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Review Article

Will repeated botulinum toxin A improve detrusor overactivity and bladder compliance in patients with chronic spinal cord injury?

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Abstract

Chronic spinal cord injury (SCI) can induce neurogenic detrusor overactivity (NDO), leading to urinary incontinence and renal damage due to low bladder compliance and high detrusor pressure during the storage and voiding of urine. In 2011, Botox® (onabotulinumtoxinA, botulinum neurotoxin serotype A [BoNT-A]) was approved by the Food and Drug Administration for the treatment of NDO. Intradetrusor injection of BoNT-A has been shown to have clinical utility for the treatment of urinary incontinence, with consequent improvements in quality of life for patients. In the past 20 years, this treatment has been shown to be an effective treatment for patients with SCI refractory to antimuscarinic medication. The present review focused on publications in MEDLINE/PubMed relating to botulinum toxin to evaluate the treatment outcomes of repeated injection of BoNT-A, the mechanisms of action, results of clinical and urodynamic studies, and adverse effects.

Keywords: *Bladder compliance, Botulinum toxin A, Detrusor overactivity, Spinal cord injury*

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Introduction

A worldwide investigation revealed the incidence of spinal cord injury (SCI) to be 12.1–57.8 per million, representing a significant cause of morbidity and mortality in most developing countries [1]. In patients with chronic SCI, there are two major problems which can occur due to neurogenic lower urinary tract dysfunction (NLUTD): (1) failure to store urine due to detrusor overactivity (DO) or urethral incompetence and (2) failure to empty the bladder due to detrusor areflexia, bladder neck dysfunction, or detrusor sphincter dyssynergia (DSD). Most patients usually exhibit complications, experiencing problems with both storage and emptying of the bladder, which results in poor quality of life (QoL) [2]. More seriously, high intravesical pressure may damage the upper urinary tract, which can cause renal scarring and chronic renal insufficiency if it is not well managed [3]. In the case of SCI, high intravesical pressure is a result of poor bladder compliance during the storage phase and DO with DSD in voiding phase. Several studies had shown good therapeutic efficacy of onabotulinumtoxinA (botulinum neurotoxin serotype A [BoNT-A]) intradetrusor injection in SCI patients to inhibit DO which improving incontinence and QoL [4,5]. However, to maintain large bladder compliance is also very important because low bladder compliance would lead to high bladder pressure with little urine volume during the storage which increased renal loading. Therefore, the aim of this study is to search the long-term outcome of improving DO and bladder compliance by repeated botulinum toxin A injection.

Bladder compliance is described by a mathematical expression of the volume of urine required to produce a unit rise in pressure, which is measured during cystometric filling [6]. This parameter indicates how the bladder wall will react to stretching. The value of bladder compliance in urodynamic study is calculated by the infusion volume divided by elevated pressure in the storage phase, which is $\Delta V/\Delta P$. According to the guidelines of the European Association of Urology, the primary goal of treatment for NLUTD is protecting renal function and preventing urinary tract infection [7]. The goal of treatment is to decrease the detrusor leak point pressure to <40 cmH_2O in the storage phase [7]. Over the last two decades, several studies have demonstrated that injection of onabotulinumtoxinA (BoNT-A) into the detrusor can have therapeutic benefits to patients with SCI in terms of neurogenic DO (NDO) and QoL [8-11]. Our previous studies have demonstrated that the repeated BoNT-A injections can improve urodynamic parameters, renal function, and bladder urothelium dysfunction [12-15]. The present article aims to

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provide a state-of-the-art review of the utility of botulinum toxin A in the case of chronic SCI with NDO and poor bladder compliance.

This review study searched relevant articles from 2000 to 2019 using MEDLINE/PubMed. The keywords included spinal cord injury, neurogenic detrusor overactivity, bladder compliance, botulinum toxin, Botox, and BTX-A, repeated injection. All papers identified were English language, full-text papers. References of retrieved articles were also hand-searched to find additional articles that may have been missed in the database search. All trials were checked the use of repeated BoNT-A injections into the detrusor for the treatment for NDO after SCI. Treatment outcomes such as urodynamic reports, urinary incontinence improvement, and adverse events were all included for discussing.

How does spinal cord injury cause low urinary tract dysfunction?

