The therapeutic use of botulinum toxin in cervical and maxillofacial conditions: an evidence-based review

Stefan K. A. Ihde, DMD,[a] and Vitomir S. Konstantinovic, MD, DDS, PhD,[b] Gommiswald, Switzerland, Olomouc, Czech Republic, and Belgrade, Serbia
GOMMISWALD DENTAL CLINIC, OLOMOUC CLINIC OF DENTISTRY, AND UNIVERSITY OF BELGRADE

Introduction. The role of botulinum toxin as a therapeutic agent for several conditions is expanding. We sought to determine if botulinum toxin is safe and effective in treating patients with cervical dystonia and maxillofacial conditions. Our purpose was to establish a safety and efficacy profile to determine whether or not this treatment may be used prophylactically in patients undergoing dental implant therapy.
Methods. We performed a systematic search of the literature to identify randomized clinical trials evaluating patients treated with botulinum toxin as an adjunct to dental implant therapy, maxillofacial conditions including temporomandibular disorders (TMD), and cervical dystonia.
Results. Four randomized controlled trials (RCTs) met our search criteria in the area of cervical dystonia and chronic facial pain. No RCTs were identified evaluating dental implant therapy. Patients with cervical dystonia exhibited significant improvements in baseline functional, pain, and global assessments compared to placebo. Adverse events were mild and transient with numbers needed to harm (NNH) ranging from 12 to 17. Patients with chronic facial pain improved significantly from baseline in terms of pain compared to placebo. Rates of adverse events were less than 1%.
Conclusion. Botulinum toxin appears relatively safe and effective in treating cervical dystonia and chronic facial pain associated with masticatory hyperactivity. No literature exists evaluating its use in dental implantology. Randomized clinical trials are warranted to determine its safety and efficacy in dental implantology and other maxillofacial conditions such as bruxism. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;104:e1-e11)**

The role of botulinum toxin as a therapeutic agent for several conditions is expanding. It has evolved from a poison to a versatile clinical tool for a growing list of conditions resulting from muscular hyperfunction. In the head and neck, this includes a spectrum of focal dystonias, vocal tics and stuttering, cricopharyngeal achalasia, various manifestations of tremor, hemifacial spasm, temporomandibular joint dysfunction, bruxism, masticatory myalgias, sialorrhea, hyperhidrosis, headache, and a number of cosmetic conditions.[1] Recently, it has reported clinical use in dental implantology for the prophylactic reduction of masseter and temporalis muscle strength after implantation in immediate load protocols.[2,3]

Botulinum toxin, the purified exotoxin of *Clostridium botulinum*, has been used since 1977 as a therapeutic agent in the treatment of numerous neuromuscular disorders.[1,4] The toxin is a protease that blocks the release of acetylcholine at the nerve terminal, rendering it nonfunctional and ultimately inhibiting muscular contraction. This is believed to be followed by the sprouting of new axon terminals, which results in the reestablishment of neuromuscular transmission. Clinical effect is typically seen 1 to 3 days after administration, followed by 1 to 2 weeks of maximum effect, which then levels off to a moderate plateau until full nerve recovery at approximately 3 months.[1]

Botulinum toxin type A is available in the United States under the trade name BOTOX (Allergan, Irvine, CA) as a pure, crystalline powder in 100-U vials. It is available in Europe as Dysport (Speywood Pharmaceuticals, Maidenhead, UK). BOTOX was approved in December 1989 by the US Food and Drug Administration (FDA) for "the treatment of strabismus, blepharospasm, and focal spasms including hemifacial spasm" and more recently for the treatment of cervical dystonia. Clinical resistance to botulinum toxin type A has been estimated as high as 6.5%,[5] and botulinum toxin type B continues to be actively investigated as an alternative therapeutic agent.[5-7] Clinical resistance to botulinum toxin results from the formulation of neutralizing antibodies but attention to handling and dosing procedures may reduce the development of resistance.[8] Botulinum toxin type B is available as Neurobloc (Elan Pharmaceuticals, Shannon, County Clare, Ireland) and

