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ORIGINAL RESEARCH

Preseptal and Pretarsal Botulinum Toxin Injection in Hemifacial Spasm and Blepharospasm: A 10-Year Comparative Study

Chutithep Teekaput[1,2], Kanokkarn Teekaput[1], Kitti Thiankhaw[1,2]

[1]Division of Neurology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, 50200, Thailand; [2]The Northern Neuroscience Centre, Faculty of Medicine, Chiang Mai University, Chiang Mai, 50200, Thailand

Correspondence: Kitti Thiankhaw, Division of Neurology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, 110, Inthawaroros Road, Sriphum, Chiang Mai, 50200, Thailand, Tel +66 5393 5899, Fax +66 5393 5481, Email kitti.th@cmu.ac.th

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Purpose: Preseptal and pretarsal botulinum toxin injections are approved for treatment of hemifacial spasm and blepharospasm. However, the long-term data is limited. We compared the efficacy, safety, and costs between preseptal and pretarsal injection in hemifacial spasm and blepharospasm.

Patients and Methods: The data were retrieved between 2011 and 2021. Consecutive hemifacial spasm and blepharospasm botulinum toxin patients were categorized as preseptal or pretarsal. Study outcomes were the difference in pre-and post-treatment modified Jankovic scale, self-reporting scales, time-related treatment, safety, and cost.

Results: Of 152 botulinum toxin-injected patients, 117 (77.0%) patients had hemifacial spasm and 35 (33.0%) patients had blepharospasm. Analysis included data pertinent to 1665 injections in hemifacial spasm (920 preseptal and 745 pretarsal) and 527 injections in blepharospasm (210 preseptal and 317 pretarsal). The difference between pre-and post-treatment modified Jankovic scale was lower in the preseptal group than in the pretarsal group in both hemifacial spasm and blepharospasm (1.5±0.8 vs 1.8±0.6, P-value <0.001 and 1.8±0.8 vs 3.1±0.9, P-value <0.001). There was no difference in duration of maximum response in hemifacial spasm between groups, while the blepharospasm with preseptal had a longer duration than blepharospasm with pretarsal. The preseptal injection was associated with more adverse events overall than the pretarsal (9.4% vs 5.2%, P-value <0.001). The total dose and cost per session in the preseptal group is lower for onabotulinum toxin but higher for abobotulinum toxin.

Conclusion: Pretarsal injections reduced symptom severity with fewer side effects. Further studies on the pharmacoeconomics of both techniques are required.

Keywords: hemifacial spasm, blepharospasm, botulinum toxin, pretarsal, preseptal

Introduction

Hemifacial spasm (HFS) and benign essential blepharospasm (BEB) are the most common and debilitating craniocervical abnormal movement disorders arising from the peripheral nervous system (PNS). HFS is characterized by involuntary unilateral eyelid twitching, which occasionally extends to the unilateral perioral and neck muscles.[1] HFS is considered a rare condition with an estimated prevalence of 14.5 per 100,000 women and 7.4 per 100,000 men globally. Asians are more affected than Western people, and most affected individuals are in early adulthood.[2] On the other hand, BEB is a focal dystonia characterized by the simultaneous contraction of agonist and antagonist periorbital muscles, resulting in involuntary eyelid closure.[3,4] The estimated global prevalence ranges from 20 to 133 cases per million and varies across geographical areas.[5] The condition is thought to be due to a structural defect that leads to neurotransmitter dysregulation.[4] However, the exact cause of BEB is not well understood, and consequently, there is no definitive cure for BEB.

The primary goal of therapy in both diseases is to reduce the abnormal muscle contractions resulting from abnormal impulse transmissions to adjacent neurons. In milder diseases, oral medication such as clonazepam, carbamazepine,

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gabapentin, anticholinergics, and haloperidol may be used to relieve the muscle spasm. However, the major drawbacks of most of these medications are the side effects, such as excessive sedation and fatigue associated with their long-term use. The advent of botulinum toxin has revolutionized the management of HFS and BEB. Onabotulinum toxin and Abobotulinum toxin are the most common botulinum toxins used in HFS and BEB. In addition, there are two main botulinum toxin injection techniques, specifically the pretarsal technique (PT) and the preseptal technique (PS).[6–9] However, there are comparatively few studies focusing on botulinum toxin injection techniques and the type of botulinum toxin in treating both BEB and HFS. Additionally, the number of long-term and real-world studies appears to be very scarce. Our study aimed to compare the efficacy and safety of PT and PS botulinum toxin injection techniques from our 10-year botulinum toxin clinic registry. The study results will guide doctors in administering botulinum toxin injections, particularly for Thai and Asian patients.

