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Safety Profile of Botulinum Toxin for Migraine Headache Prophylaxis: A Systematic Review and Meta-analysis

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Abstract

Context: Nowadays, botulinum toxin is used for migraine prophylaxis, and a wide range of adverse effects (AEs) are reported after administration.

Objectives: The present study was conducted to evaluate the safety profile of botulinum toxin for migraine headache prophylaxis.

Methods: Migraine Disorder, Disorder AND Migraine, Headache AND Sick, Headache AND Migraine, Migraine, Migrainosus, Migraine Headache, Migraines, Sick Headaches, Botulinum, Toxins AND Botulinum, Botulinum AND Neurotoxins, Toxins AND Clostridium Botulinum Neurotoxins, Botulinum Toxin, Botulinum Neurotoxin, Clostridium Botulinum Toxins, and Botulin were searched in PubMed, Scopus, EMBASE, Web of Science, and Google Scholar databases, and gray literature, including references of the studies published before April 2023.

Results: We found 3081 articles by literature search; after deleting duplicates, 1711 remained. Thirty-five articles remained for meta-analysis. The pooled prevalence of musculoskeletal weakness in the head and neck regions was 4% (95% CI: 2-5%) ($I^2 = 92.2\%$, $P < 0.001$). The pooled prevalence of neck pain was 6% (95% CI: 4-7%) ($I^2 = 95.8\%$, $P < 0.001$). The pooled prevalence of blepharoptosis was 2% (95% CI: 2-3%) ($I^2 = 91.1\%$, $P < 0.001$). The pooled prevalence of facial paralysis was 2% (95% CI: 1-4%) ($I^2 = 94.1\%$, $P < 0.001$). The pooled prevalence of injection site pain was 4% (95% CI: 2-5%) ($I^2 = 93.5\%$, $P < 0.001$).

Conclusions: The results of this systematic review and meta-analysis show that the most common AEs following botulinum toxin injection for migraine headache prophylaxis are neck pain, followed by musculoskeletal weakness and injection site pain.

Keywords: Migraine, Safety, Botulinum Toxin, Prophylaxis, Clostridium Botulinum

1. Context

The first cause of living with a disability in individuals under 50 is migraine, which is the second cause of disability all over the world (1, 2). Globally, nearly 1.04 billion people suffer from migraines (3). One of the main issues regarding migraine is its chronicity and severity, affecting the quality of life and interfering with daily activities (4). Nearly 40% of migraineurs need preventive agents, while only 13% receive these medications (5). Beta-blockers, antiepileptic drugs, topiramate, calcium channel blockers, antidepressants, botulinum toxin, and calcitonin gene-related peptide (CGRPs) monoclonal antibodies are used as preventive agents (6). Up to one-third of patients are not responsive to prophylactic medications (7).

2. Objectives

In October 2010, the United States Food and Drug Administration (FDA) approved botulinum toxin type A (BT-A) for migraine prevention (8). Now, it is used in different populations for migraine prevention, while the rates of adverse effects (AEs) vary.

We designed this systematic review and meta-analysis to estimate the pooled safety of botulinum toxin injection in migraineurs.

3. Methods

3.1. Data Sources

The search terms were Migraine Disorder, Disorder AND Migraine, Headache AND Sick, Headache AND Migraine, Migraine, Migrainosus, Migraine Headache, Migraines, Sick Headaches, Botulinum, Toxins AND Botulinum, Botulinum AND Neurotoxins, Toxins AND Clostridium Botulinum Neurotoxins, Botulinum Toxin, Botulinum Neurotoxin, Clostridium Botulinum Toxins, and Botulin.

We searched PubMed, Scopus, EMBASE, Web of Science, Google Scholar databases, and gray literature, including references of the studies published before April 2023.

3.2. Study Selection

The inclusion criteria included trials reporting the efficacy of botulinum toxin in treating headache attacks in migraineurs. The exclusion criteria included letters to the editor, case-controls, case reports, and cross-sectional/cohort studies. We extracted data regarding the total number of participants, the first author, the year of publication, the country of origin, the mean age, and the AEs of botulinum toxin in migraineurs.

3.3. Risk of Bias Assessment

We evaluated the risk of bias in randomized trials using the Cochrane Collaboration's tool (9).

3.4.. Data Extraction

All statistical analyses were performed using STATA (Version 14.0; Stata Corp LP, College Station, TX, USA). We used random effects to determine heterogeneity. Inconsistency (10) was also calculated.

