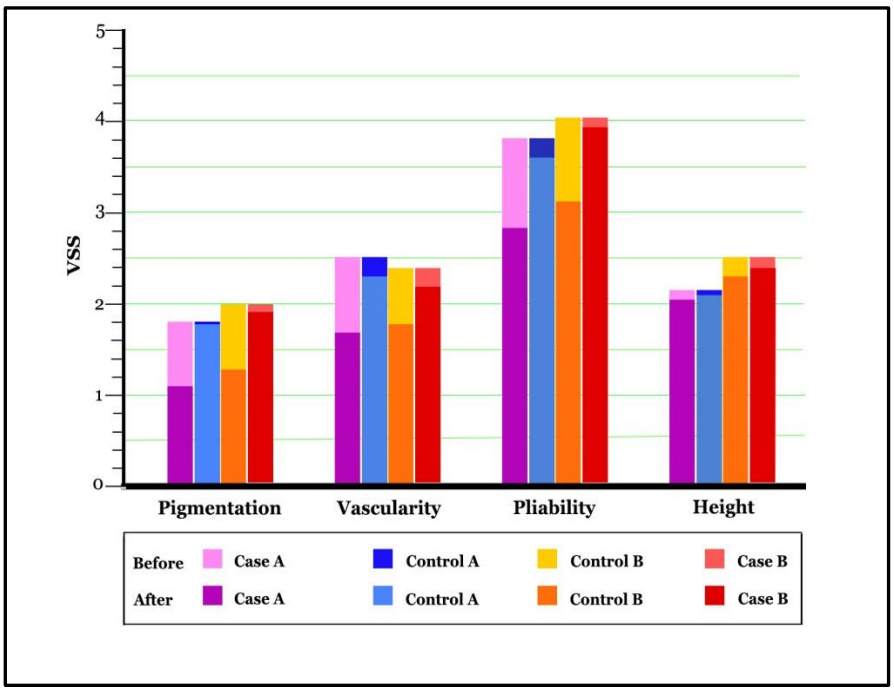

Fig.4: Vancouver Scar Scales for lesions: Pigmentation, Vascularity, Pliability and Height in both case and control groups. Except in Height index, others indices had significant changes. (p<0.05)

DISCUSSION

Keloid lesions occur as a result of excessive wound healing and contemplate the problems of physical, emotional, functional and beauty.[1] What patients with these lesions expect is shrinking and even blurring of the lesion. More patients act in one or multiple therapy methods for their lesion treatment, but they refer later because of recurrence.

Today, many treatments are used for the prevention and treatment of keloid such as Massage and pressure therapy, triamcinolone injection, surgery and a combination of these.[9,10] In new methods, the use of BTX-A has been raised. In this method, with repeated injections and in various distances, its effectiveness will be investigated for treatment of keloid.[17,18]

Xiao and colleagues[19] showed in 2010 that Botox works by temporarily paralyzing muscles and reduces tension and causes a decrease in TGF-β1 and proliferation of fibroblasts in the wound. In this way, the scar of wound restoration will be smaller and more delicate.

Gassner[20] and Wilson[21] conducted a separate study showed that the injection of BTX-A (Botox, Allergan) in the muscles around the wound will heal faster and less scar than placebo.

In the study of Andrew J[22] in 2012, Northern Ireland, 12 patients with colloid were injected, 20 to 100 units of BTX-A on their lesions. After follow-up period, and based on average VSS, the average in size, color, and lesions sign were evaluated that had a significant reduction.

Zhibo and colleagues[23] achieved good results in the treatment of 12 patients with keloid. They injected BTX-A with a concentration of 35 units per milliliters with the dose of 2.5 units per cubic centimeter of lesion in units in the keloid lesions three times monthly and followed the patients for 6 months. The therapy outcome was divided into several categories: those with a good response was 5 patients, average response was 4 patients, 3 patients gave an excellent response to the treatment and no relapse case has been reported at six months follow-up. Our study method, the method used in this study is similar, with the difference that, firstly, in our study, two groups received different doses of the toxin. Second, in any group, a lesion or part of it was selected as the control group as the same group.

