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"Botulinum toxin versus 5-flurouracil in the management of keloids and hypertrophic scars "

Authors

Fatma Abd Allah Rihan [1], Mohamedmed Mahmoud Elbaz [2], Mamdouh Morsy Abdel-gawad [3], Mostafa Mohamed Ghoneim [2]

[1] Dermatology and Andrology department

[2] Faculty of medicine Port said University

[3] Dermatology and Andrology department, faculty of medicine, Port-Said university, Port-Said, Egypt

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https://muj.journals.ekb.egdean@med.psu.edu.eg
vice_dean_postgraduate@med.psu.edu.eg

ABSTRACT:

Background: Keloid and hypertrophic (HT) scars are frequent complaints in dermatological practice. Patients and doctors may experience severe distress due to these lesions, which sometimes are difficult to cure clinically.

Aim of the work: Our study was aiming for comparing the efficacy and safety of Botulinum toxin type A (BXT-A) and 5-fluorouracil (5-FU) in management of keloids and HTS.

Patients and methods: The study was carried out on 20 cases with keloid and hypertrophic scars; they were allocated into two groups: 1st group was given intra-lesional botulinum toxin type A every one month, while the 2nd group was received weekly intra-lesional 5-Fluorouracil.

Results: Both IL botulinum toxin type A and 5- Fluorouracil were found to be effective and safe in the management of keloids and hypertrophic scars. Patients who were treated with Botulinum toxin type A, experienced less complications in comparison to patients who received 5-fluorouracil *:* less pain, no hyperpigmentation & less ulceration.

Conclusion: Our study found that the use of IL BXT-A and IL 5-FU therapeutic modalities in the management of keloids and hypertrophic scars are effective and have tolerable adverse effects.

Keywords: Botulinum toxin A and 5-fluorouracil, keloid, and hypertrophic scars.

INTRODUCTION

Keloid and hypertrophic scars (HTS) are common dermatologic problems. These cases are clinically difficult to treat and can be a cause of major challenge for both patients and doctors [(1)].

Lesions show no sex differentiation, but mainly appear in youths, white race have low probability to hypertrophic scars and keloids than Negros and Asians and if they acquired such lesions, they are less prone to be worse as those in more liable people [(2)].

Hypertrophic scars and keloid are induced by cutaneous irritation and injury .Superficial injury that above the reticular dermis doesn't induce keloidal and hypertrophic scarring. Those lesions have chronic and histologically local inflammation. So, the reticular layer of keloids and hypertrophic lesions has inflammatory cells, high numbers of fibroblast. There are predisposing factors include a group of local, generalized , and hereditary agents [(3)].

Hypertrophic lesions are usually elevated, although rarely exceed four mm above the skin; red or pink in appearance; firm; and itchy, scars do not cross the general geographic limits of the lesions and tend to decrease with time. Keloidal lesions tend to enlarge with time and invade the near tissue. Keloids appear as hard, slightly painful, bosselated swelling with a glistening surface and sometimes telangiectasia ,The colour is purple to pink and sometimes associated with hyperpigmentation[(4)].

Preventions and treatment strategies in keloid and hypertrophic scars mainly focus on reducing inflammation by: closing of the wound without tension, flavonoids, silicone sheeting. Current treatments: scar revision ,steroids ,radio therapy ,cryotherapy&5 fluorouracil .Future emerging treatments include; Mesenchymal stem cell therapy ,fat grafting ,interferon, botulinum toxin type A, Bleomycin [(5)].

Botulinum toxin, a protein neurotoxin, is generated by the anaerobic spore forming bacterium Clostridium botulinum. It has been applied to blepharospasm, hyperhidrosis, squint, and facial markings [(6)]. By lowering the amount of muscular tension that affects the healing wound, BXT-A can lessen scarring. It could lead to modifications in the cell cycle of fibroblasts originating from the hypertrophic scar in the cell cycle as well as alterations in the muscle spindle that could result in changed sensory inputs [(7)].

5-fluorouracil is a pyrimidine analogue, also can mask the effects of tumour growth-beta 1 and type I collagen gene expression. There is dose related link between decrease in the proliferation of keloid fibroblasts, the fibroblast-populated collagen, and 5 fluorouracil [8].

AIM OF THE WORK: This study compares the safety and efficacy of 5-fluorouracil and botulinum toxin type A in the management of HTS and keloids.

PATIENTS AND METHODS:

Under the supervision of the dermatology department staff at PortSaid University, **a comparative experimental study** was applied on twenty patients who attended to the outpatient clinics of Dermatology in-between October 2022 and October 2023 and had hypertrophic scars and keloids. All patients had their informed written consent obtained after a discussion of the risks, benefits, and any consequences. It was also accepted by the Institutional Review board (IRB) of The Faculty of Medicine, Port Said University (code no DRM818_004).