4. Results

We found 3081 articles by literature search; after deleting duplicates, 1711 remained. Thirty-five articles remained for meta-analysis (Figure 1).

Thirty-five articles were included. Totally, 10271 patients received botulinum toxin.

The basic characteristics of the included studies are shown in Table 1.

The pooled prevalence of musculoskeletal weakness in the head and neck regions was 4% (95% CI: 2-5%) ($I^2 = 92.2\%$, $P < 0.001$) (Figure 2).

The pooled prevalence of neck pain was 6% (95% CI: 4-7%) ($I^2 = 95.8\%$, $P < 0.001$) (Figure 3).

The pooled prevalence of blepharoptosis was 2% (95% CI: 2-3%) ($I2 = 91.1\%$, $P < 0.001$) (Figure 4).

The pooled prevalence of facial paralysis was 2% (95% CI: 1-4%) ($I2 = 94.1\%$, $P < 0.001$) (Figure 5).

The pooled prevalence of injection site pain was 4% (95% CI: 2-5%) ($I2 = 93.5\%$, $P < 0.001$) (Figure 6).

The quality assessments of included studies are shown in Table 2.

5. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis evaluating botulinum toxin safety administration in patients with migraine.

The results show that the most frequent AEs were neck pain, followed by musculoskeletal weakness in the head and neck regions, injection site pain, and blepharoptosis or eyelid ptosis.

Hollanda et al., who assigned patients with chronic migraines to botulinum toxin or placebo groups, reported pain in injection site points as the most common AEs (15).

In a 24-week double-blind study of Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT), Aurora et al. reported AEs in 59.7% of enrolled patients in the botulinum toxin group and 46.7% in the placebo group. Only 5.3% experienced severe AEs, and 13.2% discontinued treatment (28). On the other hand, in the first 24 weeks of PREEMPT 2, 65.1% of patients experienced AEs, while only 4.3% had severe AEs (43). The pooled PREEMPT 24-week analysis showed that 62.4% of onabotA-treated patients reported AEs, while only 4.8% experienced serious AEs. Most AEs were mild/moderate and self-limited, and the most common AEs were neck pain, muscle weakness, ptosis, and injection-site pain (28, 43). In another 32-week open-label trial, Aurora et al. reported AEs in 58.3%, while 25.4% discontinued the treatment based on AEs. Like previous studies, neck pain, muscle weakness, and eyelid ptosis were the most frequent AEs (44). Finally, in an over 56-week trial, AEs were found in 78.3% and 75.9% of cases who received 5 or 3 cycles of botulinum toxin treatment. Serious AEs were found in 7.8% and 4.9% of 5 or 3 treatment cycles. It was shown that the rate of AEs decreased after each treatment cycle (26).