[a]Associate Professor, Gommiswald Dental Clinic, Gommiswald, Switzerland, and Clinic of Dentistry, Olomouc, Czech Republic.
[b]Professor, Head of Department, Clinic of Maxillofacial Surgery, Faculty of Dentistry, University of Belgrade, Belgrade, Serbia.
Received for publication Sep 11, 2006; returned for revision Feb 2, 2007; accepted for publication Feb 10, 2007.
1079-2104/$ - see front matter

doi:10.1016/j.tripleo.2007.02.004

Table I. Medline search strategy and results

Step	Terms	Hits	Reviewed
1	Botulinum Toxins [MESH] OR Botox OR botulinum	8,859	0
2	Dental Implants [MESH] OR Dental Implantation [MESH]	14,391	0
3	1 and 2	0	0
4	"Osseointegrated oral implants" AND 1	0	0
5	"Crestal implants" AND 1	0	0
6	"Basal osseointegrated implants" AND 1	0	0
7	"Disk implants" AND 1	0	0
8	Temporomandibular Joint Disorders [MESH] AND 1	25	9
9	Bruxism [MESH] AND 1	14	1
10	(Torticollis OR cervical dystonia) AND 1	362	3
11	Additional non-English articles		1
	Studies summarized		14

Myobloc (Elan Pharmaceuticals, San Diego, CA) in vials of 2500 U/0.5 mL, 5000 U/mL or 10,000 U/2.0 mL.[9,10] These were approved in December 2000 by the FDA for treatment of cervical dystonia.

Although there are few reports of its use in dental implantology, our group has found it safe and effective for *prophylactic* and *therapeutic* indications.[2,11] The purpose of this review was to investigate the safety and efficacy of therapeutic botulinum toxin reported in the literature in cervical and maxillofacial conditions to establish a safety and efficacy profile that might be used as a guide for treating dental implants patients prophylactically. High-quality literature was identified only in manuscripts published on the management of cervical dystonia and chronic facial pain associated with masticatory hyperactivity; hence, the body of this review will focus on the safety and efficacy of botulinum toxin in the treatment of these conditions.

MATERIALS AND METHODS

Eligibility criteria

We performed a systematic search of the literature that met the following eligibility criteria: (1) patients treated *prophylactically* or *therapeutically* as an adjunct to dental implant therapy; (2) patients treated *therapeutically* for temporomandibular disorders (TMD); (3) patients treated *therapeutically* for other maxillofacial conditions such as bruxism, masseteric hypertrophy, and oromandibular dystonia; (4) patients treated therapeutically for cervical dystonia; (5) studies of high methodological quality (systematic reviews or randomized controlled trials). Case series, case reports, animal studies, and studies evaluating blepharospasm or cosmesis were not included.

Identification of studies

We conducted a Medline search of articles published from 1969 to December 2005. The search strategy and results are listed in Table I. Additional strategies to identify relevant articles included (1) a search for safety reports or Web sites that might provide dosing or adverse event information, (2) a search for review articles that may report dosing or adverse event information, (3) a review of the bibliographies of the article identified, and (4) searching the Cochrane database.

Statistical analysis

The number needed to harm (NNH) using adverse event rates was calculated if adequate data were available from the published manuscript. The NNH represents the number of patients needed to treat before observing an adverse event. Number needed to treat (NNT) was not calculated as outcomes were measured continuously and we did not want to arbitrarily make divisions with respect to what should be considered successful or not.

RESULTS

Literature search

We identified 4 randomized clinical trials (RCTs) that form the basis of this review. Additional review articles, a technical report, and 2 company Web sites also provided useful information. No clinical studies evaluating the use of botulinum toxin in dental implantology were identified, apart from the case reports from our group. There were several studies identified evaluating botulinum toxin use for cervical dystonia; however, we restricted our review to those studies with the highest level of evidence—3 RCTs. With respect to other maxillofacial conditions, the overall quality of evidence was poor and primarily consisted of case-series. One randomized trial evaluating the safety and efficacy of treating chronic facial pain associated with masticatory hyperactivity was identified and therefore included in this review. A review article summarizing adverse events reported to the FDA in therapeutic and cosmetic cases was identified and used as supplemental information. A safety report was identified outlining the

Table II. Summary of articles reporting on botulism toxin (BTX) treatment for temporomandibular disorders (TMD)

