

Comparison between hyaluronic acid filler and botulinum toxin type A in the treatment of thyroid upper eyelid retraction

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Ther Adv Ophthalmol

2020, Vol. 12: 1–8

DOI: 10.1177/
2515841420979113

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Abstract

Purpose: The aim of this study was to compare between hyaluronic acid filler (HA) and botulinum toxin type A (BTX-A) in the treatment of thyroid upper eyelid retraction.

Study design: This was a prospective comparative study.

Methods: A total of 50 eyes with upper thyroid eyelid retraction were divided into 2 groups. Each group included 25 eyes, (a) hyaluronic acid filler (HA) group: received subconjunctival HA injection and (b) botulinum toxin (BTX-A) group: received subconjunctival botulinum toxin type A injection. Full ophthalmic examination and thyroid profile were done. Marginal reflex distance 1 (MRD1) and total palpebral fissure height (TPFH) were measured before and after injection weekly for 6 months.

Results: There is no significant difference between the two groups regarding MRD1 till the 10th week of follow up, then it became significant from the 11th to 15th week with better results in HA filler group, then the difference between the two groups become highly significant from the 16th week afterward with better results for the HA filler over the BTX-A. With regard to TPFH, there were significant differences between the BTX-A group and the HA group with a better result in BTX-A group in the first 8 weeks. Then the difference became insignificant till the 18th week. Then the difference became significant from the 19th till the 24th week with a better result in HA group.

Conclusion: HA filler has better result in treating thyroid upper eyelid retraction than BTX-A due to its predictable controllable effect, also, due to the longer duration of action and fewer side effects.

Keywords: Botulinum toxin type A, hyaluronic acid filler, thyroid eyelid retraction

Received: 28 April 2020; revised manuscript accepted: 12 November 2020.

Introduction

Thyroid eye disease (TED) is the most common cause of upper eyelid retraction. It occurs in 90% of patients during the disease activity. One-fifth of patients have unilateral presentation. The lateral part of the upper eyelid is usually more affected than the medial part which is known as the lateral flare sign.¹

The mechanisms of upper eyelid retraction, in patients with TED, include (a) the increase in sympathetic tone, which leads to secondary changes of proptosis and lid tissue fibrosis²; (b) a tight inferior rectus muscle leads to secondary lid retraction, this

is characterized by overshooting on up gaze of the affected eyelid; and (c) widening of the palpebral fissure, as a result of proptosis, may share in lid retraction, mostly the lower eyelid position.³

One way to quantify or define upper eyelid retraction would be to determine the marginal reflex distance, which is measured from the center of the cornea to the margin of the upper eyelid in the primary position (MRD1). It has been stated that the average MRD1 in a non-thyroidal patient is 3.5 ± 0.9 mm on the right and 3.4 ± 0.8 mm on the left.¹ With this definition, retracted upper eye lid would have MDR1 more than 4.5 mm.⁴

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Retraction of the upper eyelid causes conjunctival and corneal exposure with ocular discomfort, dryness, foreign body sensation, tearing, and photophobia. Lagophthalmos makes the symptoms to be more severe. Also, the patients' appearance may be staring, frightened, or angry. Correction of upper eyelid retraction is important to improve the quality of life of TED patients.^{5,6}

The surgical correction of upper eyelid retraction includes levator aponeurosis recession, Muller-ectomy (recession of the Muller muscle), or graft insertion. However, surgical management is relatively complex, and changes in eyelid contour or preexisting double-fold lines may occur. Furthermore, the surgical outcome is difficult to be predicted in many cases.²

The minimally invasive techniques are very useful in patients non-candidate for surgery or refusing surgery. Also, the minimally invasive technique can be easily used in the office setting and avoid the side effects of surgery.

The main two non-invasive techniques are the injection of botulinum toxin and hyaluronic acid (HA). Hyaluronic acid, a natural component of the extracellular matrix, has been widely used as a cosmetic gel filler and more recently in the non-surgical management of lower eyelid retraction,⁷ paralytic lagophthalmos, and for pediatric eyelid malposition such as congenital ectropion and epiblepharon. It offers the advantages of avoiding the need for anesthesia and a rapid post-injection recovery. The treatment can also be repeated to adjust eyelid position and can usually be reversed with the use of hyaluronidase if needed.⁸

Botulinum toxin type A (BTX-A) is a very potent neurotoxin affecting the neuromuscular junction. It has many ophthalmic uses included in the management of strabismus, idiopathic blepharospasm,^{5,6} entropion, sixth nerve palsy, and nystagmus.⁶⁻⁹

In our study, we compared between the effects of subconjunctival injection of HA filler and BTX-A in the treatment of thyroid upper eyelid retraction with regard to efficacy, duration of action, and side effects.