Sample size:

The sample size was determined using the following equation: [9]

$$\mathbf{n = 2\left(\frac{Z_{\frac{\alpha}{2}} + Z_{\beta}}{P_1 - P_2}\right)^2 x\, P(1-P)}$$

Where:

n = sample size

Zα/2 = 1.96 (The critical value that divides the central 95% of the Z distribution from the 5% in the tail)

Zβ = 0.80 (The critical value that separates the lower 20% of the Z distribution from the upper 80%)

P_1 = proportion of excellent improvement in large sized keloid lesions among patients who had intra-lesional botulinum toxin-A = 75% [10].

P_2 = proportion of excellent improvement in large sized keloid lesions among patients who had intra-lesional 5-Fluorouracil = 0 % [10].

q = 1-p

Therefore, the calculated sample size was 8 participants in each group. However, after adding 10% dropout the calculated sample size was10 participants in each group.

Inclusion criteria: cases had keloid or HTS due to any etiology, with scar age at least 6 months.

Exclusion criteria: Individuals who had undergone further keloid therapy in the previous four months, instances of current local infection, women who are pregnant or nursing, cases with antecedent cardiovascular, hepatic, renal, or neuromuscular disorders, individuals taking drugs that inhibit neuromuscular transmission (such as calcium channel blockers, aminoglycosides, penicillamine, and quinine) as well as those experiencing a botulinum toxin allergy.

The following was applied to each participant:

Complete history taking includes personal history; current hypertrophic scars or keloid history, including (onset, duration, colour, and distribution);

past medical history, including any skin diseases or disorders; past medication history; drug allergies; and family history**.**

Local examination: number of lesions, location, and size.

Protocol of treatment: cases were divided into 2 groups.

Group (1): IL- BXT-A injection was used to treat ten patients with keloid and hypertrophic scar. 2.5 U/cm3 was the dose, and several injections were spaced 1 cm apart. Intra-lesional injection of botulinum toxin type A (Irvine ,Botox Allergan, C A; 100U vacuum dried powder in a single use vial for reconstitution diluted in 2mL of sterile, preservative free 0.9 % saline to constitute a solution at a concentration of 4U/ 0.1 mL) and maximum dose of 100 units per session with monthly interval for a total of four months .

Group (2): Ten cases were treated with IL injection of 5-florouracil and it was weekly administered at (fifty mg / ml). Several injections were given at 1cm apart on average 0.2–0.4 ml /cm3. The injected dose was adapted according to scar size. The maximum dose was two ml per session with weekly interval, until reaching complete flattening of the lesion or for a maximum of six sessions whichever will be nearer.

We used a disposable insulin syringe in both treatment groups. No analgesic or sedative was administered prior to the session.

Clinical evaluation:

The effectiveness and safety of the treatments were reviewed by the Vancouver Scar Scale (VSS) and the opinions of two medical professionals. The VSS includes assessment of pigmentation, pliability , height, shape ,and vascularity of the keloid [(11).]

Table (1): **Vancouver Scar Scale (vss)** [(11)]

Pigmentation (0–2)	Normal	0
	Hypopigmentation	1
	Hyperpigmentation	2
Vascularity(0–3)	Normal	0
	Pink	1
	Red	2
	Purple	3
Pliability(0–5)	Normal	0
	Supple	1
	Yielding	2
	Firm	3
	Banding	4
	Contracture	5
Height(0–3)	Normal(flat)	0
	0–2mm	1
	2–5mm	2
	>5mm	3

At the finish of the study, patients' satisfaction will be ranked as follows: excellent (improvement of more than 75%), good (improvement of 50–75%), moderate (improvement of 25–50%), and poor (improvement of less than 25%)[(12).]

Complications and side effects (pain, pigmentation changes, and ulceration) were noted.

STATSTICAL ANALYSIS:

Data were entered into the computer and analyzed using **IBM SPSS software, version 20.0.(IBM Corp, Armonk, New York)** percent and number were used to describe qualitative variables. The **Shapiro Wilk test** assessed the normality of the distribution.

Quantitative data were described using range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR). The 5% level was used to determine the significance of the results. The tests that were used: **Chi square test** for categorical information when comparing both groups. **Monte Carlo correction or Fisher's Exact** when above 20 percent of the cells have an expected count of less than 5, chi-square must be corrected. **Student t-test** when comparing two groups under study with normally distributed quantitative variables, **Mann Whitney test** for comparing both groups under study using quantitative variables that have an irregular distribution.