Study	*Study design*	*Population*	*Treatment method*	*Efficacy assessment*	*Safety assessment*
von Lindern (2003)[12]	RCT	N = 90 Female: NR Mean age: NR F/U time: 4 weeks F/U rate: 100%	• 1Group 1: 35MU BTX-A (Botox) into masticatory muscles (n = 60)	Results at 4 weeks post-injection: • Improvement in local facial pain symptoms: 91% (n = 55/60 in BTX-A group)	• Dysphagia and temporary paralysis of muscle affecting facial expression: 1% (n = 1)
			• Group 2: saline (n = 30)	Average improvement based on visual analogue pain scale: • Group 1: 3.2 points vs Group 2: 0.4 points ($P < .01$) • Patients with greater initial pain (>6.5 VAS) showed a greater improvement (>3.5, n = 26) • Patients with less initial pain (<6.5 VAS) showed less improvement (<3.5, n = 27)	
Umstadt (2004)[13]	Case-series	N = 18 Female: 89% Mean age: 35 years F/U time: 36 weeks F/U rate: 100%	BTX-A • 335-50 U, masseter, localized areas	Outcomes Pre-treat 36 weeks • VAS pain (1 to 10) 7.4 2.9 • Pain with opening 1.86 0.86 • Pain in masticatory muscles 2.6 0.9 • Impairment in jaw mobility 1.4 1.0 • Reduction chewing force due to pain 2.0 0.86 • Dejection caused by symptoms 2.71 1.0	• Difficulty chewing hard food (38%) • Transient complaints (mean 10 days): 14.3%
Freund (2000)[14]	Case-series	N = 46 Female: 83% Mean age: 40.5 yrs (16-75) F/U time: 8 weeks F/U rate: 100%	BTX-A (Allergan) • 50 U masseter • 25 U temporalis (both sides injected regardless of symptoms)	Outcomes Pre-treat 8 weeks • VAS pain (1 to 10) 8 (3-10) 5 (0-9)* • Function Disability Index 5.3 (1-9) 3.9 (0.6-9.5)* • Jaw opening (mm) 29.5 (12-54) 34.5 (18-53)* • Max voluntary contract (MVC) (lb) 12 (1-37) 14 (1-37)*† • Tenderness 15.5 (5-30) 6 (0-30)*	• No adverse events reported
von Lindern (2001)[15]	Case-series	N=41 female: NR mean age: NR F/U time: 6.7 months (3-12) F/U rate: 100%	BTX-A • 200 U per masseter muscle	• Improvement in local pain by 45% on VAS seen in 80% of patients (n = 33) • Second injection for recurrent pain: 17% (n = 7)	• Dysphagia and dystonia: 2.4% (n = 1)
Freund (2002)[16]	Case-series	N = 60 N = 46 with CTH Female: 83% Mean age: 36.2 yrs (17-65) F/U time: 3 months F/U rate: 100%	BTX-A (Allergan) • 50 U masseter • 25 U temporalis	• Improvement in facial pain by 50% during 3-month follow-up period: 63% (n = 38) • Improvement in headache pain by 50% during 3-month follow-up period: 100% of CTH patients (n = 46 of 46)	• No adverse events reported

Table II. Continued.

Study	Study design	Population	Treatment method	Efficacy assessment	Safety assessment
Borodic (2002)[17]	Case-series	N = 44 Female:73% Mean age: 54.2 years (34-89) F/U time: 7.6 months (4-20) F/U rate: 100%	Initial < 5 LD 50 U; injections tailored to location of pain Average total dose per 2-week injection: 48.3 IU (25-75), maximum 7.5 IU per puncture Mean no. injection cycles: 2.12 (1-4)	• Response to BTX-A, (patient definition): 75% (n = 33) • Response by diagnosis group: • Migraine: 73% (n = 8/11) • TMJ syndrome: 75% (n = 6/8) • Essential Headache: 66% (n = 8/12) • Neuralgia-trigeminal: 73% (n = 8/11) • Postsurgical: 85% (n = 11/13) • Reduction - other medication: 48% (n = 16/33 responders) • Patients without history of migraine & response to BTX-A: 76% (n = 25/33) • Duration of Effect: 2-4 months	• Temporary facial asymmetry and weakness: • 66% (n = 29); • 17% (n = 5/29) found the complications troublesome
Ziegler (2003)[18]	Case-series	N = 21 Female: 66% Mean age: 23-91 yrs F/U time: 1 year F/U rate: 100%	BTX-A (Dysport)	• No further dislocations for at least 8 months: 90% (n = 19) • 150-100 MU each lateral pterygoid muscle, 3-month intervals for 6-18 months • 19% (4/19) had single dislocations 9, 11, 14, and 17 months after the last BTX injection.	• No adverse events reported
Karacalar (2005)[19]	Case-series	N = 26 Female: 69% Mean age: 28.5 yrs (±10.2) F/U time: 3 months F/U rate: 100%	BTX-A • 112.5 U lat pterygoid • 225 U temporalis • 312.5 U med pterygoid • 425 U masseter if severe tenderness	Statistically significant post-injection improvement from pretreatment (time not specified): • Pain scores- of right joint: (P = .0019),left joint: (P = .000) • Improved mouth opening: 92% (n = 24/26)* (P = .002) • Subjective functional dysfunction: (P = .65) • Clicking of the left joint: (P = .001) Duration of Effect: 2 months (n = 24)	• Reversible dysphonia and dysphagia: 4% (n = 1/26) • Worsening of symptoms: 8% (n = 2/26)