Patients and methods

A total of 50 eyes of 30 patients (21 females and 4 males) suffering from upper eyelid retraction due to TED were included in this study, which was conducted in the Department of Ophthalmology

at Al-Zahraa University Hospital in Egypt between Mach 2018 and November 2018.

The patients were divided into 2 groups, each group included 25 eyes: (a) HA group: received subconjunctival HA injection and (b) botulinum toxin group: received subconjunctival HA injection.

We used HA filler in patients with lateral flare sign to address this sign by increasing injection at lateral side. While for other patients, we used BTX-A as it affects the lid muscles symmetrically. In case of bilateral affection, we used the same treatment modality in both eye lids.

Inclusion criteria included upper eye lid retraction due to TED, clinically activity score ≤ 3 , and patients on medical treatment of thyroid disease. The exclusion criteria included restrictive strabismus, optic neuropathy needing urgent orbital decompression, severe corneal ulcers, clinical activity score (CAS) > 3 , history of previous steroid, or surgical treatment of thyroid lid retraction (TLR) and pregnancy.

The full ophthalmic examination was done with stress on the signs of ocular surface affection such as dry eye and punctate epithelial erosion. Thyroid profile and CAS were done. Marginal reflex distance 1 (MRD1) is the distance between the upper lid margin and the corneal light reflex in the primary position. Also, total palpebral fissure height (TPFH), which is the distance between upper and lower lid margin in the primary position, was measured.

Technique of HA injection in the upper eyelid

Topical eye drops were used to anesthetize the conjunctiva. Exposure of the conjunctiva just superior to the upper edge of the tarsus was done by everting the upper lid with looking down. A single bolus of HA is injected centrally in the subconjunctival levator-Muller plane using a 30-gauge needle. The globe is very close in this region, so care should be taken. Volumes of 0.1 to 0.5 mL were injected. The lateral eyelid flare was addressed by adding material temporally. The results could be achieved with 1 to 2 injections in a single session.

Technique of BTX-A injection in the UL

The eyes were anesthetized with topical local anesthetic and then eversion of the upper eyelid was done with the patient looking down, two injections

were applied, medially and laterally, one-third of the way in from the lid extremities. Botulinum toxin type A was injected using a 30-gauge needle into the subconjunctival space at the superior margin of the tarsal plate, via a conjunctival approach. The concentration of BTX-A was 5 unit per 0.1 mL. Dose of 3–6 units of BTX-A were administered at each injection site depending on the severity of the retraction. Injection was done once for each patient.

Patients were followed up every week for 6 months for signs of ocular surface affection and by remeasuring MRD1 and TPFH.

Statistical method

Data were collected, revised, coded, and entered into the Statistical Package for Social Science (IBM SPSS) version 20. Chi-square test, independent *t*-test, and paired *t*-test were used to analyze the data.

Results

The patients in the HA filler group included 15 (60%) females and 10 (40%) males, while the botulinum toxin group included 21 (84%) females and 4 (16%) males. The mean age of the HA is 45.08 ± 10.37 years, while the botulinum toxin group is 47.36 ± 8.63 years.

With regard to thyroid function, in the HA group, 8 (32.0%) were hyperthyroid patients and 17 (68.0%) were euthyroid patients. In botulinum toxin group, 9 (36.0%) were hyperthyroid patients and 16 (64.0%) were euthyroid patients with non-significant change in both groups with regard to thyroid function with *p*-value = 0.765.

The mean of pre-MRD1 in the HA filler group was 7.20 ± 1.38 mm and in the BTX-A group was 7.84 ± 1.05 mm with no significant difference between the two groups with *p*-value = 0.424. The mean of pre-TPFH in the HA filler group was 14.40 ± 2.42 mm and in the BTX-A group was 13.28 ± 1.81 mm with no significant difference between the two groups with *p*-value = 0.070.