RESULTS:

Our study was carried out on 20 cases with an age mean of group 1 were 36.30 ± 19.24 and it was 17.40 ± 4.22 for patients of group 2.

Table 2: Comparison between studied groups regarding site and sizes of lesions.

The mean of Vancouver scar scale for patients at the start of the treatment; group 1 was 7.00 ± 1.89 and it was 9.20 ± 1.55for patients of group 2, and this was statistically significant(p value=0.011) **Table(2).**

Table 2: Comparison between studied groups regarding Vancouver scar scale Prior to treatment

Vancouver scar scale Pre		Group 1	Group 2	Test value	P-value
		No. = 10	No. = 10		
Vascularity	Range	0 – 2	1 – 2	-0.935	0.350
Pigmentation	Range	0 – 2	0 – 2	-1.378	0.168
Pliability	Range	2 – 3	2 – 5	-2.770	0.006
Height	Range	1 – 3	2 – 3	-1.161	0.246
Total	Mean ± SD	7.00 ± 1.89	9.20 ± 1.55	-2.851•	0.011
	Range	4 – 9	7 – 11		

Spearman coefficient, statistically significant at $p \leq 0.05$

The mean of Vancouver scar scale for patients one month after the treatment; group 1 was 2.90 ± 0.99 and it was 3.40 ± 1.58 for patients of group 2, and this was statistically insignificant **Table(3).**

Table 3: Comparison between studied groups regarding Vancouver scar scale Post treatment.

VSS Post		Group 1	Group 2	Test value	P-value
		No. = 10	**No. = 10**		
Vascularity	Range	0 – 1	0 – 1	-0.503	0.615
Pigmentation	Range	0 – 1	0 – 2	-0.750	0.453
Pliability	Range	0 – 1	0 – 3	-0.608	0.544
Height	Range	0 – 2	0 – 2	-0.376	0.707
Total	Mean ± SD	2.90 ± 0.99	3.40 ± 1.58	-0.848•	0.408
	Range	1 – 4	2 – 7		

Spearman coefficient, statistically significant at $p \leq 0.05$

Regarding the two-doctor assessment, the first doctor assessment (90.0% of the patients in group 1 improved, while 60.0% improved in group 2), and this was statistically insignificant. The Second doctor assessment (90.0% of the patients in group 1 improved, while 80.0% improved in group 2), and this was statistically insignificant **Table (4)**.

Table 4: Comparison between studied groups regarding two doctor assessments

Two doctor assessment		Group 1		Group 2		Test value*	P-value
		No.	**%**	**No.**	**%**		
1st doctor	Improved	9	90.0%	6	60.0%	2.933	0.231
	Markedly improved	0	0.0%	2	20.0%		
	Slightly improved	1	10.0%	2	20.0%		
2nd doctor	Improved	9	90.0%	8	80.0%	3.059	0.217
	Markedly improved	1	10.0%	0	0.0%		
	Slightly improved	0	0.0%	2	20.0%		

Spearman coefficient, statistically significant at $p \leq 0.05$

Regarding the Patient satisfaction there were four cases who were satisfied with an Excellent degree and six cases who were satisfied with an Good degree, in Group 1, while in group 2 there were two cases who were satisfied with an Excellent degree and eight cases who were satisfied with an Good degree, and this was statistically insignificant **Table(5).**

Table (5): Comparison between studied groups regarding Patient satisfaction

Patient satisfaction	Group 1		Group 2		Test value	P-value
	No.	**%**	**No.**	**%**		
Excellent	4	40.0%	2	20.0%	0.952	0.329
Good	6	60.0%	8	80.0%		

Spearman coefficient, statistically significant at $p \leq 0.05$

Regarding the Complications there were three cases with pain in Group 1,

While in group 2 there were ten cases with pain, eight cases with hyperpigmentation and eight cases had ulceration. There was highly statistically significant difference between both groups as regard pain, hyperpigmentation and ulceration **Table (6).**