RCT, randomized controlled trial; NR, not reported; CHT, Chronic Tension Headache; F/U, follow-up.
*Significant difference between pretreatment and all posttreatment values ($P < .05$).
†Voluntary muscle contaction at 2 weeks was 9 lbs (1-27), leveled off to 11 (0-30) at 4 and 6 weeks, and showed an increase at 8 weeks.

use of Dysport in dental implantology.[8] The following sections are divided as follows: (1) an RCT evaluating the safety and efficacy of botulinum toxin A in chronic facial pain associated with masticatory hyperactivity, (2) RCTs evaluating the safety and efficacy of botulinum toxin B in cervical dystonia, and (3) a review of dosing and adverse event data obtained from various sources.

Safety and efficacy of botulinum toxin associated with chronic facial pain

One RCT (N = 90) was identified comparing botulinum toxin Type A to saline in patients with chronic facial pain associated with masticatory hyperactivity, Table II. With respect to *safety*, adverse events were relatively mild and transient. Dysphagia and temporary paralysis of the muscles effecting expression occurred in 1 patient. NNH was not calculated because of the very low adverse event rate in the botulinum toxin group and no events in the saline group. With respect to *efficacy*, 4 weeks after treatment, 91% of patients receiving botulinum toxin A had improved facial pain symptoms. Mean improvement based on a visual analogue scale (VAS) for pain was significantly better in the botulinum toxin group compared with the saline group (3.2 points versus 0.4 points, $P < .01$). Patients with greater initial pain (>6.5 points on the VAS) showed a greater improvement than those with less initial pain.

Safety and efficacy of botulinum toxin associated with cervical dystonia

Three RCTs were identified and reviewed, all of which evaluated botulinum toxin type B in cervical dystonia, Table III. With regard to *safety*, adverse events were relatively mild and transient in all studies. Dysphagia occurred in 0% to 27% of patients[5-7] and dry mouth was reported in 3% to 33%.[5,7] Dystonia, injection site reactions, and general reactions such as flu-like symptoms, nausea, or headache were also reported and appear to be relatively infrequent particularly at lower doses.[5-7] The number and severity of complications appeared to be dose dependent.[7] Rates of adverse event reporting varied from

Table III. Summary of articles reporting on botulism toxin (BTX) treatment for other craniomaxillofacial applications: bruxism, masseteric hypertrophy and oromandibular dystonia

Study	*Study design*	*Population*	*Diagnosis*	*Treatment*	*Efficacy assessment*	*Safety assessment*
Sankhla (1998)[21]	Case series	**Peripheral OMD:** N = 27 Femal: 66% Onset Age: 50.1 years (± 14.2) F/U time: NR F/U rate: 100% **Primary OMD:** N=21 Female: 71% Onset Age: 51.5 years (± 2.51) F/U time: NR F/U rate: 100%	• Peripheral OMD • Primary OMD	BTX-A • 25-195U (reported in 2 illustrative cases) • submentalis complex jaw-opening OMD • masseter muscle jaw-closing OMD	Functional Improvement: • Peripheral OMD: 57% (n = 12/ 21) • Primary OMD: 68% (n = 13/19) BTX-A therapy superior to medical therapy in both groups: ($P <$ .005)	Complications post-injection (e.g., jaw weakness, loss of smile, dysphagia, nasal regurgitation, or jaw tremor): • Peripheral OMD: 24% (n = 5/21) • Primary OMD: 58% (n = 11/ 19)
Tan (2000)[22]	Case series	N=18 Female: 94% Age: 50.6 years (±20.7) F/U time: 3.3± 2.8 yrs (0.4-8) F/U rate: 100%	• Severe Bruxism	BTX-A (Botox) • 61.7 ±11.1 MU per masseter (range 25-100 MU)	• Mean Effect: 3.4 ± 0.9 (4 = total abolishment of grinding) • Mean Duration of effect: 19.1 ±17 wks (6-78 wks) • Mean Maximum Effect: 11.7 ±4.1 wks (2.5-18 wks)	• Dysphagia: 5.6% (n = 1)
Kim (2003)[23]	Case series	N=11 Female: 82% Age: 32.7 ± 6.7 years (25-45) F/U time: 12 weeks F/U rate: 100%	• Bilateral subjective Masseteric Hypertrophy (MH)	BTX-A (Botox) • 30 U per masseter	• Masseteric volume decrease: 82% (n = 9). • Maximum reduction: 35.4% (8.1-35.4%) • Aesthetic results=good/ excellent: 82% (n = 9) (12 wks): • Effect duration : >50% (n = 6/11) regained muscle volume by 6 months	• Mastication force decrease: 64% (n = 7) • Facial expression change: 27% (n = 3) • Sunken cheek: 18% (n = 2) • Taste change: 27% (n = 3)