With regard to the HA filler group, there is a significant difference between the pre-MRD1 and the post-MRD1 all over the period of 6 months (Figure 1).

While in the BTX-A group, there were highly significant differences between the pre-MRD1 and the post-MRD1 till the 18th week and the difference became significant from the 19th till the 21st



Figure 1. Effect of hyaluronic acid filler (HA) in thyroid upper eyelid retraction: (a) before injection, (b) Rt upper lid 3 months after injection of HA filler, and (c) Rt upper lid 6 months after injection of HA filler.

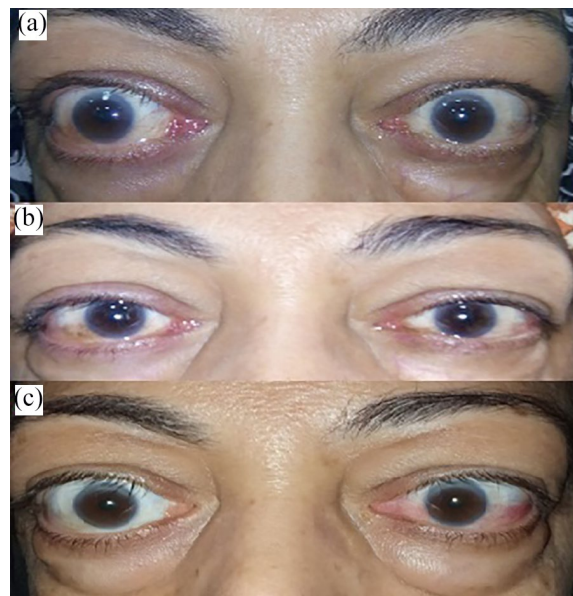


Figure 2. A case of bilateral upper eyelid retraction who is treated by subconjunctival BTX-A: (a) before injection; (b) normalization of the upper lid position in both eyes 2 weeks post injection; and (c) 6 months after injection, the upper lids were returned to the pre-treatment position.

week, then it became insignificant from 22nd afterward (Figure 2).

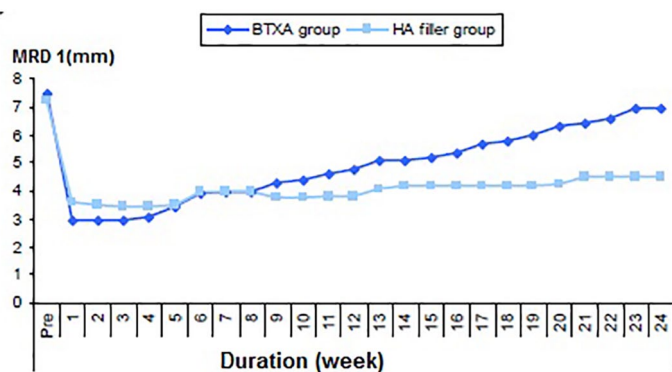


Figure 3. Comparison between hyaluronic acid filler and botulinum toxin type A on the marginal reflex distance 1 (MRD1). There is no significant difference between the two groups with regard to MRD1 till the 10th week of follow up, then it became significant from the 11th to the 15th week with better results in HA filler group, then the difference between the two groups become highly significant from the 16th week afterward with better results for the HA filler over the BTX-A.

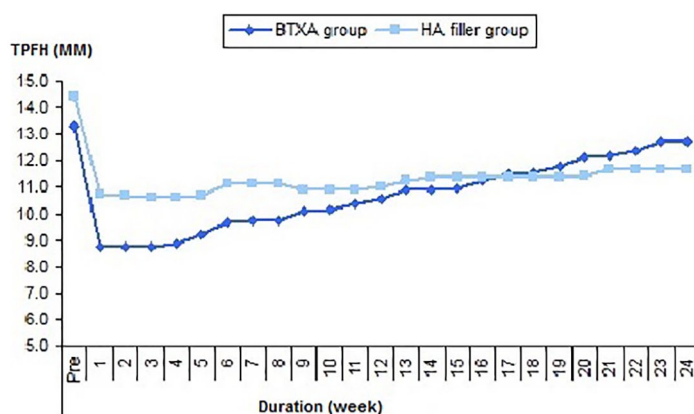


Figure 4. Comparison between hyaluronic acid filler and botulinum toxin type A on total palpebral fissure height (TPFH). There was a significant difference between the BTX-A group and the HA group with a better result in BTX-A group in the first 8 weeks. Then the difference became insignificant till the 18th week. Then the difference became significant from the 19th till the 24th week with a better result in the HA.

