Complications After Botulinum Neurotoxin Type A and Dermal Filler Injections: Data From a Large Retrospective Cohort Study

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In a recent Letter published in *Aesthetic Surgery Journal*,[1] the incidence of filler-related vascular adverse events (VAEs), which can lead to tissue necrosis and blindness,[1–4] was estimated by Schelke et al.[1] Based on a national survey among cosmetic doctors, they approximated the total numbers of filler injections in the Netherlands, and considering the number of patients referred to their clinic for filler-induced VAEs, they calculated that the risk of VAE per treatment ranged from 1/5300 to 1/8000.[5,6] All of Schelke et al's patients fully recovered after an outpatient treatment with hyaluronidase injections and no cases of blindness or tissue necrosis were reported.[1] Here we present the largest database to date with recent and detailed information on the incidence of complications following botulinum neurotoxin type A (BoNT-A) and dermal filler treatments, which we would like to share with the readers of this *Journal*. Furthermore, we were able to determine the influence of professional experience and the academic degree of the injector on the incidence of these complications.

To this end, we conducted a retrospective cohort study. Between April 1, 2020 and June 10, 2022 (800 days), data of all consecutive clients of 17 outpatient cosmetic clinics at various locations in the Netherlands (Faceland Clinics, headquartered in Capelle aan den IJssel, the Netherlands) were systematically recorded electronically. These medical records included client demographics, the indication for treatment, the product employed, any related complications, and subsequent treatment. Each single treatment for 1 indication on a certain day (eg, BoNT-A injections for glabellar rhytides, or filler injections for lip augmentation) was calculated as 1 treatment, independent of the total number of units or milliliters injected. The identity of the 60 doctors of medicine (MDs) and 13 registered nurses (RNs) who treated the clients was also recorded. In the Netherlands there are no legal restraints per se to the injection of hyaluronidase or the use of ultrasound by RNs. Within Faceland Clinics, however, only MDs are trained to use ultrasound and hyaluronidase, and therefore only MDs use ultrasound guidance to inject hyaluronidase. In the case of a suspected VAE, an MD at Faceland Clinics diagnosed the VAE and the ultrasounds and salvage procedures were either performed via referral to cosmetic physicians working at the filler complication division of an academic center (Erasmus MC, Rotterdam, the Netherlands), or by a consultant radiologist at Faceland Clinics. Data on the injectors' professional experience in cosmetic medicine (measured in months) and academic degrees were collected. All

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Table 1. Reported Complications Related to Cosmetic Injectable Procedures

BoNT-A complications														
Region and indication	Total N	Percentage of total	Infection	Hypersensitivity reactions		Muscular					Other			
				Type I allergy	Type IV allergy	Levator palpebrae ptosis	Asymmetric perioral facial expression	Eyebrow ptosis	Mephisto/ Spock	Asymmetry	Malar edema	Scarring	Hyperpig-mentation	Diplopia
Glabellar (frown lines)	90,985	45.5%	1	1		23		8	11	4	3			
Frontalis (horizontal forehead lines)	40,733	20.4%				4		34	4	1				
Orbiculairs oculi (crow's feet)	37,955	19.0%	1			1	1	1			6			
Orbicularis oculi (brow lift)	10,915	5.5%				3		1						
Orbicularis oris (lipflip)	5504	2.8%					1							
Depressor anguli oris (depressed oral commisures)	3222	1.6%					3			2				
Levator labii superioris alaeque nasi (gummy smile)	2405	1.2%												
Mentalis (chin)	2337	1.2%					3							
Masseter/temporal	2047	1.0%					6							
Nasalis (bunny lines)	1724	0.9%												
Orbiculair oris (perioral rhytides)	581	0.3%					1							
Depressor septi nasi (nasal tip lift)	480	0.2%												
Axillary (hyperhydrosis)	328	0.2%												
Unspecified	307	0.2%					2	2	1					
Platysma (Nefertiti lift)	304	0.2%					1							
Unspecified (tension headache or migraine)	272	0.1%												
Total	200099	100,0%												
			2	1	0	31	18	46	16	7	9	0	0	0