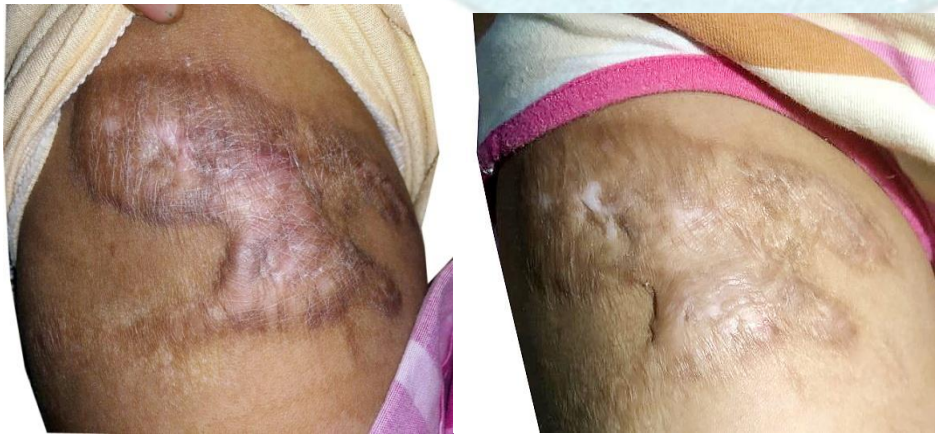
Table 6: Comparison between studied groups regarding Complication

Complication	Group 1		Group 2		Test value*	P-value
	No.	**%**	**No.**	**%**		
Pain	3	30.0%	10	100.0%	10.769	0.001
Headache	0	0.0%	0	0.0%	–	–
Hyperpigmentation	0	0.0%	8	80.0%	13.333	0.000
Ulceration	0	0.0%	8	80.0%	13.333	0.000
Flu like symptoms	0	0.0%	0	0.0%	–	–

Spearman coefficient, statistically significant at $p \leq 0.05$

Figures display clinical images for a subset of the study participants (1-4):

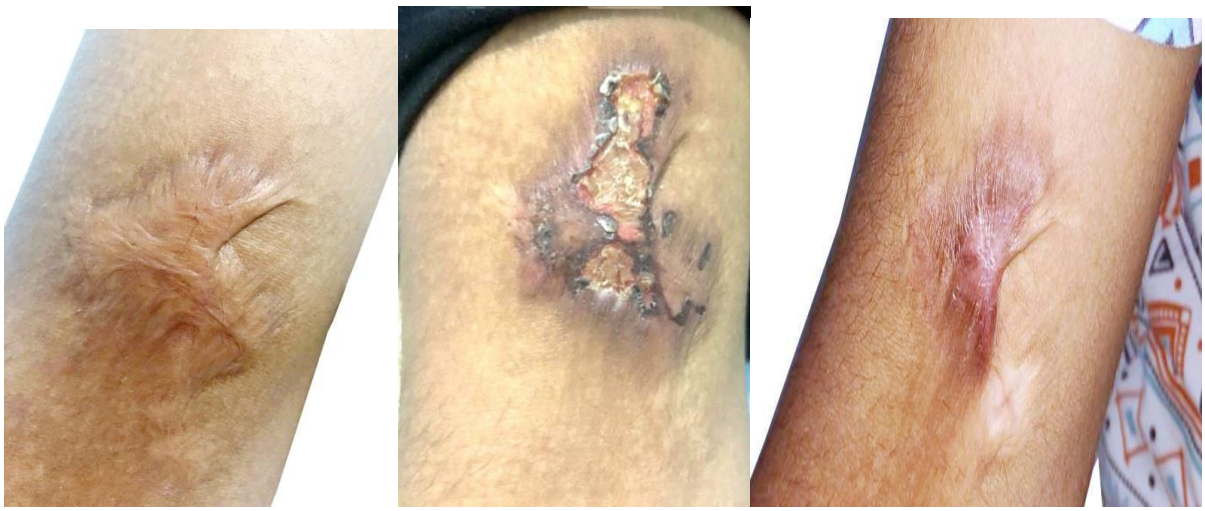
Figure (1): 17 years old female case, with keloidal scarring on the sternum, treated with **BXT-A**. Patient didn't experienced pain or itching during sessions, with no necrosis or hyperpigmentation after sessions.



(A) **(B)**

Figure (1): (A) at the start of study, (B) after sessions.

Figure (2): 18 years old male with HTS on ventral surface of right cubical fossa, treated with **5-FU**. Patient experienced pain that lasted for few minutes up to days after sessions, marked tissue sloughing and hyperpigmentation were noticed, but no headache or flu like symptoms.



(A) (B) (C)

Figure (2): (A) at the start of study, (B) tissue ulceration. (C) After sessions

Figure (3): 32 years old male patient with hypertrophic scar lesion on ventral surface of right forearm treated with **BXT-A**. Patient experienced mild pain after sessions only for few minutes, with no necrosis or hyperpigmentation, neither headache nor flu like symptoms.