With regard to comparison between the HA and BTX-A groups, there is no significant difference between the two groups regarding MRD1 till the 10th week of follow up (this was due to the development of ptosis in some patients in BTX-A group), then it became significant from the 11th week to the 15th week with better results in HA filler group, then the difference between the two groups become highly significant from the 16th week afterward with better results for the HA filler over the BTX-A due to long duration of action of HA filler (Table 1) (Figure 3).

In the HA filler group, there was high significant difference between the measured TPFH before injection and throughout the follow-up period. The variations in TPFH decrease throughout the period was very minimal. It may be due to the fluctuation in systemic control of the disease.

In the BTX-A group, the TPFH showed high significant difference between that measured before the injection and during follow up till the 18th week, then the difference became non-significant afterward.

With regard to the TPFH, there was a significant difference between the BTX-A group and the HA group with a better result in BTX-A group in the first 8 weeks due to ptosis occurred in some cases. Then the difference became insignificant till the 18th week. Then the difference became significant from the 19th week till the 24th week with a better result in the HA group due to prolonged duration of action of HA filler (Table 2) (Figure 4).

With regard to the occurrence of complications, in our study, there were seven eyes (28%) of BTX-A group who developed mild ptosis that resolved spontaneously within 4–6 weeks after injection. Ptosis had no impact on life quality. However, three patients were unsatisfied in the early period. Ecchymosis was reported in one eye in the BTX-A group that resolved spontaneously within 2 weeks. We did not face any cases of diplopia or periocular pain in our study. No complication occurred in HA group.

Discussion

Eyelid retraction is one of the challenges of TED. Conventionally, a waiting period is needed before correction of the lid retraction surgically. This waiting period may be due to orbital decompression or a strabismus surgery.

The surgical procedures have unpredictable outcome and course in some cases, particularly for patients in an acute phase.⁶ The use of topical guanethidine eye drops is one of non-surgical alternatives that may be used, but the results are usually disappointing due to miosis, undercorrection, and conjunctival hyperaemia.^{3,6} So, the minimally invasive techniques have gained popularity.

Hyaluronic acid has a dual mechanism of action. The first is by the mechanical weight effect, as it

Table 1. Difference between BTX-A and HA filler groups in MRD1.

	BTX-A group	HA filler group	Independent <i>t</i> -test		
	Mean \pm SD	Mean \pm SD	Test value	<i>p</i> -value	Sig.
Pre MRD1 (mm)	7.48 \pm 1.05	7.20 \pm 1.38	0.807	0.424	NS
(1) MRD1 (mm)	2.96 \pm 1.51	3.56 \pm 0.87	-1.719	0.092	NS
(2) MRD1 (mm)	2.96 \pm 1.51	3.48 \pm 0.77	-1.531	0.132	NS
(3) MRD1 (mm)	2.96 \pm 1.51	3.40 \pm 0.76	-1.298	0.201	NS
(4) MRD1 (mm)	3.04 \pm 1.43	3.40 \pm 0.76	-1.111	0.272	NS
(5) MRD1 (mm)	3.40 \pm 1.53	3.48 \pm 0.87	-0.227	0.821	NS
(6) MRD1 (mm)	3.88 \pm 1.59	3.96 \pm 1.65	-0.175	0.862	NS
(7) MRD1 (mm)	3.96 \pm 1.51	3.96 \pm 1.65	0.000	1.000	NS
(8) MRD1 (mm)	3.96 \pm 1.51	3.96 \pm 1.65	0.000	1.000	NS
(9) MRD1 (mm)	4.28 \pm 1.79	3.72 \pm 1.10	1.332	0.189	NS
(10) MRD1 (mm)	4.36 \pm 1.70	3.72 \pm 0.94	1.645	0.106	NS
(11) MRD1 (mm)	4.60 \pm 1.55	3.80 \pm 1.15	2.066	0.044	S
(12) MRD1 (mm)	4.76 \pm 1.64	3.80 \pm 1.15	2.393	0.021	S
(13) MRD1 (mm)	5.08 \pm 1.80	4.08 \pm 1.44	2.168	0.035	S
(14) MRD1 (mm)	5.08 \pm 1.80	4.16 \pm 1.40	2.014	0.050	S
(15) MRD1 (mm)	5.16 \pm 1.72	4.16 \pm 1.40	2.248	0.029	S
(16) MRD1 (mm)	5.36 \pm 1.70	4.16 \pm 1.40	2.716	0.009	HS
(17) MRD1 (mm)	5.68 \pm 1.70	4.16 \pm 1.40	3.445	0.001	HS
(18) MRD1 (mm)	5.76 \pm 1.83	4.16 \pm 1.40	3.465	0.001	HS
(19) MRD1 (mm)	6.00 \pm 1.87	4.16 \pm 1.40	3.932	0.000	HS
(20) MRD1 (mm)	6.32 \pm 1.70	4.24 \pm 1.42	4.690	0.000	HS
(21) MRD1 (mm)	6.40 \pm 1.61	4.48 \pm 1.66	4.153	0.000	HS
(22) MRD1 (mm)	6.56 \pm 1.56	4.48 \pm 1.66	4.568	0.000	HS
(23) MRD1 (mm)	6.92 \pm 1.44	4.48 \pm 1.66	5.547	0.000	HS
(24) MRD1 (mm)	6.92 \pm 1.44	4.48 \pm 1.66	5.547	0.000	HS