Materials and Methods

Study Design and Population

This is a retrospective study and data were retrieved from Maharaj Nakorn Chiang Mai Hospital botulinum toxin clinic registry from January 2011 to December 2021. Data pertinent to consecutive adult patients who were aged 18 years or over and diagnosed with HFS or BEB was prospectively collected from the registry. The study was approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University, certificate of approval number 2565–08941.

Data Collection and Outcomes

HFS and BEB patients would have consulted experienced neurologists at the botulinum toxin clinic to have a verified diagnosis. The neurologists subsequently reviewed the clinical data and evaluated the pre-treatment modified Jankovic scale (mJS). The score is divided into five categories, ranging from 0 to 4, a zero score implying no impairment, and a score of four indicating a severe, incapacitating spasm.[10] After a thorough evaluation, neurologists would administer botulinum toxin injections, the choice of the toxin type depending on their assessment. In the case of the PS injection technique, two injections were subcutaneously administered in the upper septal region, and two injections subcutaneously placed in the lower septal region of the orbicularis oculi muscles. (see Figure 1A). The PT injection technique, on the other hand, involved four separate injection sites with two injections subcutaneously administered to the medial and lateral pretarsal segments of the upper eyelid and the remaining two to the middle and lateral pretarsal segments of the lower eyelid. (See Figure 1B) Subcutaneous injections were administered in all cases with 30-gauge, 0.5-inch needles, and an insulin syringe while laying supine with their eyelids closed. In the case of HFS, botulinum toxin injections were given at the affected site in the orbicularis oris, zygomaticus major, levator labii superioris, and the mentalis muscles.

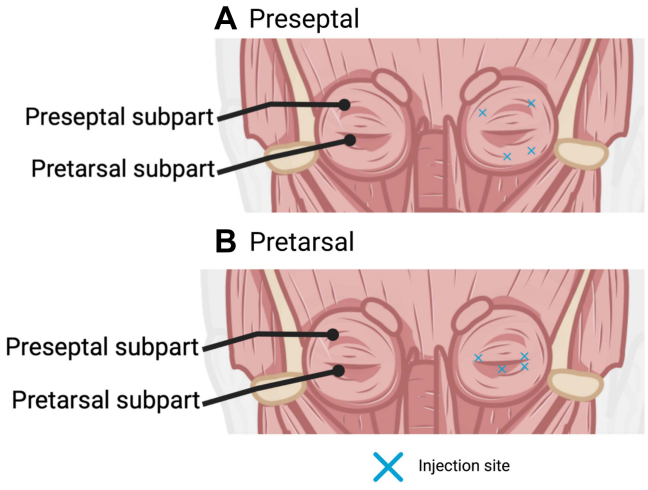

Figure 1 Botulinum Toxin Injection Techniques and Location of Injection. (**A**) Preseptal injection. (**B**) Pretarsal injection.

A three-month follow-up was carried out in all cases to evaluate the post-treatment mJS and collect the data from the self-rating scales. The patient's level of satisfaction was recorded using self-rating scales ranging from 0 to 10 were. A score of 0 stood for very unsatisfied and the score of 10 stood for very satisfied. At the follow-up time, other clinical outcomes, including latency to response, duration of response, adverse events and additional use of clonazepam, were also documented. Additionally, the cost of therapy per injection was investigated. Cost of therapy included botulinum toxin cost, syringe and needles, sterilization equipment, and treatment-related fees. PT and PS injection techniques, as well as botulinum toxin types (Onabotulinum toxin and Abobotulinum toxin), were also compared in terms of the aforementioned parameters.