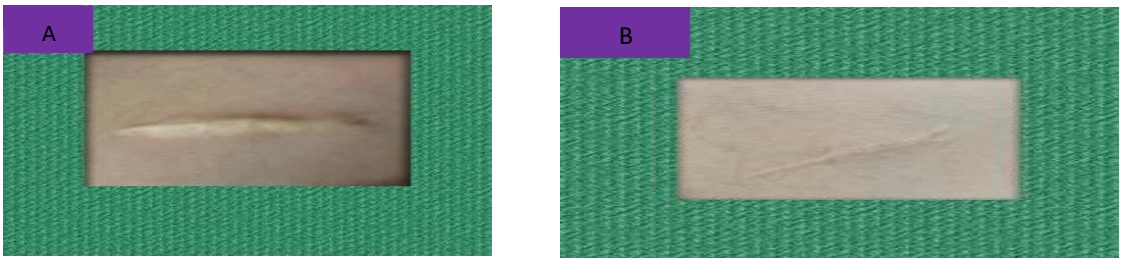
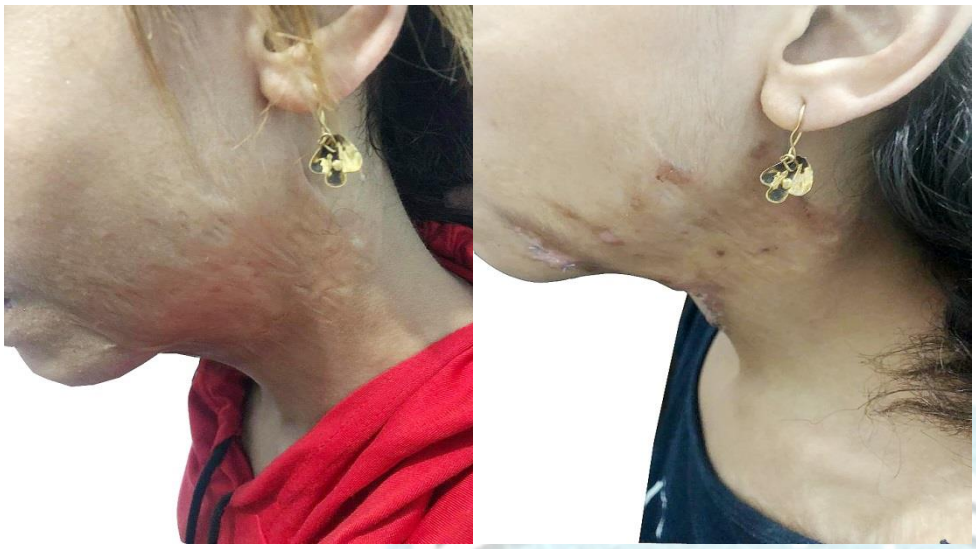


Figure (3): (A) at the start of study, (**B**) after sessions

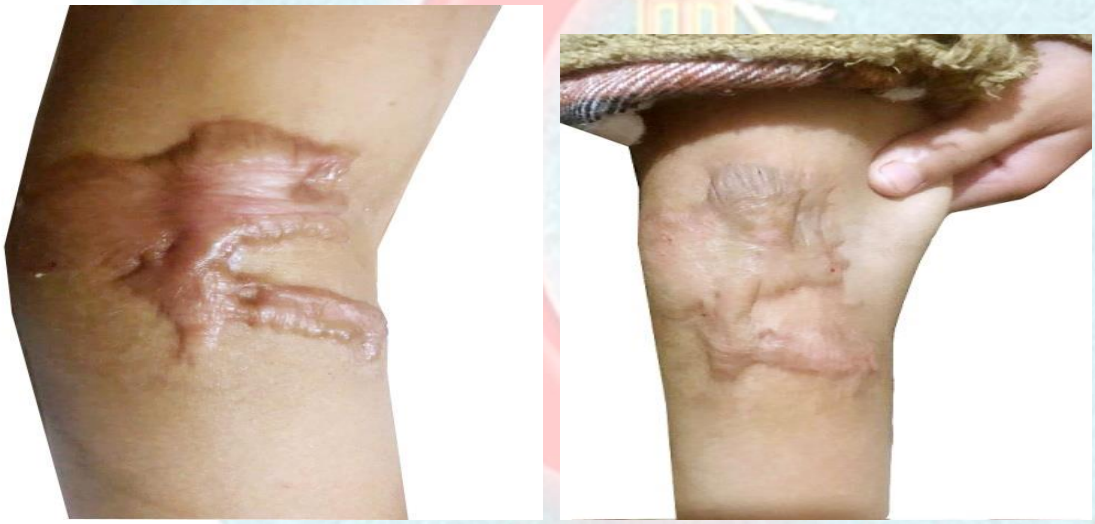
Figure (4): 20 years old female with hypertrophic scar lesion over the face and neck treated with **5-FU**. Patient experienced pain that lasted from hours up to two days after some sessions. Also, ulceration and marked hyperpigmentation were noticed, but no headache or flu like symptoms.