Abbreviations: BXT-A, botulinum toxin type A; HA filler, hyaluronic acid filler; MRD, marginal reflex distance; SD, standard deviation.
p-value > 0.05: non-significant; *p*-value < 0.05: significant; *p*-value < 0.01: highly significant.

acts as an upper eyelid load. Also, it acts as a physical stent that inhibits the levator functions. These two mechanisms lower the upper eyelid.⁸

Botulinum toxin type A is a neurotoxin that affects the neuromuscular junction. Its effect on the smooth muscle is more specific than the

Table 2. Difference between BXT-A and HA filler in TPFH.

	BTX-A group	HA filler group	Independent <i>t</i> -test		
	Mean \pm SD	Mean \pm SD	Test value	<i>p</i> -value	Sig.
Pre TPFH (mm)	13.28 \pm 1.81	14.40 \pm 2.42	-1.854	0.070	NS
(1) TPFH (mm)	8.76 \pm 2.17	10.76 \pm 2.11	-3.310	0.002	HS
(2) TPFH (mm)	8.76 \pm 2.17	10.68 \pm 1.95	-3.293	0.002	HS
(3) TPFH (mm)	8.76 \pm 2.17	10.60 \pm 1.96	-3.151	0.003	HS
(4) TPFH (mm)	8.84 \pm 2.15	10.60 \pm 1.96	-3.023	0.004	HS
(5) TPFH (mm)	9.20 \pm 2.16	10.68 \pm 2.04	-2.493	0.016	S
(6) TPFH (mm)	9.68 \pm 2.25	11.16 \pm 2.59	-2.156	0.036	S
(7) TPFH (mm)	9.76 \pm 2.17	11.16 \pm 2.59	-2.072	0.044	S
(8) TPFH (mm)	9.76 \pm 2.17	11.16 \pm 2.59	-2.072	0.044	S
(9) TPFH (mm)	10.08 \pm 2.47	10.92 \pm 2.27	-1.253	0.216	NS
(10) TPFH (mm)	10.16 \pm 2.37	10.92 \pm 2.20	-1.175	0.246	NS
(11) TPFH (mm)	10.40 \pm 2.25	10.92 \pm 2.20	-0.826	0.413	NS
(12) TPFH (mm)	10.56 \pm 2.33	11.00 \pm 2.29	-0.673	0.504	NS
(13) TPFH (mm)	10.88 \pm 2.47	11.28 \pm 2.41	-0.580	0.565	NS
(14) TPFH (mm)	10.88 \pm 2.47	11.36 \pm 2.31	-0.710	0.481	NS
(15) TPFH (mm)	10.96 \pm 2.39	11.36 \pm 2.31	-0.602	0.550	NS
(16) TPFH (mm)	11.24 \pm 2.28	11.36 \pm 2.31	-0.185	0.854	NS
(17) TPFH (mm)	11.48 \pm 2.40	11.36 \pm 2.31	0.180	0.858	NS
(18) TPFH (mm)	11.56 \pm 2.53	11.36 \pm 2.31	0.292	0.772	NS
(19) TPFH (mm)	11.80 \pm 2.55	11.36 \pm 2.31	0.640	0.525	NS
(20) TPFH (mm)	12.12 \pm 2.45	11.44 \pm 2.35	1.001	0.322	NS
(21) TPFH (mm)	12.20 \pm 2.36	11.68 \pm 2.54	0.749	0.458	NS
(22) TPFH (mm)	12.36 \pm 2.27	11.68 \pm 2.54	0.997	0.324	NS
(23) TPFH (mm)	12.72 \pm 2.13	11.68 \pm 2.54	1.566	0.124	NS
(24) TPFH (mm)	12.72 \pm 2.13	11.68 \pm 2.54	1.566	0.124	NS