Statistical Analysis

Clinical data are presented as numbers and proportions, mean and standard deviation (SD), or median and interquartile range (IQR) as appropriate. Comparisons between groups were performed using Student's *t*-test, Mann–Whitney *U*-test, Chi-square test or Fisher's exact test as appropriate. A two-sided test at a p-value of < 0.05 was used to indicate statistical significance. All statistical analyses were performed using licensed Stata statistical software version 16.0 (Stata Statistical Software: Release 16.0, Stata Corporation, College Station, TX, 2019).

Results

Demographic Data and Difference of mJS by Injection Techniques

During this 10-year-period, 180 patients who met the inclusion criteria were included in the study. 28 patients had incomplete data and were excluded. Out of those remaining, 152 patients, 117 (77.0%) patients had HFS. In 60.7% of HFS patients, 71 out of 117, were treated using the PS method. HFS patients in the PS group had a shorter disease duration before botulinum toxin administration than the PT group (2.8±1.0 vs 3.4±1.1 years, *P*-value = 0.009). There is no evidence of any differences between the two groups in the remaining characteristics, including age, gender, symptomatic left-side, pre-treatment mJS, or type of botulinum toxin used. On the contrary, 65.7% of BEB patients (23 out of 35) were injected using the PT technique and had a higher pre-treatment mJS, compared to the PS group (3.3±0.8 vs 2.5±0.5 points, *P*-value = 0.004). There were no significant differences in the remaining parameters for BEB patients (Table 1). The difference between pre-treatment and post-treatment mJS is lower in the PS group than in the PT group in both HFS and BEB (1.5±0.8 vs 1.8±0.6, *P*-value <0.001 and 1.8±0.8 vs 3.1±0.9, *P*-value <0.001, respectively) (Table 2).

Table 1 General Demographic Data of HFS and BEB Categorized by PS and PT Injection Techniques

Characteristics	HFS			BEB		
	PS (n=71)	PT (n=46)	*P*-value	PS (n=12)	PT (n=23)	*P*-value
Age (years) - mean±SD	58.7±10.4	61.0±13.9	0.316	63.0±10.2	60.5±8.9	0.463
Female (n, %)	62 (87.3)	38 (82.6)	0.593	12 (100.0)	23 (100.0)	1.000
Symptomatic left side (n, %)	46 (64.8)	22 (47.8)	0.085	NA	NA	NA
Duration of disease (years) - mean±SD	2.8±1.0	3.4±1.1	0.009*	2.5±0.9	1.8±1.2	0.100
BMI (kg/m2) - mean±SD	22.0±4.4	22.9±4.3	0.237	20.1±3.8	21.4±2.3	0.230
Pre-treatment mJS (points) - mean±SD	2.2±0.6	2.4±0.5	0.063	2.5±0.5	3.3±0.8	0.004*
Onabotulinum toxin use (n, %)	49 (69.0)	31 (67.4)	1.000	9 (75.0)	9 (39.1)	0.075
Abobotulinum toxin use (n, %)	22 (31.0)	15 (32.6)	1.000	3 (25.0)	14 (60.9)	0.075

Note: *Statistically significant.
Abbreviations: BEB, blepharospasm; HFS, hemifacial spasm; mJS, modified Jankovic scales; NA, not available; PS, preseptal; PT, pretarsal; SD, standard deviation.

Table 2 Mean Difference of Pre- and Post-Treatment Modified Jankovic Scales of HFS and BEB Categorized by PS and PT Injection Techniques*

Difference of Pre- and Post-Treatment mJS	PS	PT	*P*-value
HFS (points) - mean±SD	1.5±0.8	1.8±0.6	<0.001**
BEB (points) - mean±SD	1.8±0.8	3.1±0.9	<0.001**

Notes: *All data analyzed from all botulinum toxin sessions comprising 1665 injections in HFS (920 PS and 745 PT) and 527 injections in BEB (210 PS and 317 PT). **Statistically significant.
Abbreviations: BEB, blepharospasm; HFS, hemifacial spasm; mJS, modified Jankovic scales; PS, preseptal; PT, pretarsal; SD, standard deviation.