Although the underlying pathophysiology of DO and altered compliance induced by chronic SCI were well studied, the mechanisms are not fully understood. In healthy individuals, the bladder afferent pathways consist of small, myelinated A-delta and unmyelinated C-fibers. The A-delta fibers primarily transmit signals from mechanoreceptors which detect bladder fullness or wall tension, while the C-fibers transmit noxious signals and initiate painful sensations. In patients with SCI, the reflex connections of the spinal cord appear to undergo considerable reorganization following interruption of the descending pathways from the brain. As a result of this aberrant neural input, such patients commonly experience extensive fibroproliferative remodeling of the bladder, resulting in diminished functional capacity and DO, with consequent poor bladder compliance [16]. Elevated bladder pressure during the storage phase due to either low bladder compliance or DO is the major cause of renal deterioration [17].

In 1990, de Groat *et al*. demonstrated that the C-fibers compensate as the afferent limb of the voiding reflex in a rat model of SCI [18]. Besides, rapid disruption of the uroepithelial barrier in SCI bladder, which manifests as loss of cell–cell interactions, decreased transepithelial resistance and increased water and urea permeability [19]. The bladders of patients with SCI exhibit decreased expression of urothelial adhesion protein E-cadherin and junction protein zonula occludens-1, while suburothelial inflammation and urothelial cell apoptosis are increased. These molecular features suggest that urothelial dysfunction, increased suburothelial inflammation, and apoptosis coexist in patients with chronic SCI [20]. Together, these factors might also alter the expression of sensory molecules including purinergic receptor P2X ligand-gated ion channel 3 (P2X3), transient receptor potential vanilloid receptor subfamily 1, adenosine triphosphate, and nitric oxide (NO). Urothelial dysfunction may also lead to increased excitability of C-fibers, which then become the predominant afferent nerves involved in regulation of the micturition reflex after SCI. Changes in the bladder reflex pathway may result in NDO and urinary incontinence after SCI.

The observed neuroplasticity of bladder afferents after SCI might be attributable to urothelial dysfunction or changes in the expression of urothelial sensory proteins [21]. Proteins including M2, M3, and endothelial NO synthase have been shown to be significantly downregulated in bladder urothelium samples of patients with SCI compared with healthy individuals, demonstrating the influence of sensory proteins on the pathophysiology of NDO [22]. Disruption of the urothelial barrier initiates a cascade of bladder dysfunction events, eventually resulting in suburothelial inflammation and vulnerability to chronic or recurrent cystitis and/or bacterial infection. Suburothelial inflammation might also affect urothelial function, leading to a perpetuating cycle.

The evolution of botulinum toxin type a in treatment of neurogenic detrusor overactivity

In the 20th century, anticholinergics were the standard first-line treatment for NDO in patients with chronic SCI. However, many patients are unable to tolerate the side effects long-term treatment with these drugs, which include dry mouth, visual disturbance, and constipation. Intravesical therapy became popular in the 1990s, with the instillation of vanilloid compounds such as capsaicin and resiniferatoxin becoming the subject of much research into the treatment of neurogenic and non-NDO. Capsaicin acts selectively on unmyelinated C-fibers, which are thought to become predominant in reflex contractions of the bladder after SCI [23,24]. Resiniferatoxin is an ultrapotent analog of capsaicin which induces similar desensitization effects as capsaicin with less undesirable effects [25,26]. However, although resiniferatoxin exhibits superior efficacy, the duration is not consistent [26].

In 2000, Schurch *et al*. [8] published the first report on the injection of botulinum toxin type A (Botox, Allergan® 200/300 units) into the detrusor muscle of patients with SCI for the treatment of NDO. The authors reported the induced bladder paresis to persist for at least 9 months. In 2005, Schurch reported the results of the first randomized, placebo-controlled study of injection of BoNT-A into the detrusor, which demonstrated the rapid, well-tolerated, clinically significant decrease in urinary incontinence in response to the drug [27]. Another type of botulinum toxin type A (Dysport®, Ipsen Biopharm, Slough, UK) is also currently used for the treatment of NDO, with the administration of around 750–1000 U by injection into the detrusor reported to be effective [3,5]. A review of the use of neurotoxins for the treatment of urinary incontinence in patients with SCI concluded that BoNT-A therapy required fewer treatments with longer intervals between treatments than resiniferatoxin [28]. Compared with traditional therapy, injection of BoNT-A injection is significantly more efficacious than oral oxybutynin in terms of the improvement in urinary continence, urodynamic parameters, and QoL [29]. In the last two decades, several open-label studies have revealed that detrusor injection of 200 or 300 U of BoNT-A can improve clinical and urodynamic parameters and QoL in patients with refractory NDO following SCI [4,9,11,30,31].