Abbreviations: BXT-A, botulinum toxin type A; HA filler, hyaluronic acid filler; SD, standard deviation; TPFH, total palpebral fissure height.
p-value > 0.05: non-significant; *p*-value < 0.05: significant; *p*-value < 0.01: highly significant.

striated muscle. So, the lid-lowering effect is mainly due to the effect on Muller muscle rather than the levator muscle.⁴

Both HA and BTX-A have an anti-inflammatory effect. HA has been proved to have an anti-inflammatory effect in osteoarthritis and in wound healing.¹⁰ So, it is effective in both active and fibrotic stages in TED. Also, it prevents fibrosis during the active stage of disease.¹ Morgenstern postulated that BTX-A injection may release an 'inflammatory contracture' that prevents fibrosis caused by restricted motion and subsequent muscle tethering and shortening.⁴

In this study, we chose the transconjunctival approach for both BTX-A and HA injection. In HA, it decreases the side effects such as the hump effect and bluish discoloration. In BTX-A, the transconjunctival approach increases the effect on the Muller muscle and decreases the undesirable weakening of the orbicularis muscle which occurs with the percutaneous approach.⁴

With regard to the use of HA, our results matched with Mancini and colleagues⁸ and Kohn and colleagues.¹ The eyelid retraction has improved just after the injection till the end of follow-up period by just a single injection. No complications occurred in our patients. Complications are typically temporary and minimal, including edema, ecchymosis, and transient erythema, at the injection site. Blue or dark color changes, fluid buildup, and contour irregularity and lumps may occur in the injection area.¹¹ No foreign body sensation has been reported in our patients.

With regard to the BTX-A group, our result matches with several studies.^{4,6,9,12-15} We had complications in the form of ptosis and ecchymosis which have been reported in some studies. Other complications as diplopia and ocular mobility affection have been reported by Uddin and Davies.⁹ There was a decrease in flicking caused by BTX-A injection which could be a risk of dry eye treated by tear substitutes.

With regard to the duration of action, HA was effective all over the period of study (6 months) by just a single injection. This agrees with Kohn and colleagues¹ who *found* persistence in the effect of HA for 15 months. The effect of BTX-A remained for (19.00 ± 1.71 weeks) by a single session. This matches with Ozkat and colleagues,¹²

Shih and colleagues,¹⁴ Costa and colleagues,¹⁵ and Salour and colleagues⁶ but does not match with Uddin and Davies⁹ as their patients received multiple injections.

This study is the first to compare the effect of HA and BTX-A in thyroid lid retraction. The minimally invasive techniques are good choices for patients who refuse surgery or are poor surgical candidates. Our study showed that HA has better results, longer duration, and fewer side effects in comparison with Botox. Also, its effect can be reversible by injection of hyaluronidase.⁸

This study has some limitations. The first one is the small number of patients. The second is the limited follow-up period. In addition, the baseline severity of upper eyelid retraction was variable.

In conclusion, HA filler has better result in treating thyroid upper eyelid retraction than BTX-A due to its predictable controllable effect, also, due to longer duration of action and fewer side effects.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.


Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Ethics statement

This study followed the Declaration of Helsinki. The study was approved by the Research Ethics Committee of Faculty of Medicine for Girls, Cairo, Al-Azhar University (FMG IRB No. 202001082). The study participants provided written informed consents.

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