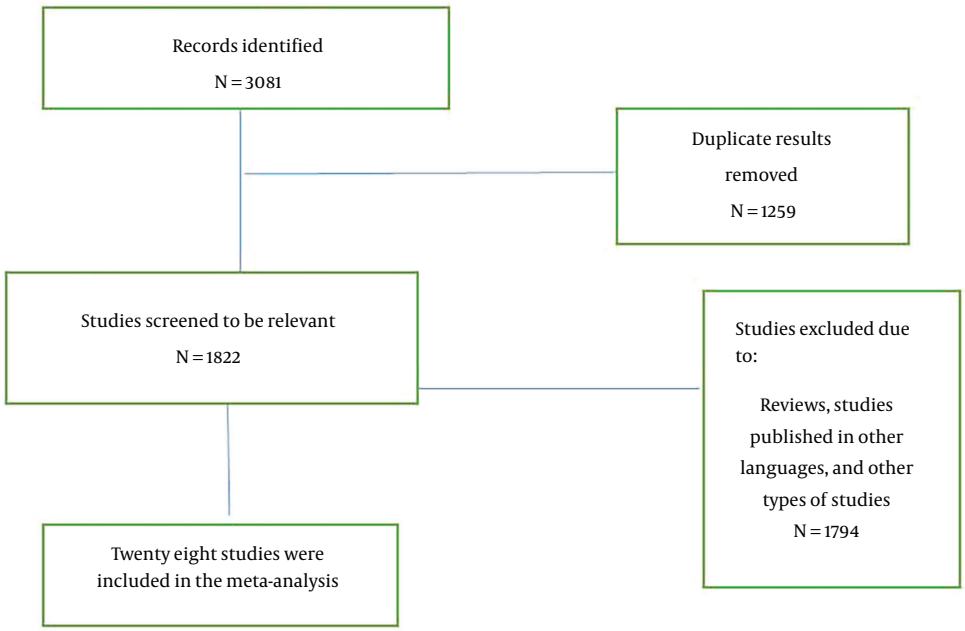

Figure 1. The flow diagram summarizing the selection of eligible studies

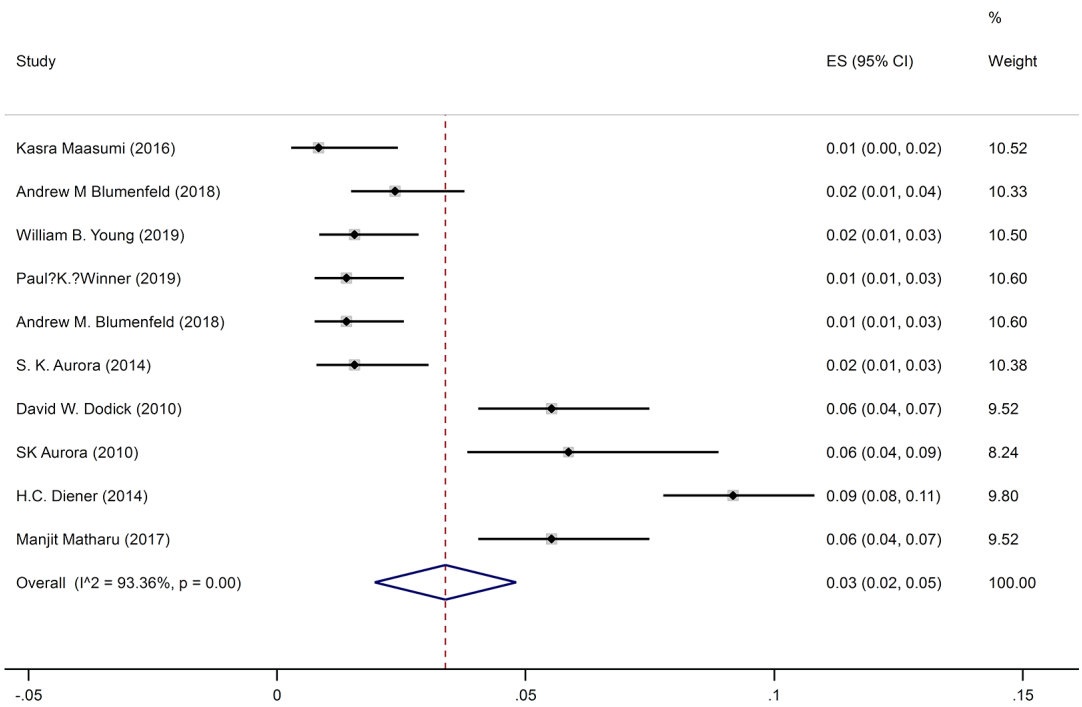

Figure 2. The pooled prevalence of musculoskeletal weakness in the head and neck regions