In 2011, Botox® (onabotulinumtoxinA) was approved by the USA Food and Drug Administration for the treatment of NDO associated with conditions such as SCI and multiple sclerosis [32]. The dose of BoNT-A for such treatment was controversial until recent global, phase III, multicenter trials revealed that administration of either 200 or 300 U of BoNT-A caused a significant reduction in urinary incontinence and improved urodynamic parameters and QoL of patients with NDO. No clinically relevant differences were observed in terms of efficacy or duration of effect between the two doses. However, the 200-U dosage was associated with fewer adverse effects [10,33]. After BoNT-A treatment, the subjective primary outcome of "dryness" was achieved in 62.9% of patients receiving 200 U of BoNT-A and 61.6% of those receiving 300 U [34]. Therefore, recent consensus for the ideal dose is 200 U for the treatment of NDO [35]. A recent systemic meta-analysis including 17 studies and 1455 patients with SCI demonstrated BoNT-A to be effective in increasing maximum cystometric capacity, volume at first involuntary detrusor contraction, cystometric bladder capacity (all $P < 0.00001$), bladder compliance ($P = 0.001$), and complete dryness ($P = 0.0003$) and in decreasing detrusor pressure (Pdet) and the incidence of DO (both $P < 0.00001$) [36]. Several reports have shown combined detrusor and urethral injection to decrease detrusor leak-point pressure in the case of DSD [37-40].

With regard to adverse effects of BoNT-A, patients should be made aware of the risks of high post-void residual volume or retention with the potential requirement of self-catheterization, mild hematuria, and urinary tract infection. Other rare (<5%) side effects include nausea, vomitus and flu-like symptoms, depression, muscle spasm, constipation, muscle weakness, insomnia, dizziness, diarrhea, and *de novo* autonomic dysreflexia [41]. Wyndaele and Van Dromme reported distant muscular weakness to be a side effect of administration of 300 U Botox or 1000 U Dysport [42].

Pathophysiology and mechanism of botulinum toxin type A in the treatment of neurogenic detrusor overactivity and bladder compliance

Botulinum toxin was first described by van Ermengem in 1897, which was extracted from the bacterium *Clostridium botulinum* [43]. The toxin mediates proteolytic cleavage of protein subunits of soluble N-methylmaleimide-sensitive attachment protein receptor (SNARE) proteins in the synaptic terminal. There are seven BoNT serotypes (A–G); each serotype specifically and noncompetitively cleaves one site of one member of the SNARE protein family: BoNT-A cleaves synaptosomal-associated protein with a molecular weight of 25 kDa (SNAP-25); BoNT-C cleaves syntaxin; and serotypes B, F, and G cleave vesicle-associated membrane protein/synaptobrevin [44]. The SNARE proteins play a ubiquitous role in vesicle-membrane fusion during neurotransmitter release in both the peripheral and central nervous systems; thus, BoNT-A blocks presynaptic neurotransmitter release by binding to gangliosides and interacting with synaptic vesicle protein 2, in order to cleave SNAP-25. As SNAP-25 is necessary for the fusion of synaptic vesicles at the cellular membrane, SNARE-mediated exocytosis of several neurotransmitters is therefore inhibited [45]. Several studies have demonstrated that treatment of neuronal systems and cell cultures with BoNT-A inhibits the release of acetylcholine, substance P, glutamate, and calcitonin gene-related peptides [46-49]. Furthermore, botulinum toxin may also act on afferent pathways, particularly via subepithelial neuromediators. Patients with NDO have been demonstrated to have increased transient receptor potential cation channel subfamily V member 1 and purinergic receptor P2X3-immunoreactive suburothelial innervation. Another study has shown that BoNT-A inhibits the release of adenosine triphosphate from the urothelium [50]. Bladder levels of neurotrophic growth factor have been reported to decrease significantly in patients with NDO who receive treatment with BoNT-A [51]; the toxin appears to inhibit the release of norepinephrine to alpha- and beta3-adrenoreceptors, which are involved in bladder neck contraction and detrusor relaxation [52]. Therefore, BoNT-A has a complex inhibitory effect on vesicular release of excitatory neurotransmitters as well as the axonal expression of other proteins in the urothelium or suburothelium. Above evidence indicated that BoNT-A inhibits both the sensory and motor arms of the micturition reflex which can reduce NDO.