Clinical Outcomes of Preseptal and Pretarsal Botulinum Toxin Injection Techniques in HFS and BEB

A statistical difference in latency to response was observed in both diseases. HFS patients in the PS group had a longer duration of latency to the first response (1.3±0.9 vs 1.2±0.9 weeks, *P*-value <0.001), in comparison to the PT group of BEB patients (1.0±0.4 vs 1.4±0.8 weeks, *P*-value <0.001). In addition, BEB patients treated with the PS technique had a more sustained maximal response and higher post-treatment mJS (12 (9, 12) vs 9 (8,12) weeks, *P*-value <0.001 and 1 (0, 1) vs 0 (0, 1), *P*-value <0.001, respectively). There was no evidence of any statistical difference between the two techniques in these parameters in HFS patients. A higher proportion of additional clonazepam used was found in HFS patients treated with the PS injection method but it did not result in different daily doses of the medication used. In both conditions, the injection by PS technique used less total dose per injection of onabotulinum toxin, resulting in lower medication cost per visit. Contrarily, the PS technique using more abobotulinum toxin per visit than the PT injection method (Table 3).

Safety and Adverse Events

Considering all 2192 botulinum toxin injection sessions, there was a higher incidence of adverse events in the PS group than in the PT group (9.4% vs 5.2%, *P*-value <0.001). Ptosis, ecchymosis and irritation occurred significantly more frequently in the PS group than in the PT group (3.3% vs 2.5%, *P*-value = 0.013, 0.5% vs 0.0%, *P*-value = 0.031, and 5.0% vs 2.3%, *P*-value 0.011, respectively). In this registry, 1633 sessions of onabotulinum toxin injection and 559 sessions of abobotulinum toxin injection were administered. There was no difference in overall adverse events between onabotulinum toxin and abobotulinum toxin sessions (Table 4).

Discussion

HFS and BEB are regarded as two of the most problematic movement diseases since they interfere with everyday life and cause cosmetic concerns. Since the adoption of botulinum toxin for the treatment of HFS and BEB in 1984–1985,[11,12] extensive studies have demonstrated its efficacy and safety. To date, three A subtypes (onabotulinum toxin, incobotulinum toxin, and abobotulinum toxin) and one B subtype (rimabotulinum toxin) have been approved for clinical use.[13]

HFS is characterized by involuntary unilateral eyelid twitching, which occasionally extends to the unilateral perioral and neck muscles. In most cases, the underlying pathology is the impingement of aberrant and ectatic blood vessels on the facial nerves at the nerve exit site.[1,2] Neurovascular decompression is considered the treatment of choice but carries worrisome risks. In 1984, botulinum toxin was initially administered to three patients, followed by 15 patients in one observational trial in 1985.[11,12] Since then, several studies have examined its effectiveness and also adverse effects.[14–16] However, the degree of improvement across HFS studies varies. The mJS (scale 0–4 from no to severe symptoms), global clinical improvement scale (scale 0–3 ranging from no improvement to complete improvement), Fahr-Marsden scale (scale 0–4 ranging from no dystonia to resting dystonia), HFS rating scale (scales 0–4 from no spasm to severe spasm), and visual analog scale (VAS) were examples of clinical scales used for evaluation of severity and comparative parameters after treatment.[10,17] The mJS was implemented in our research due to its applicability. Our study revealed that the PT technique was more effective for treating HFS as shown by the greater difference between pre-and post-treatment mJS. This finding was compatible with previous studies. Çakmur et al demonstrated that the patients injected with the PT

Table 3 Clinical Outcomes of HFS and BEB Categorized by PS and PT Injection Techniques*