(A) (B)

Figure (4): **(A)** before the first session, **(B)** after sessions.

Figure (5): 20 years old Female patient with keloidal lesion on right Cubital fossa received BXT-**A**. Patient didn't experienced pain, ulceration and pigmentation.



(A) (B)

Figure (5): **(A)** before the first session, (B) after sessions.

DISCUSSION

Hypertrophic scars and keloids result from skin injury that penetrates to the dermal layer. They may appear following burns, surgery, bites from insects, tattoos, chickenpox or acne, and piercings. Several associations are considered to influence the creation of these aberrant scars, while the precise mechanisms are still unknown. The risk of both scar hypertrophy and keloid has been linked to circumstances that elevate systemic inflammatory markers [13].

Botulinum toxin-type A, 5-fluorouracil (5-F U), triamcinolone acetonide (TAC),bleomycin, and verapamil are often used local drug injections for treating pathological scars; however, opinions on the selection and effectiveness of these medications vary [14].

Ismail et al., 2021[10] found in contrast to our work, a substantially superior treatment response for keloids following IL BXT-A than following IL 5-FU; IL BXT-A produced excellent and good lesions flattening (58.8% and 20.6%) as opposed to (31.4% and 17.1%) following IL 5-FU, respectively. This contrast may be due to larger number of studied patients and prolonged use of IL BXT up to 6 sessions instead of 4 sessions in our study.

In accordance to our study, **Shaarawy et al., (2015)** [15] examined the effects on 24 female patients with keloid scars, comparing the result of intra-lesional BXT-A injection versus intra-lesional steroid therapy. Patients were randomly assigned to group A, which received IL BXT-A, and group B, which received IL steroid (10 mg/mL triamcinolone). All patients showed a decrease in keloid volume compared to baseline (82.7 % for group A, 79.2 % for group B; a comparable trend was seen in terms of a decrease in height and redness. however, at study's end, no statistical significance was found between groups, with higher percentage of satisfied patients on group A. This agreement may be due to nearly similar study size (24 cases vs 20 cases) and effectiveness of triamcinolone in keloid treatment

Regarding the two-doctor assessment, the first doctor assessment was; all patients were improved, 9 cases (90.0%) were improved and one case (10%) was slightly improved in group 1, while 6cases (60.0%) improved and 2 cases (20%) were markedly improved and 2cases (20%) slightly improved in group2. The Second doctor assessment also was that all patients were improved, one case (10%) was markedly improved and 9 cases (90.0%) were improved but not markedly in group 1 , while 8 cases (80.0%) improved and 2cases (20%) were slightly improved in group 2, without statistical significant difference between both groups.

Also, Regarding the Patient satisfaction there were 4 cases (40%) were satisfied with an excellent degree and 6 cases (60%) were satisfied with an good degree, in Group 1, while in group 2 there were 2 cases (20%) were satisfied with an excellent degree and 8cases (80%) of cases who were satisfied with an good degree with no statistical significant difference between both groups.

In accordance with our research **Zhibo et al., 2009**[16] examined the effects of BXT-A on keloid scars in 12 patients. Photo records and a 5-point patient satisfaction scale, ranging from no improvement to good, were used to measure the patients' reaction to therapy. An independent doctor also recorded observations on keloid height, induration, flattening, and size; evaluations were carried out at the onset of BXT-typeA injection (day 1) and at one-, three-, and twelve-month intervals after the injection. Overall, three patients had excellent therapeutic outcomes with BXT-A, five had good outcomes, and four had fair outcomes (i.e., no patient encountered therapy failure).

Twenty individuals with hypertrophic scars were enrolled in **Elhefnawy et al., 2016**[17] study. Each patient had a monthly intra-lesional injection of botulinum toxin type A for three months, with a six-month follow-up. Both the patient's and the doctor's therapeutic satisfaction were noted. Itching, pliability, and erythema of the lesions were evaluated. Every item was graded out of five. Six patients had 'excellent' therapeutic satisfaction, compared to 14 who had 'fair' satisfaction. The average scores for erythema, pliability, and itching dropped from 3.2 to 1.0, 2.7 to 0.7, and 3.3 to 0.8, respectively. Patient satisfaction in **Elhefnawy** study was lower than our study result, and this may be due to shorter use of IL BXT (only 3 months), prolonged follow up and larger size of lesions.