Table 1. Continued

HA filler complications																				
			Vascular			Infection		Hypersen-sitivity reactions		Neurologic	Other									
Region and indication	Total N	Percen-tage of total	Local signs of impaired perfusion	Necrosis	Blindness		Flare of labial herpes	Type I allergy	Type IV allergy	Neura-praxia	Malar edema	Asymmetric or inhibited perioral facial expression	Scarring	Hyperpig-mentation	Uncorrec-table nodules	Eczema	Correctable bumps/lumps/ irregularities	Correctable asymmetry	
Lips	44,175	46.7%	4			6	5		3						1		16	4	
Unspecified	11,221	11.9%									1						4		
Nasolabial folds	7600	8.0%	1					1	1						1		1	1	
Zygomatic/ infraorbital	5544	5.9%	2								2						1	1	
Marionette lines	5418	5.7%							1							1		1	
Profhilo (head and neck area)	4422	4.7%									1								
Chin	4083	4.3%	6			2			2										
Tear trough	4027	4.3%				1					21						2		
Perioral rhytides	3075	3.3%															3		
Cheeks	1843	1.9%															1		
Jawline	1595	1.7%																	
Nasal (with or without BoNT-A)	648	0.7%	1							1									
Temporal	388	0.4%															1		
Liquid facelift (HA and/or and/or BoNT-A)	223	0.2%																	
Glabellar	82	0.1%																	
Scar	54	0.1%																	
Neck/cleavage	37	0.0%																	
Belotero Hydro (facial)	37	0.0%																	
Forehead	22	0.0%																	
Earlobe	17	0.0%																	
Crow's feet	8	0.0%																	
Hands	2	0.0%																	
Total	94521	100.0%	13	0	0	9	5	1	7	1	25	0	0	0	2	1	29	7	0

Table 1. Continued

CaHA filler complications																		
			Vascular			Infection		Hypersensitivity reactions			Other							
Region and indication	Total N	Percentage of total	Local signs of impaired perfusion	Necrosis	Blindness		Flare of labial herpes	Type I allergy	Type IV allergy		Malar edema	Asymmetric or inhibited perioral facial expression	Scarring	Hyperpigmentation	Uncorrectable nodules		Correctable bumps/lumps/irregularities	Correctable asymmetry
Zygomatic	2222	41.4%															2	
Jawline	1461	27.2%													1		3	
Cheeks	474	8.8%															1	
Chin	394	7.3%	1															
Nasolabial folds	279	5.2%																
Marionette lines	217	4.0%																
Unspecified	162	3.0%																
Hands	92	1.7%				2											1	
Temporal	40	0.7%																
Cleavage	24	0.4%																
Total	5365	100.0%	1	0	0	2	0	0	0	0	0	0	0	0	1	0	7	0

Hyaluronidase complications					
			Hypersensitivity reactions	Infectious	
	Hyaluronidase		Type I allergy	Infection	Correctable bumps/lumps/irregularities
	Total N				
	1438		0	0	1

BoNT-A, botulinum neurotoxin type A; CaHA, calcium hydroxylapatite; HA, hyaluronic acid.

Table 2. Demographic Variables Pertaining to Clients and Their Injectors

Clients			Professionals		
Overall			Overall		
N	131,025		N	73	
Gender	Female	94.2%	Months of professional experience in cosmetic medicine	Mean	25.3
	Male	5.8%		SD	23.3
Age (years)	Mean	39.9		Range	2-103
	SD	12.4			
	Range	18-87			
Clients with complications			Professionals grouped by academic degrees		
N	249		Doctors of medicine		
Gender	Female	95.6%	N	60	
	Male	4.4%	Months of professional experience in cosmetic medicine	Mean	29.1
Age (years)	Mean	42.2		SD	23.9
	SD	12.2		Range	3-103
	Range	20-76	Registered nurses		
			N	13	
			Months of professional experience in cosmetic medicine	Mean	8.0
				SD	8.4
				Range	2-31

SD, standard deviation.

injectors were required beforehand to successfully complete a thorough postacademic inhouse training program developed by Faceland Clinics.

As a result, the following data were obtained: a total of 301,804 cosmetic injectable treatments were performed, of which 200,257 were BoNT-A injections, 94,521 were hyaluronic acid (HA) filler injections, 5588 were calcium hydroxylapatite (CaHA) injections, and 1438 were hyaluronidase injections (detailed information is given in Table 1). The injected regions of Profhilo included either the entire facial region or the neck, according to the manufacturer's injection protocol, and Belotero Hydro (Merz Pharma GmbH & Co. KGaA, Frankfurt, Germany) was used in the entire facial region. A total of 249 complications of varying severity were reported (Table 1). Demographic variables pertaining to clients and their injectors are displayed in Table 2. Data on 14 consecutive patients with filler-related VAEs are displayed in Table 3. Treatment of all of these patients resulted in complete resolution of all signs and symptoms of VAEs through hyaluronidase treatment, with or without ultrasound guidance.[7]

Multiple linear regression analyses were performed. No statistically significant regression equations were found to predict the overall complication rate ($P = 0.618$), BoNT-A–related complications ($P = 0.838$), or filler-related complications ($P = 0.159$). However, for the incidence of VAEs, a statistically significant regression equation was found ($F(2,72) = 3.898$; $P = 0.025$), with an r^2 of 0.100. Injectors' predicted incidence of filler-related VAEs was equal to 0.014% (constant) + [0.000% × (experience)] − [0.016% × (degree)] where "experience" was measured in months of professional experience in cosmetic medicine and "degree" was coded as 0 (RN) or 1 (MD). The percentage of VAEs increased (95% CI) 0.000% to 0.001% for each month of professional experience and MDs had a (95% CI) 0.033% lower to 0.001% higher incidence than RNs. "Experience" ($P = 0.012$) was a statistically significant predictor of VAE incidence, whereas "degree" was not ($P = 0.069$).