Characteristics	HFS			BEB		
	PS (n=920)	PT (n=745)	*P*-value	PS (n=210)	PT (n=317)	*P*-value
Self-reporting scale (points) – median (IQR)	8.0 (7.0, 10.0)	8.0 (8.0, 9.5)	0.201	8.0 (7.0, 10.0)	9.0 (8.0, 9.5)	<0.001**
Post-treatment mJS (points) – median (IQR)	1 (0, 1)	1 (0, 1)	0.794	1 (0, 1)	0 (0, 1)	<0.001**
Latency to response (weeks) – median (IQR)	1.3±0.9	1.2±0.9	<0.001**	1.0±0.4	1.4±0.8	<0.001**
Duration of maximum response (weeks) – median (IQR)	10 (8, 12)	10 (8, 12)	0.509	12 (9, 12)	9 (8, 12)	<0.001**
Additional clonazepam used (n, %)	350 (38.0)	40 (5.4)	<0.001**	0 (0.0)	0 (0.0)	1.000
Dose of clonazepam use per day (mg) – median (IQR)	1 (1, 1)	1 (1, 1)	0.405	NA	NA	1.000
Onabotulinum toxin (n, %)	617 (72.9)	582 (78.1)	0.016**	162 (77.1)	218 (68.8)	0.038**
Abobotulinum toxin (n, %)	249 (27.1)	163 (21.9)	0.016**	48 (22.9)	99 (31.2)	0.038**
Total dose per time (Onabotulinum) (units) - mean±SD	14.5±5.7	25.6±8.0	<0.001**	19.7±1.5	23.8±3.0	<0.001**
Total dose per time (Abobotulinum) (units) - mean±SD	45.9±12.2	35.4±11.4	<0.001**	77.3±4.9	52.7±9.3	<0.001**
Cost per time Onabotulinum toxin (x1000 THB) - mean±SD	2.4±0.7	3.8±1.0	<0.001**	3.0±0.1	3.6±0.4	<0.001**
Cost per time Abobotulinum toxin (x1000 THB) - mean±SD	1.9±0.4	1.6±1.6	<0.001**	2.8±0.1	2.1±0.3	<0.001**

Notes: *All data analyzed from all botulinum toxin sessions comprising 1665 injections in HFS (920 PS and 745 PT) and 527 injections in BEB (210 PS and 317 PT). **Statistically significant.
Abbreviations: BEB, blepharospasm; HFS, hemifacial spasm; IQR, interquartile range; mJS, modified Jankovic scales; PS, preseptal; PT, pretarsal; SD, standard deviation; THB, Thai Baht.

Table 4 Safety and Adverse Events of Botulinum Toxin Injection Classified by Injection Techniques and Type of Botulinum Toxin Used

Adverse Events	Injection Technique			Type of Botulinum Toxin		
	PS (n=1130)	PT (n=1062)	*P*-value	Onabotulinum Toxin (n=1663)	Abobotulinum Toxin (n=599)	*P*-value
Total event (events) - (n, %)	106 (9.4)	55 (5.2)	<0.001*	120 (7.3)	41 (7.4)	1.000
Ptosis (events) - (n, %)	37 (3.3)	17 (2.5)	0.013*	43 (2.6)	11 (2.0)	0.433
Ecchymosis (events) - (n, %)	6 (0.5)	0 (0.0)	0.031*	3 (0.2)	3 (0.5)	0.177
Tearing (events) (n, %)	26 (2.3)	18 (1.7)	0.362	33 (2.0)	11 (2.0)	1.000
Irritation (events) (n, %)	56 (5.0)	30 (2.3)	0.011*	61 (3.7)	25 (4.5)	0.449
Others (events) (n, %)	10 (0.9)	0 (0.0)	0.002*	10 (0.6)	0 (0.0)	0.074

Note: *Statistically significant.
Abbreviations: PS, preseptal; PT, pretarsal.

technique had lower post-treatment scores (score 0 to 4, from no spasm to severe spasm) and a higher score from the modified Toronto Western Spasmodic Torticollis Rating Scale (TWSTR) (score −1 to 5, from worse response to striking improvement).[9] Lolekha et al demonstrated that the PT group had favorable outcomes, as shown by considerably lower

post-treatment mJS.[18] Patients treated with the PS technique had higher self-reporting scales but the differences were not statistically significant, however, this pattern was consistent with earlier research. Our findings showed the latency to response in the PS group was longer than in the PT group. Contrarily, the previous studies showed no difference between the two techniques.[9] In our study, the peak response lasted roughly 10 weeks in both the PS and PT groups. However, a previous study reported a shorter response duration in the PS group.[9] Differences between observational and randomized-controlled trials may account for inconsistent results. In the PT group, the rescue dosage of clonazepam was considerably lower. We also showed that independent of botulinum toxin type, the cost per session of PT was less than the PS technique.