NR, not reported; MU, mouse unit; OMD=oromandibular dystonia; F/U, follow-up.

80% of patients having at least 1 adverse event[7] to no reported adverse events.[5] For events where the NNH could be calculated, numbers ranged from 12 for dysphagia to 17 for total adverse events, although all were transient and mild. With regard to *efficacy*, botulinum toxin improved overall symptoms of cervical dystonia based on the Toronto Western Spasmodic Torticollis Rating Scale scores (TWSTRS), the Patient Analogue Pain Assessment, and the Patient Global Assessment and Physician Global Assessment.[5-7] The TWSTRS total score at 4 weeks was significantly different in both trials between placebo and 10,000 U botulinum toxin type B, with differences of 7.2 ($P < .0004$)[6] and 8.7 ($P < .0001$),[5] respectively. The TWSTRS total score at 4 weeks was significantly different between placebo and all botulinum toxin type B dose groups in another trial.[7] This trial demonstrated that the number of responders to botulinum toxin type B, defined as 20% or greater improvement in TWSTRS week 4 scores, increases with increased dosage (2500 U, 5000 U, and 10,000 U) compared with placebo. A significant dose-response across treatment groups was noted for the total TWSTRS score as for the subscales. The duration of treatment effect has been reported as ranging from 12 to 16 weeks.[5-7]

Table IV. Botulinum toxin (BTX) in treatment of cervical dystonia (CD)

Study	*Population*	*Treatment method*	*Efficacy assessment*	*Safety assessment*
Lew (1997)[7]	(Both A-responsive and A-resistant patients) N = 122 Female: 67% Mean Age: 50 years (19-81) F/U period: 4 weeks (26-120 days) F/U rate: 100%	Single Dose injection of BTX-B to 2-4 clinically involved muscles Group 1: 10,000 U (n = 31) Group 2: 5000 U (n = 30) Group 3: 2500 U (n = 30) Group 4: Placebo (n = 31)	• TWSTRS* Total Score, Mean Improvement at Week 4: Group Mean Pre/post† vs. Placebo‡ 1 16.4 $P < .05$ .0001 2 12.5 $P < .05$ .0005 3 11.6 $P < .05$ .0016 4 3.3 $P < .05$ • Analysis of dose response across groups: $P = .0001$ • Percent of Patient Response at Week 4: Group BTX-B Responders§ BTX-A Resistant** 1 77% (n = 23) 82% (n = 9) 2 61% (n = 19) 83% (n = 5) 3 58% (n = 18) 50% (n = 4) 4 27% (n = 8) 22% (n = 2)	• Patients with at least 1 event: 80% (n = 98/122) • Most common adverse events by group: Group Dry mouth Dysphagia CD Pain 1 33% (n = 10) 27% (n = 8) 23% (n = 7) 2 10% (n = 3) 10% (n = 3) 10% (n = 3) 3 3% (n = 1) 16% (n = 5) 10% (n = 1) 4 3% (n = 1) 0% (n = 0) 13% (n = 4) ††SAE: 1.6% (n = 2) Basal cell carcinoma and hospitalization for elective cardiac catheterization; neither event was deemed to be study drug related.
Brashear (1999)[6]	(Populations BTX-A responsive)	Single dose injection of BTX-B (Neurobloc) to 2-4 clinically involved muscles	• TWSTRS Total Score (mean ± SD) Group Baseline 4 weeks *P* value†	• Dysphagia and other events by group: Group Total AE Dysphagia SAE

Table IV. Continued.