Pruksapong et al., 2017[18] conducted a placebo-controlled trial with 42 patients who had lesions ranging in length from 5 to 11 cm. BXT-A was injected into half of each patient's keloid scar, and normal saline was put into the other half. At three and six months, independent observers evaluated the look of the scar, and Visual Analogue Scale was used to gauge patient satisfaction. Examining the areas where normal saline injections were made to the scar tissue revealed that the keloid scar formation tendency persisted. On the other hand, sites that received BXT-A treatment showed more malleable scar formation and a notable improvement in pain at the 3rd and 6th month.

Regarding the side effects in our study there were 3 cases had pain for short period after injection and no hyperpigmentation or ulceration in group 1, while in group 2 there were ten cases acquired pain only for few hours after the session , eight cases had hyperpigmentation and eight cases had tissue sloughing and there were no systemic side effects such as flue like symptoms and headache in all patient .There was highly statistical

significance difference between both group as regard Pain, hyperpigmentation and tissue sloughing.

In lines with our study **Kontochristopoulos et al., 2005** [19] administered intralesional injection of 5-fluorouracil (50 mg/mL) once a week to 20 patients (11 males and 9 females). After an average of seven treatments, 17 patients (85%) had more than 50% improvement. The most common side effects were pain, hyperpigmentation on all patients and ulceration (6 of 20).this accordance with our results may be because of similar study methodology and similar patient demography.

Additionally, in line with our research, **Bui et al., 2020** [20] examined the effectiveness and safety of intra-lesional 5-fluorouracil on the management of facial scars and discovered that the most frequently reported adverse effect was pain during injection. Also, another two studies reported more significant occurrences like ulceration, superficial necrosis, and local infection.this agreement with our study and frequency of this side effects may be due to 5-FU mechanism of action as an antineoplastic agent that inhibits DNA and RNA synthesis causing cellular apoptosis .In addition, 5-FU also inhibits the expression of the type I collagen gene that is induced by transforming growth factor-β.

A study by **Rasaii et al., (2019)** [21] involved forty skin lesions in twenty-three patients. The study compared the effect of intra-lesional triamcinolone acetonide (TAC) injection plus placebo (normal saline) (group 1) vs TAC plus BXT type A (group 2), and the authors found that intra-lesional injection of triamcinolone and BXT-A significantly reduced pain and itching because of combining intra-lesional triamcinolone to BTA, The steroid served to reduce the inflammatory infiltrate, whereas BTA had an inhibitory effect on the cell cycle of fibroblasts.

According to **Mari et al., (2015)** [22], intralesional 5-FU may cause skin erythema, discomfort, and ulceration, among other possible adverse effects.

Consistent with our findings, **Xiao et al., 2009**[23] assessed intralesional injections of BXT-A on 19 patients suffering from hypertrophic scar lesions. High percentage of cases expressed satisfaction with their treatment. Following the BXT-A injection, the erythema, pliability and itchy sensation scores were all much lower than they were prior to the injection.

Conclusion: According to the outcomes of the current study, Both IL botulinum toxin type A and 5-Fluorouracil are effective and safe in the management of keloids and hypertrophic scars but Patients who were treated with 5-Fluorouracil experienced more complications in comparison to patients who received IL botulinum toxin type A: less pain, no hyperpigmentation & less ulceration

RECOMMENDATIONS & LIMITATIONS

This study involves a limited sample of the Egyptian population. Thus, more extensive, multicentre research is needed to assess the safety and effectiveness of 5-fluorouracil and botulinum toxin type A in the management of hypertrophic scars and keloids. A longer follow-up observation of at least 12 months is recommended, particularly to determine whether keloids have returned. Furthermore, IL 5-FU was given once a week; it can be used at longer duration (every two or four weeks).

REFERENCES:

1-Anderson, J. B., Foglio, A., Harrant, A. B., et al. (2021). Scoping Review ofTherapeutic Strategies for Keloids and Hypertrophic Scars. Plastic and Reconstructive Surgery Global.

2-Truong, K., Prasidha, I., & Wain, T. (2021). A systematic review of randomised controlled trials investigating laser assisted drug delivery for the treatment of keloid and hypertrophic scars. Lasers in medical science .

3- Ogawa, R. (2017). Keloid and hypertrophic scars are the result of chronic inflammation in the reticular dermis. International journal of molecular sciences, 18(3), 606 .

4- Chen, C., Zhang, M., Yu, N., et al. (2021). Heterogeneous features of keloids assessed by laser speckle contrast imaging: A cross-sectional study. Lasers in Surgery and Medicine, 53(6), 865-871 .