Bladder compliance is determined by the viscoelastic properties of bladder components such as the smooth muscle, collagen, and elastin, and poor compliance is correlated with the presence of neurological conditions and degree of inflammation [53]. Persistent inflammation including suburothelial inflammation leads to urothelium dysfunction [21]. Several studies have presented evidence of the anti-inflammatory effects of BoNT-A injection. Using an animal model, Khera *et al*. showed that adenosine triphosphate (ATP) is significantly inhibited by intravesical instillation of BoNT-A in the bladders of rats with SCI [50]. NO can be released from bladder urothelium in response to stretch [54]. Smith *et al*. reported that abnormal levels of urothelial ATP and NO improved following BoNT-A treatment [55]. Lucioni *et al*. reported BoNT-A injection to significantly inhibit the release of substance *P* and calcitonin gene-regulated peptide in the case of acute and chronic bladder inflammation in rats [56]. In our previous study, we found that intradetrusor injection of BoNT-A improved urothelium dysfunction; urothelial barrier function recovered after BoNT-A injections due to improvements in the adhesive and tight-junction protein levels [15,57]. This result might, in part, explain the mechanism of BoNT-A through the anti-inflammatory effects which altered compliance.

The efficacy of repeated injection of botulinum toxin Type A

A Phase III clinical trial revealed the median time to retreatment request to be greater following administration of 200 or 300 U of BoNT-A than placebo (256 and 254 days, respectively, vs. 92 days) [10]. Our previous study found the regained urinary continence or improved urgency of single detrusor injection of 200 U of BoNT-A to be 73.3% among patients with SCI and NDO, with therapeutic effects lasting 3–9 months (mean, 5.3 months) [11].

Giannantoni *et al*. reported that 17 cases, during 6 years of follow-up after repeated injection of BoNT-A, experienced significant improvements in the first uninhibited detrusor contraction and maximum bladder capacity ($P < 0.001$ for both) and significantly decreased maximum pressure of contractions ($P < 0.01$). Fifteen (88.2%) patients were completely continent after treatment [58]. Hori *et al*. reported that 67% SCI patients were still actively undergoing repeat BoNT-A injections, and among the 48 patients, 43 (90%) were satisfied with BoNT-A for long-term management of NDO [59]. Pannek reported 27 patients underwent repeated BoNT-A treatments for a mean period of 7.1 years, the long-term success rate was 74%, and bladder compliance increased from 42.2 ± 38.4 to 73.1 ± 70.2 (mL/cmH_2O). However, the therapeutic effects were insufficient in around one quarter of patients who required major surgical intervention [60]. Our previous study reported that, among 30 patients who received four injections of 200 U of BoNT-A, the mean bladder capacity increased from 207 ± 111 to 412 ± 33 mL and the mean detrusor pressure decreased from 39.8 ± 21.7 to 20.6 ± 19.1 cmH_2O. All patients exhibited improvements in the grade of incontinence, but some patients did not show significant improvement in bladder compliance and thus required surgical intervention as the high detrusor pressure leads to impairment of renal function [12]. We discovered that patients for whom bladder compliance increased by <10 cmH_2O or Pdet decreased by <10 cmH_2O following treatment exhibited decreased glomerular filtration rate, and further aggressive treatment was needed.