Study	*Population*	*Treatment method*	*Efficacy assessment*	*Safety assessment*
	N = 109 Group 1 Female: 76% Age: 56.2 years ± 11.8 Group 2: Female: 50% Age: 57.6 years ± 12.3 Group 3: Female: 58% Age: 57.6 years ± 12.3 F/U time: 16 weeks F/U rate: 94%-97%	Group 1: 10,000 U (n = 37) Group 2: 5000 U (n = 36) Group 3: Placebo (n = 36)	1 46.9 ± 9.6 35.2 ± 12.3 *P* = .0004 2 46.4 ± 10.4 37.1 ± 15.1 *P* = .0115 3 43.6 ± 9.0 39.3 ± 11.7 • Patient Analogue Pain Assessment (means ± SD) Group Baseline 4 Weeks *P* value† 1 35.1 ± 24.6 62.3 ± 25.7 *P* = .0002 2 40.8 ± 25.8 61.7 ± 26.3 *P* = .0010 3 43.6 ± 25.8 43.7 ± 27.0 • Global Assessments of Change (comparison to baseline) Group PGAC *P* value PIGAC *P* value 1 64.6 ± 21.0 .0001 64.2 ± 16.0 .0038 2 60.6 ± 21.9 .0010 65.3 ± 18.0 .0011 3 43.6 ± 21.7 52.0 ± 17.5 • Group 1 vs Group 3 at 4 weeks Measures Difference *P* value) TWSTRS 7.2 .0004	1 81% (n = 30) 22% (n = 8) 33% (n = 10) 2 89% (n = 32) 11% (n = 4) 10% (n = 3) 3 83% (n = 36) 2.8% (n = 1) 3% (n = 1) SAE: None deemed to be study-drug related (myocardial infarction (patient died), pathologic fracture, colitis, coronary occlusion, bladder stenosis, bladder cancer and atrial flutter).

Table IV. Continued.

Study	*Population*	*Treatment method*	*Efficacy assessment*	*Safety assessment*
			PGAC 21.2 .0001 PIGAC 11.8 .0001 PAPA 21.8 .0002	
			• Duration of Treatment Effect: 12 -16 weeks	
Brin (1999)[5]	(Population BTX-A resistant‡‡) N = 77 Group 1 Female: 69% Median Age: 56.6 ± 11.7 Group 2: Female: 68% Median Age: 52.6 years ± 13.3 F/U time: 16 wks F/U rate: 97%-100%	BTX-B (Neurobloc) Single Dose injection to 2-4 clinically involved muscles Group 1: 10,000 U (n = 39) Group 2: Placebo (n = 38)	• TWSTRS Total Score, (means ± SD) 1 52.8 ± 8.6 41.8 ± 9.8 .0001 2 51.2 ± 9.5 49.2 ± 12.3 • Patient Analogue Pain Assessment, (PAPA) (means ± SD) Group Baseline 4 Weeks P value 1 41.1 ± 26.6 57.7 ± 23.0 .001 2 33.6 ± 20.5 37.3 ± 24.0 • Global Assessments of Change (comparison to baseline†) Group PGAC *P* value PIGAC *P* value 1 60.2 ± 22.9 .0001 60.6 ± 14.4 .0001 2 39.5 ± 16.0 47.9 ± 10.7	Adverse Events (AEs) Group 1: 0% (n = 0) Group 2: 2.6% (n = 1) A single patient reported neck pain, headache, urticaria, eye pain, asthenia, and nausea. The patient was disenrolled before completion of the study.

Table IV. Continued

Study	*Population*	*Treatment method*	*Efficacy assessment*	*Safety assessment*
			Comparison: Groups 1 and 2 at 4 weeks-difference in mean Measures Difference *P* value‡ TWSTRS 8.7 .0001 PGAC 12.7 .0001 PIGAC 12.7 .0001 PAPA 15.9 .0010	

*Toronto Western Spasmodic Torticollis Rating Scale, see Appendix II.
†*P* values, pretreatment vs 4-week data
‡*P* values, placebo vs active treatment groups
§Responders defined as those patients having a ≥20% improvement in TWSTRS Total Score at Week 4.
**Includes patients who met clinical BTX-A resistant criteria and those who did not respond to their last dose only
††SAE, Serious adverse event; AE, adverse event.
‡‡BTX-A resistance defined as patients who (1) responded to a previous BTX-A treatment; (2) failed to respond to the last 2 treatments; and (3) received a higher dose of toxin during the last dosing session than the dose at which a clinically meaningful response had previously occurred, and confirmed with frontalis-type A test.