5- Lee, H. J., & Jang, Y. J. (2018). Recent understandings of biology, prophylaxis and treatment strategies for hypertrophic scars and keloids. International journal of molecular sciences, 19(3), 711.

6- Jankovic, J. (2017). Botulinum toxin: State of the art. Movement Disorders, 32(8), 1131-1138 .

7- Rahman, S. H. A., Mohamed, M. S., & Hamed, A. M. (2021). Efficacy and safety of Nd: YAG laser alone compared with combined Nd: YAG laser with intralesional steroid or botulinum toxin A in the treatment of hypertrophic scars. Lasers in medical science, 36(4), 837-842 .

8- Khalid, F. A., Mehrose, M. Y., Saleem ,M., et al. (2019). Comparison of efficacy and safety of intralesional triamcinolone and combination of triamcinolone with 5-fluorouracil in the treatment of keloids and hypertrophic scars: Randomised control trial. Burns, 45(1), 69-75 .

9- Charan J, Biswas T. How to calculate sample size for different study designs in medical research?. Indian journal of psychological medicine. 2013 Apr;35(2):121.

10- Ismail, S. A., Mohammed, N. H. K., Sotohy, M., et al. (2021). Botulinum toxin type A versus 5-Fluorouracil in treatment of keloid. Archives of Dermatological Research, 313(7), 549-556. doi:10.1007/s00403-020-02132-8

11- Thompson, C. M., Sood, R. F., Honari, S., et al. (2015). What score on the Vancouver Scar Scale constitutes a hypertrophic scar? Results from a survey of North American burn-care providers. Burns, 41(7), 1442-1448. doi:10.1016/j.burns.2015.04.018.

12- Sohrabi, C., & Goutos, I. (2020). The use of botulinum toxin in keloid scar management: a literature review. Scars, Burns & Healing, 6, 2059513120926628.

13- Wang, Z.-C., Zhao ,W.-Y., Cao, Y., et al. (2020). The roles of inflammation in keloid and hypertrophic scars. Frontiers in Immunology, 11, 603187 .

14- Limmer, E. E., & Glass, D. A., 2nd. (2020). A Review of Current Keloid Management: Mainstay Monotherapies and Emerging Approaches. Dermatol Ther (Heidelb), 10(5), 931-948. doi:10.1007/s13555-020-00427-2

15- Shaarawy, E., Hegazy, R. A., & Abdel Hay, R. M. (2015). Intralesional botulinum toxin type A equally effective and better tolerated than intralesional steroid in the treatment of keloids: a randomized controlled trial. Journal of Cosmetic Dermatology, 14(2), 161-166 .

16- Zhibo, X., & Miaobo, Z. (2009). Intralesional botulinum toxin type A injection as a new treatment measure for keloids. Plast Reconstr Surg, 124(5), 275e-277e .

17- Elhefnawy, A. M. (2016). Assessment of intralesional injection of botulinum toxin type A injection for hypertrophic scars. Indian journal of dermatology, venereology and leprology, 82, 279.

18- Chatchai Pruksapong, M. D., Sanipreeya Yingtaweesittikul, M. D., & Chairat Burusapat, M. D. (2017). Efficacy of botulinum toxin A in preventing recurrence keloids: double blinded randomized controlled trial study: intraindividual subject. J Med Assoc Thai, 100(3), 280-6.

19- Kontochristopoulos, G., Stefanaki, C., Panagiotopoulos, A., et al. (2005). Intralesional 5-fluorouracil in the treatment of keloids: an open clinical and histopathologic study. Journal of the American Academy of Dermatology, 52(3), 474-479 .

20- Bui, A. D., Grob, S. R., & Tao, J. P. (2020). 5-Fluorouracil management of oculofacial scars: a systematic literature review. Ophthalmic Plastic and Reconstructive Surgery, 36(3), 222-230.

21- Rasaii, S., Sohrabian, N., Gianfaldoni, S., Hadibarhaghtalab, M., Pazyar, N., Bakhshaeekia, A., ... & Feily, A. (2019). Intralesional triamcinolone alone or in combination with botulinium toxin A is ineffective for the treatment of formed keloid scar: A double blind controlled pilot study. Dermatologic therapy, 32(2), e12781.

22- Mari, W., Alsabri, S. G., Tabal, N., et al. (2015). Novel insights on understanding of keloid scar: article review. Journal of the American College of Clinical Wound Specialists, 7(1-3), 1-7 .

23- Xiao, Z., Zhang, F., & Cui, Z. (2009). Treatment of hypertrophic scars with intralesional botulinum toxin type A injections: a preliminary report. Aesthetic plastic surgery, 33, 409-412.