In another study, we found that the therapeutic efficacy of BoNT-A decreased slightly after the fourth injection. The overall rate of satisfaction after repeated injections was 59.3%, and the failure rate was 33.9%. Of these, 16.9% reported no significant improvement and the remaining patients dropped out due to adverse events of urinary tract infection and autonomic dysreflexia [14]. We also found that repeated 6 monthly detrusor injection of 200 or 300 U of onabotulinumtoxinA did not lead to significant improvements in urodynamic parameters, renal function, or severity of incontinence [13]. Despite the clinical evidence of initial efficacy of BoNT-A (lasting around 24–36 weeks), we recommend that injections should be repeated every 24 weeks to maintain lower detrusor pressure. Other indicators of bladder urothelial dysfunction, such as the expression of adhesive and junction proteins in the bladders of patients with SCI, improved after three cycles of BoNT-A treatment [15].

Leitner *et al*. reported the results of a >15-year study, which revealed that around 60% of patients continued to receive intradetrusor injection of BoNT-A for NDO, which was associated with sustained improvements in urodynamic parameters. Bladder compliance increased from 36 ± 28 to 92 ± 64 (mL/cmH_2O), and P(detmax) decreased from 46 ± 30 to 30 ± 26 cmH_2O. DO rate decreased from 100% to 71%. However, 21% of the study population did not exhibit a clinical and/or urodynamic response and switched to other treatments [61]. A Phase III, multicenter, 4-year trial of BoNT-A for NDO found that administration of 200 U of BoNT-A consistently reduced the number of episodes of urinary incontinence by 3.2–4.1 per day after six treatments, which was similar to 300 U [62]. The most common adverse events were urinary tract infections, urinary retention, and *de novo* CIC, in which the occurrence rates were 29.5%, 3.4%, and 6.0% in 200 U, and 43.0%, 15.0%, and 4.8% in 300 U, respectively [62]. However, this study did not report urodynamic findings, and so we cannot know the precise effects on bladder compliance. Koschorke *et al*. suggested that urinary continence alone is not sufficient to evaluate the treatment outcomes of detrusor injection of BoNT-A for NDO because high intravesical pressure may be missed in continent patients. In their study, 98 of the 148 patients (66%) with NDO incontinence were continent after BoNT-A treatment; however, 18 of these had a maximum Pdet of >40 cmH_2O during the storage phase due to poor bladder compliance which may lead to renal function impairment [63]. Therefore, the actual success rate might be overestimated.

In a study involving myelodysplastic children and patients with SCI and NDO with a median follow-up of 4.5 years, Akbar *et al*. found repeated BoNT-A treatments at least 3 treatment cycles to be effective, with no antibody formation or fibrosis of the detrusor muscle observed [64]. The bladder compliance was 16.28 ± 14.01 before treatment and was 37.39 ± 20.12 after first injection and was sustained 38.95 ± 20.39 after the third treatment [64]. Grosse *et al*. showed that, in terms of therapeutic outcomes, including subjective satisfaction and objective parameters, such as compliance and cystometric capacity, showed that repeated BoNT-A injections were just as effective as the first treatment [5]. Stoehrer *et al*. reported a 7 years experiences of repeated detrusor injection of 300 U of Botox® or 750 U of Dysport for NDO were both effective, long-lasting, and repeatable. No significant differences were noted in outcomes between the two preparations [31]. A recent study compared onabotulinumtoxinA with abobotulinumtoxinA for NDO showed that sustainable long-tern outcomes were achieved following both treatments. However, if the efficacy was not satisfactory, switching to another type of BoNT-A did not improve the response [65].

Another systematic review and meta-analysis of repeat BoNT-A injection for NDO showed that patients who received ≤4 injections reported stable improvements in QoL after the first and last injections, whereas patients who received ≥5 injections reported a significant decrease in QoL after the final injection. Male patients, underlying neurological disorder, and high maximum Pdet during storage prior to treatment appear to be risk factors for poor urodynamic outcomes [63]. Our previous study showed lack of bladder compliance or Pdet improvement after BoNT-A injection lead bad outcomes [13]. In patients with poor therapeutic effects of repeated BoNT-A treatment, which may cause frequent UTI and renal function impairment, advanced surgery such as augmentation enterocystoplasty or urinary diversion was needed. Based on the recent literature, repeated detrusor injection of BoNT-A appears to offer sustainable benefits for most patients with SCI and NDO, although a proportion of patients will experience a gradual decrease in efficacy. Most studies used "by patients request" protocol when patient subjective feels symptoms relapse. The median duration of clinical