Table V. Adverse events reported for cervical dystonia and craniomaxillofacial conditions*

Localized effects	*General effects*	*Cervical/oromandibular- specific effects*
• Tenderness/bruising at injection site • Mild skin reaction at injection site • Itching at injection site	• Diffusion to neighboring tissue† • Headache • Flu-like symptoms • Reversible denervation atrophy in muscles injected • Diminished type IIB fibre size in muscles distant from injection site. • Generalized toxicity‡ • Acquired resistance to botulinum toxin therapy	• Dysphonia • Dysphagia • Dry mouth • Temporary weakening of the muscles • Drooling is possible, but spread of the toxin may also lead to decreased salivation and dry mouth • Paralysis of the mimic muscles may lead to unwanted cosmetic changes

*This list is not all-inclusive and does not address the issue of dose-response relationships with adverse events.
†Diffusion effect is dose and injection point dependent.
‡e.g., reduction in lacrimation and salivation, or more severely a botulism-like syndrome

Dosing and adverse events

The effect of botulinum toxin is transient, nondestructive, and largely limited to the area of administration, characteristics that add to its appeal both as a safe therapeutic agent and as a useful diagnostic tool.[1] However, there are a number of common, nonserious adverse events reported in the literature. A list of the more common adverse events identified in this review from clinical studies and company literature can be found in Table IV. A more comprehensive look at reported adverse events associated with botulinum toxin Type A can be obtained from a recent review article that summarizes both serious and nonserious adverse events reported to the FDA over the past 13.5 years.[20] In summary, this review found that adverse events were most common among patients with therapeutic use who received higher doses (> 100 U) and had complicated underlying systemic diseases (specific diseases not listed) with an elevated risk of mortality (Table V).

With respect to recommended doses of botulinum toxin, total dose and injection volumes vary by indication; however, company literature or Web sites often provide recommendations. Note that dose required for each patient cannot be determined in advance and may

vary by several orders of magnitude between patients. A record of dose and effect should be kept for each patient and indication.

A Dysport safety report suggests that injections to the masseter muscles during dental implantology are expected to lead to the same general adverse events for neck and oromandibular use.[8] These events are expected to follow the same time course as the therapeutic effects. A suggested dosage of 400 U total is less than that recommended for torticollis (1000 U maximum), decreasing the likelihood of the adverse events.[8] This report provides the disclaimer, "No safety data or data from controlled clinical trials in this indication are available to the manufacturer. This is a theoretical analysis of the possible risks of the use of Dysport® in this indication and does not represent an endorsement by the manufacturer."

DISCUSSION

Botulinum toxin appears both safe and efficacious for use in cervical dystonia and chronic facial pain associated with masticatory hyperactivity; however, 1 RCT alone is not enough to establish firm evidence. Most studies in the maxillofacial region were of low quality (noncomparative, nonrandomized trials). Case-series with "before-after" analyses are subject to some potential bias because of the lack of a control group that should be considered with respect to efficacy analyses. In general, complications appear to be transient and follow the same time course as therapeutic effects. Dysphagia, dystonia, and dry mouth are the most common adverse events reported in the literature. Events appear to be dose dependent. Some patients may exhibit resistance to botulinum toxin and alternate treatments may need to be considered. Although not the focus of this review, botulinum toxin has been reported to decrease voluntary muscle contraction (MVC) and bite force and relieve severe bruxism.[8] These effects, combined with pain relief noted in several other non-RCT studies on facial pain and TMD,[12-19] may be of benefit during the initial osseointegration phase for dental implants, although this indication is purely experimental at this point. The authors have found it to be safe and effective in immediate loading protocols. Published randomized controlled trials are needed to evaluate the safety and effectiveness of botulinum toxin use in dental implantology.

CONCLUSION

The focus of this systematic review was to evaluate the literature on cervical dystonia and oral maxillofacial conditions including dental implantology. No literature was identified evaluating its use in dental implantology; however, the role of botulinum toxin as a therapeutic agent for several clinical conditions is expanding. Although most of the published literature is of questionable methodological quality, it appears that botulinum toxin is relatively safe and effective in treating cervical dystonia. Further, it appears to be safe and effective in treating facial pain attributable to chronic facial pain associated with masticatory hyperactivity, although more randomized trials should be performed to confirm these findings. Its use in dental implantology may be worthwhile exploring as immediate loading becomes more popular and even patients providing poor bone request this type of protocol. The possibility of reliably reducing masticatory and nocturnal forces may allow it to perform treatments with less bone or shorter or even fewer implants. Reducing and controlling forces may favor the successful integration of immediately loaded dental implants and the preservation of their stability, even during the period of strong postoperative osteonal remodeling.