In the case of BEB, the PT technique also demonstrated favorable outcomes, specifically a higher mean difference of pre-and post-treatment mJS and a higher self-reporting scale, both compatible with previous studies.[9,19] Most studies showed that the PT injection carried shorter latency to response duration and more extended maximum response. No additional clonazepam use was reported in BEB patients in our study. Intriguingly, the cost per session of PT was lower than that of PS, demonstrating the same trend as HFS.

The PT approach is associated with a lower incidence of adverse events. Irritation, ptosis, and ecchymoses were less frequently reported in the PT group, again findings which were coherent with previous studies.[9,14,19] We also analyzed the differences between botulinum toxin types, but there were no significant differences in the occurrence of adverse events. We may assume that, regardless of the types of botulinum toxin, all adverse effects were mediated by different techniques.

The orbicularis oculi muscle is the muscle primarily affected in both HFS and BEB. The muscles can be divided into two groups, the orbital and palpebral parts, the latter being further subdivided into preseptal and pretarsal subparts. Even though both subparts are responsible for eyelid closures, there are histologically different. The pretarsal subpart has more skeletal muscles and a higher innervation density per region than the preseptal subpart, resulting in greater responsiveness to botulinum toxin therapy.[6,14] Furthermore, the pretarsal component contains a higher proportion of type 2 muscle fibers, which are generally shorter in length, resulting in greater botulinum toxin injection penetration than the preseptal subpart, which contains significantly larger type 1 fibers.[6,20]

Similar to earlier studies, the PS injection presents a greater risk of adverse effects, including ptosis, irritation, tears, and ecchymosis.[7,8,18] The preseptal subpart of orbicularis oculi is located closer to the muscle that assists with eyelid elevation, the levator palpebrae, and an injection of botulinum toxin at the location might result in ptosis. Histologically, the preseptal component includes more adipose tissue, resulting in inadequate support for the eyelid muscles.[20,21] Ecchymosis was reported when utilizing the PS approach, as shown in earlier investigations. This observation can be explained by the abundance of underlying subdermal capillaries in the preseptal subpart. Our findings indicate that all botulinum toxin-associated problems were related to injection technique, not the kind of toxin.

The cost per session for onabotulinum toxin is greater in both HFS and BEB due to the significantly larger doses required to achieve the desired therapeutic effect. Contrarily, injections in the PT technique of abobotulinum toxin appeared cheaper than the PS technique. A previous study showed that the PT technique is cheaper than PS in all HFS, BEB, and cervical dystonia.[22] The differences may result from variations in dosage, injection site, and treatment costs across studies.

Although our study was a long-term and real-world registry of botulinum toxin injection in a university-based clinic, there were some limitations. First, the natural characteristics of a retrospective observational study would involve some missing data. Second, we used mJS and self-reporting scales to define the clinical outcomes, which might bring a minor variation when comparing findings with other studies. Lastly, the ability for peer review was limited as there are few studies focusing on the cost-effectiveness and cost-safety associated with botulinum toxin type and injection technique. We believe that a well-designed study on the cost-effectiveness and cost-safety of individual injection techniques is warranted.

Conclusion

The PT botulinum toxin injection is efficacious in both HFS and BEB, resulting in greater patient satisfaction with a lower incidence of adverse events in comparison to the PS technique. In addition lower dosage and cheaper cost per session were observed in the PT group. Further cost-effective and cost-safety studies are required.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

The study was approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University, certificate of approval number 2565-08941. The requirement for informed consent was waived because the retrospective and noninterventional study collected data from previous electronic medical records and did not involve personal privacy and commercial interests. The study involves no more than minimal risk to subjects, and the waiver will not adversely affect the rights and welfare of the subjects. The data were anonymized or maintained with confidentiality. The publication of this study is in accordance with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

All authors report no conflicts of interest in this work.

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