In Gauglitz study,[24] 2012 in Munich of Germany, 4 patients with keloid were injected by the BTX-A. Injections were performed every 2 months for 6 months and the results were examined in terms of its effect on the size and volume of lesions. In the end, no result was seen an evidence the effects of BTX-A on keloid lesions and molecular index. The study because of the small sample size, 4 intervention patients, seems to have a bias in the conclusion. On the other hand, it had a short follow-up period and did not use Vancouver Scar Scales for final evaluation. Therefore, there is a need to study more inclusive. Also in this study, metabolism and fibroblasts proliferation in the lesion, the amount of collagen, TGF-β1 and smooth muscular fibers of alpha (α-SMA) were evaluated by genetic PCR but no result was seen to indicate the effect of BTX-A on them and this is in contrast to results obtained with the Byung -Joo Lee and colleagues.[25] They showed that BTX-A is effective in reducing fibrosis of the wound. Their study was done on 15 laboratory rats in both groups. In one group, Botox was injected into the wound behind the animal and the wounds of the second group were monitored. In this study, the diameter of the wound, amount of fibrosis and inflammation, the amount of cell proliferation and the amount of TGF-β1 were studied. In the group receiving Botox, the wound diameter was significantly different and the inflammation was less in the second week. The amount of fibrosis and the number of fibroblasts was lower ($P < 0.05$). Also in this group, in the eighth week, stronger collagen was made and the amount of TGF-β1 was significantly low.

In Xiao Z. and Zhang F. 2009 study,[26] in 19 patients with hypertrophic scar lesions, BTX-A were injected in lesions. The injection was repeated three times monthly. Then, patients were followed for 6 months. A satisfactory result has been declared in this study, so that 4 patients had good results and 15 patients had excellent results. Average redness of lesions decreased from 3.41 to 1.23. Average consistency of the masses decreased from 3.85 to 0.78 and the itch decreased from 3.5 to 0.83. However, this study emphasizes that further studies should be taken to prove the effectiveness. In their study, VSS was not used to assess the patients.

Currently, there are various methods for measuring the results of the intervention and comparing them together. The most common application of these methods is Vancouver Scar Scales. This method was defined for the first time in 1990 by the Sullivan[27] for the characterization of a scar in Burn Patients that later due to its appropriate and comprehensive in determining the properties of scar lesions and keloid, it was used for burning reasons.

Among the positive points of the study is using VSS in the final evaluation of lesions. The other strong and positive point of this study is having two groups of control and experimental in each group and another point is the strength of intervention with two different doses of BTX-A which was not performed in previous studies. The limitations of this study were the intervention on resistant and old lesions so that most patients were under a variety of treatment interventions.

However, intervention in both groups showed the effects of intralesional injection of BTX-A as softer lesions and changes in color. After three monthly injections of BTX-A, the patients' evaluation were done in ninth months by observers and based on VSS. In this study, there is a significant correlation in reducing pigmentation and the vascularity index of the lesion. The average of the vascularity index in both groups decreased 0.9 units and the average of Pigmentation decreased 0.74 units ($0.01 > P$), but this relationship was not significant in the reduction of lesion height ($P = 0.32$). In other words, it can be concluded that BTX-A has been able to bring pigmentation lesions closer to natural skin and the average of lesion pliability in the two groups decreased almost one unit and this means softer lesion after the injection of Toxin ($0.01 > P$).

CONCLUSION

It seems that the injection of BTX-A in keloid lesions as an independent and a single method of treatment did not fade or make the lesions smaller but using it along with other methods of treatment such as surgery can be useful to control and improve symptoms caused by scar.

The authors' propose to achieve a better and more result that is accurate is studying with more patients, longer follow-up and intervention in fresher lesions.

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