REFERENCES

1. Blitzer A, Sulica L. Botulinum toxin: basic science and clinical uses in otolaryngology. Laryngoscope 2001;111(2):218-26.
2. Ihde S. Utilisation of prophylactique de la toxine botulique en implantologie dentaire. Implantodontie 2005;14:51-55 [French].
3. Ihde S. Utilisation therapeutique de la toxine botulique dans le traitment d'entretien en implantologie dentaire. Implantodontie 2005;14:56-61 [French].
4. Yin S, Stucker FJ, Nathan CA. Clinical application of botulinum toxin in otolaryngology, head and neck practice [brief review]. J La State Med Soc 2001;153(2):92-7.
5. Brin MF, Lew MF, Adler CH, Comella CL, Factor SA, Jankovic J, et al. Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-resistant cervical dystonia. Neurology 1999;53(7):1431-8.
6. Brashear A, Lew MF, Dykstra DD, Comella CL, Factor SA, Rodnitzky RL, et al. Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-responsive cervical dystonia. Neurology 1999;53(7):1439-46.
7. Lew MF, Adornato BT, Duane DD, Dykstra DD, Factor SA, Massey JM, et al. Botulinum toxin type B: a double-blind, placebo-controlled, safety and efficacy study in cervical dystonia. Neurology 1997;49(3):701-7.
8. Caird D. Dysport in aesthetic medicine safety report: the upper face, forehead, glabella and lateral canthus (crow's feet). Ettlingen, Germany: Ipsen Pharma; 2005.
9. Myobloc [product information]. Malvern, PA: Solstice Neurosciences; 2005.
10. NeuroBloc [product overview]. San Francisco, CA: European Medicines Agency; 2005.
11. Ihde S. Prophylactic use of botulinum toxin in dental implantology. CMF Impl Dir 2007;1:29-34.
12. von Lindern JJ, Niederhagen B, Berge S, Appel T. Type A botulinum toxin in the treatment of chronic facial pain associated with masticatory hyperactivity. J Oral Maxillofac Surg 2003;61(7):774-8.
13. Umstadt HE. Behandlung hyperaktiver Kaumuskulatur mit Botulinum toxin A. Zahnheilkunde 2004;20:475-484 [German].
14. Freund B, Schwartz M, Symington JM. Botulinum toxin: new treatment for temporomandibular disorders. Br J Oral Maxillofac Surg 2000;38(5):466-71.

15. von Lindern JJ. Type A botulinum toxin in the treatment of chronic facial pain associated with temporo-mandibular dysfunction. Acta Neurol Belg 2001;101(1):39-41.
16. Freund BJ, Schwartz M. Relief of tension-type headache symptoms in subjects with temporomandibular disorders treated with botulinum toxin-A. Headache 2002;42(10):1033-7.
17. Borodic GE, Acquadro MA. The use of botulinum toxin for the treatment of chronic facial pain. J Pain 2002;3(1):21-7.
18. Zieglar CM, Haag C, Mühling J. Treatment of recurrent temporomandibular joint dislocation with intramuscular botulinum toxin injection. Clin Oral Invest 2003;7:52-5.
19. Karacalar A, Yilmaz N, Bilgici A, Bas B, Akan H. Botulinum toxin for the treatment of temporomandibular joint disk disfigurement: clinical experience. J Craniofac Surg 2005;16(3):476-81.
20. Cote TR, Mohan AK, Polder JA, Walton MK, Braun MM. Botulinum toxin type A injections: adverse events reported to the US Food and Drug Administration in therapeutic and cosmetic cases. J Am Acad Dermatol 2005;53(3):407-15.
21. Sankhla C, Lai EC, Jankovic J. Peripherally induced oromandibular dystonia. J Neurol Neurosurg Psychiatry 1998;65:722-8.
22. Tan EK, Jankovic J. Treating severe bruxism with botulinum toxin. J Am Dent Assoc 2000;131:211-6.
23. Kim HJ, Yum KW, Lee SS, Heo SS. Effects of botulinum toxin type A on bilateral masseteric hypertrophy evaluated with computed tomographic measurement. Dermatol Surg 2003;29:484-9.

Reprint requests:

Stefan K. A. Ihde, DMD
CH-8737 Gommiswald
Switzerland
dr.ihde@bluewin.ch