Table 1: Description of studies of repeated botulinum toxin for treat chronic spinal cord injury bladders

First author	Study design/ treatment duration	Sample size of SCI	Amount of Botox, U	Treatment outcome of DO and bladder compliance after repeated BoNT-A
Grosse *et al*. [5]	Open-label/twice	*n*=66	BoNT-A 300 U or Dysport 750 U	Repeat injections outcome were same as first time in DO and compliance
Akbar *et al*. [64]	Open-label/4.5 years	*n*=25	Dysport 750 U in adults and 20 units/kg of body weight in children	Bladder compliance increased from 16.28 to 38.95 (mL/cmH_2O), and P(detmax) decreased from 51.76 to 24.60 cmH_2O
Giannantoni *et al*. [58]	Open-label/6 years	*n*=17	BoNT-A 300 U	P (detmax) decreased from 97.6 to 23.8 cmH_2O, and cystometric capacity increased from 243 to 408 mL
Pannek *et al*. [60]	Open-label/7.1 courses	*n*=27	BoNT-A 300 U	The long term success rate was 74%. Bladder compliance increased from 42.2 to 73.1 (mL/cmH_2O), and P (detmax) decreased from 52.6 to 29.1 cmH_2O
Kuo and Liu [12]	Open-label/4 courses	*n*=33	BoNT-A 200 U	30 (90.9%) patients improved in incontinence, Bladder compliance increased from 26.9 to 40.1 (mL/cmH_2O), and P (detmax) decreased from 39.8 to 20.6 cmH_2O
Chen and Kuo [14]	Open-label/2-6 courses	*n*=59	BoNT-A 200 U	Dryness rate was 25.4% at baseline to 74% after fourth injection. Bladder compliance increased from 35.4 to 38.5 (mL/cmH_2O), and P(detmax) decreased from 37.4 to 24.8 cmH_2O
Leitner *et al*. [61]	Open-label/12 years	*n*=32	BoNT-A 300 U and 200 U	22 (68.7%) patients are continuing with intradetrusor BoNT-A injections. Bladder compliance increased from 36 to 92 (mL/cmH_2O), and P(detmax) decreased from 46 to 30 cmH_2O. DO decreased from 100% to 71%.
Kennelly *et al*. [62]	Open-label/6 courses	*n*=396	BoNT-A 300 U and 200 U	The urge incontinence/day reduced 75%-84% and improve I-QOL were consistently.
Lombardi *et al*. [65]	Open-label/15 years	*n*=60	Dysport® 500 U or 750 U and BoNT-A 300 U or 200 U	Long-term BoNT-A for NDO did not increase failures, independent of the types of treatments and switching. Six months dryness (%) achieved was 18%-29%

DO: Detrusor overactivity, I-QOL: Incontinence quality of life, NDO: Neurogenic detrusor overactivity, BoNT-A: OnabotulinumtoxinA, SCI: Spinal cord injury

effects was 36 weeks, although some lasted shorter and some longer. However, our protocol of repeated injection is periodic 24-week injection rather than by patient request. We think the benefit of this is to maintain low intravesical pressure in storage phase which achieves the treatment goal. For patients with NDO, urinary continence is not sufficient alone as an outcome assessment of intradetrusor BoNT-A injection, as high intravesical pressures during storage might be missed in a significant proportion of continent patients. Therefore, we strongly recommend that urodynamic parameters should be assessed as a routine part of follow-up [66]. Table 1 summarizes the repeated intradetrusor BoNT-A injection in the current study.

Conclusions

Patients with chronic SCI and NDO can achieve long-term improvements in DO and bladder compliance through repeated injection of BoNT-A. However, there is evidence of decreasing efficacy over time for some patients. Urinary continence alone is not a sufficient evaluation of outcome, because some continent patients may have poor compliance and high detrusor pressure, which can cause renal damage. If bladder compliance increases by <10 cmH_2O and Pdet decreases by <10 cmH_2O through treatment, treatment is considered to have failed. Annual assessment of urodynamic parameters should be considered an important aspect of the standard care for NLUTD.

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Conflicts of interest

Dr. Hann-Chorng Kuo, the Editor-in-Chief of *Tzu Chi Med J*, had no role in the peer review process and the decision to publish this article. The other author declared that he has no conflicts of interest.

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