In sum, we found the incidence of overall complications to be 0.065% (1/1539) for BoNT-A treatments, 0.106% for HA filler treatments (1/945), and 0.205% for CaHA treatments (1/487), which is in line with earlier reports of filler complication rates (~0.00%-1.25%).[8–14] For filler-related VAEs, the overall incidence in this study was 0.014%

Table 3. Consecutive Patients with Filler-Related Vascular Adverse Events

Patient	Gender	Age (years)	Region	Impaired perfusion diagnosis	Radiographic diagnosis	Delay in treatment time (hours)	Clincally guided HYase units	Ultrasound-guided HYase units	STS[a] dose	Injection technique	Product	Injector experience in cosmetic medicine (months)	Injector academic degree
1	F	27	Chin	Clinical symptoms	—	46	1000	0	0	Needle 27G	HA	31	RN
2	F	40	Zygomatic	Clinical symptoms	—	23	1500	0	0	Needle 27G	HA	31	RN
3	F	46	Lips	Clinical symptoms	—	0	600	0	0	Needle 27G	HA	38	MD
4	F	58	Nasolabial	Clinical symptoms	—	26	600	0	0	Needle 27G	HA	32	MD
5	F	21	Lips	Clinical symptoms	—	24	1500	0	0	Needle 27G	HA	31	RN
6	F	31	Chin	Clinical symptoms + ultrasound	Submental artery (occlusion)	0	3000	60	0	Needle 27G	HA	39	MD
7	F	32	Nasal bridge	Clinical symptoms	—	11	2250	0	0	Needle 27G	HA	40	MD
8	F	56	Infraorbital	Clinical symptoms + MRI	Angular artery (occlusion)	24	3150	0	0	Needle 27G	HA	51	MD
9	F	31	Lips	Clinical symptoms + ultrasound	Inferior labial artery (external compression)	0	150	0	0	Needle 27G	HA	17	MD
10	F	24	Lips	Clinical symptoms + ultrasound	Superior labial artery (occlusion)	21	2000	15	0	Needle 27G	HA	40	MD
11	F	36	Chin	Clinical symptoms + ultrasound	Submental (occlusion)	0	700	70	0	Needle 27G	HA	39	MD
12	F	35	Chin	Clinical symptoms + ultrasound	Submental perforator (occlusion)	72	0	120	0	Needle 27G	CaHA	54	MD
13	F	28	Chin	Clinical symptoms + ultrasound	Mental artery branch (occlusion)	15	1500	20	0	Needle 27G	HA	32	MD
14	F	29	Chin	Clinical symptoms	—	16	1200	0	0	Needle 27G	HA	15	RN

CaHA, calcium hydroxylapatite; HA, hyaluronic acid; HYase, hyaluronidase; MD, doctor of medicine; RN, registered nurse; STS, sodium thiosulfate. [a]Currently not used because of absence of observed effect on CaHA microsphere degradation.[15]

(1/7134); with rates of 0.014% for HA fillers (1/7220) and 0.019% for CaHA (1/5365). This VAE incidence is in line with the estimations by Schelke et al.[1]

Furthermore, our analyses showed that the influence of professional experience and academic degree on the incidence of complications was limited as the regression model only explained 10% of the total variance in VAEs. A statistically significant predictive effect, albeit of limited clinical relevance, of professional experience on VAE incidence was detected, whereas academic degree was found to be insignificant. This suggests that MDs and RNs are both likely to be capable of performing cosmetic injections and able to recognize and treat complications (or refer these for treatment), provided that they have had substantial training (and/or supervision) in cosmetic medicine.

However, the number of reported complications in this study may be underreported. Some professionals may not recognize a problem in their patient, and others may feel reluctant to report a complication.[1] Although this study is limited by its retrospective design, currently[1,10] these are the most detailed and extensive data on the incidence of complications after BoNT-A and dermal filler treatments.

The risk incidence rates observed in this study indicate that cosmetic professionals will most likely encounter general complications and VAEs more than once during their career.[1] As VAEs can lead to skin necrosis or blindness (which in the case of HA is 32% partially to completely reversible),[13] these are considered the most alarming complications of filler treatments.[1–4] Nevertheless since 2018 a total of 58 VAEs out of a total of ~240,000 filler treatments in the Netherlands have been reported in the literature by Schelke et al[1] ($n = 44$; January 2018-January 2020) and the present study ($n = 14$). Interestingly, no cases of blindness were recorded, suggesting a risk of less than 0.0004% (<1/240,000), and all patients with VAEs fully recovered (no cases of tissue necrosis were recorded), indicating that both high-dosed pulsed hyaluronidase[16] and ultrasound-guided hyaluronidase[7] treatment of VAEs are effective. In conclusion, our data support the emerging body of evidence that cosmetic injections are relatively safe procedures in the hands of adequately trained cosmetic professionals.

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