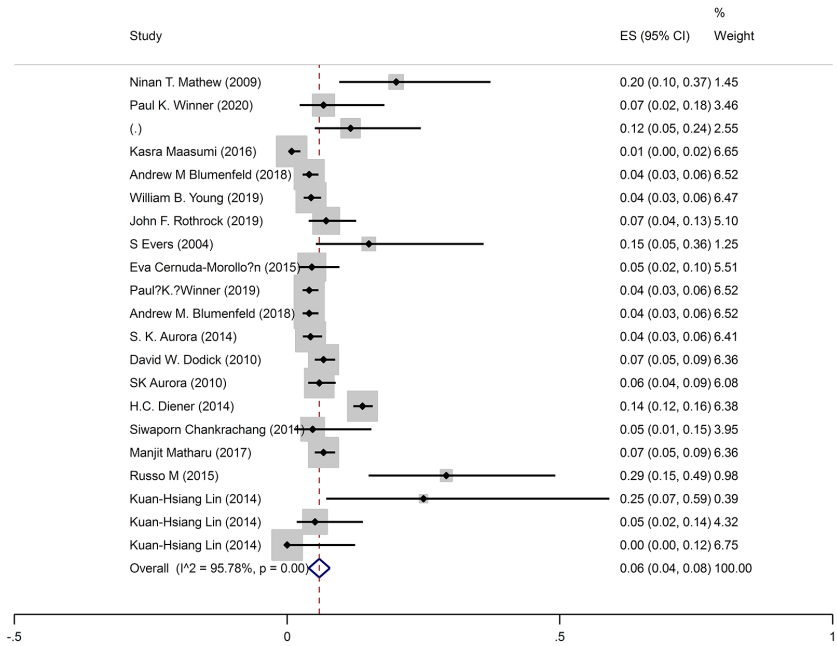

Figure 3. The pooled prevalence of blepharoptosis

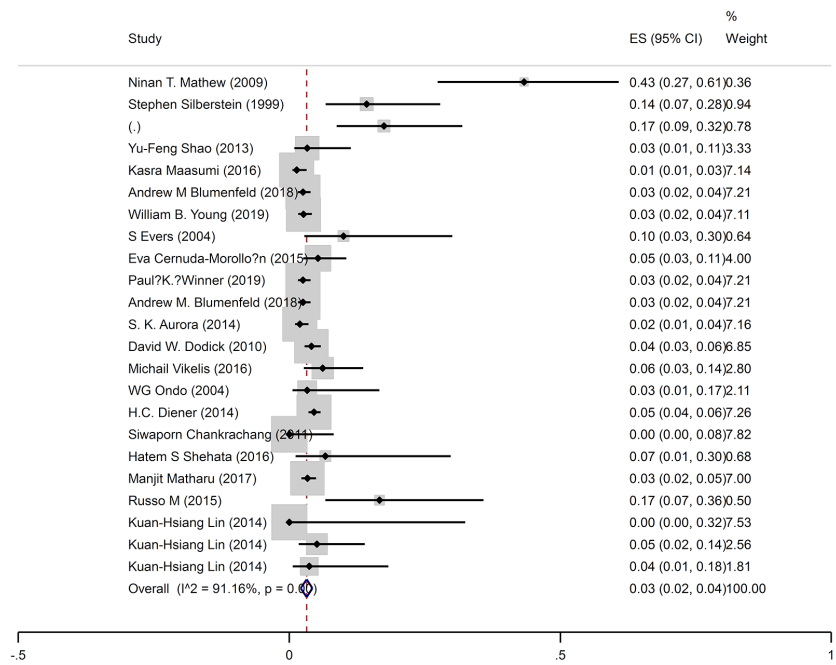

Figure 4. The pooled prevalence of blepharoptosis

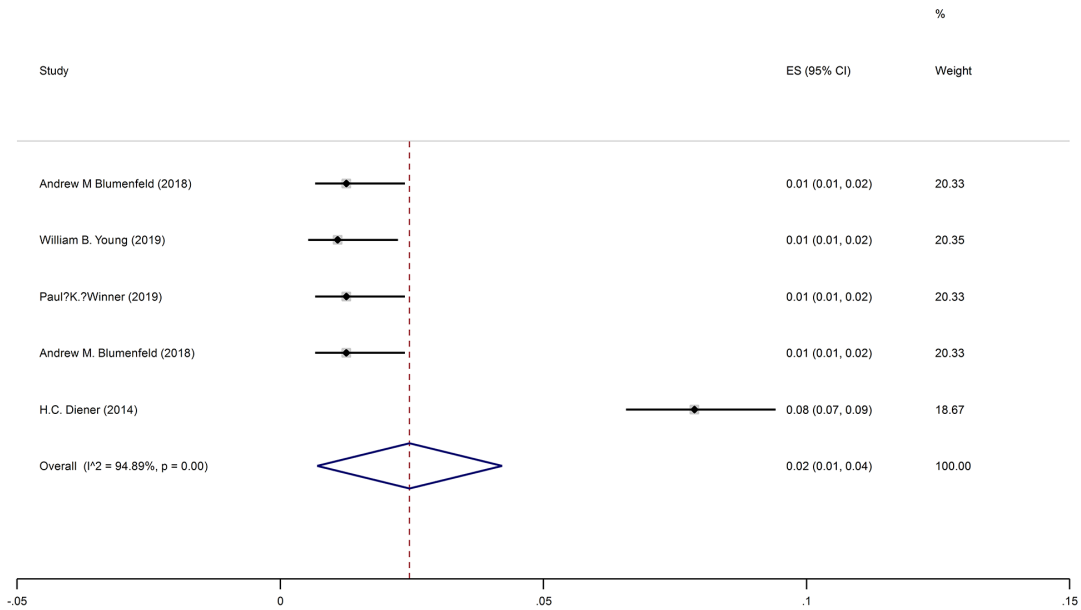

Figure 5. The pooled prevalence of facial paralysis

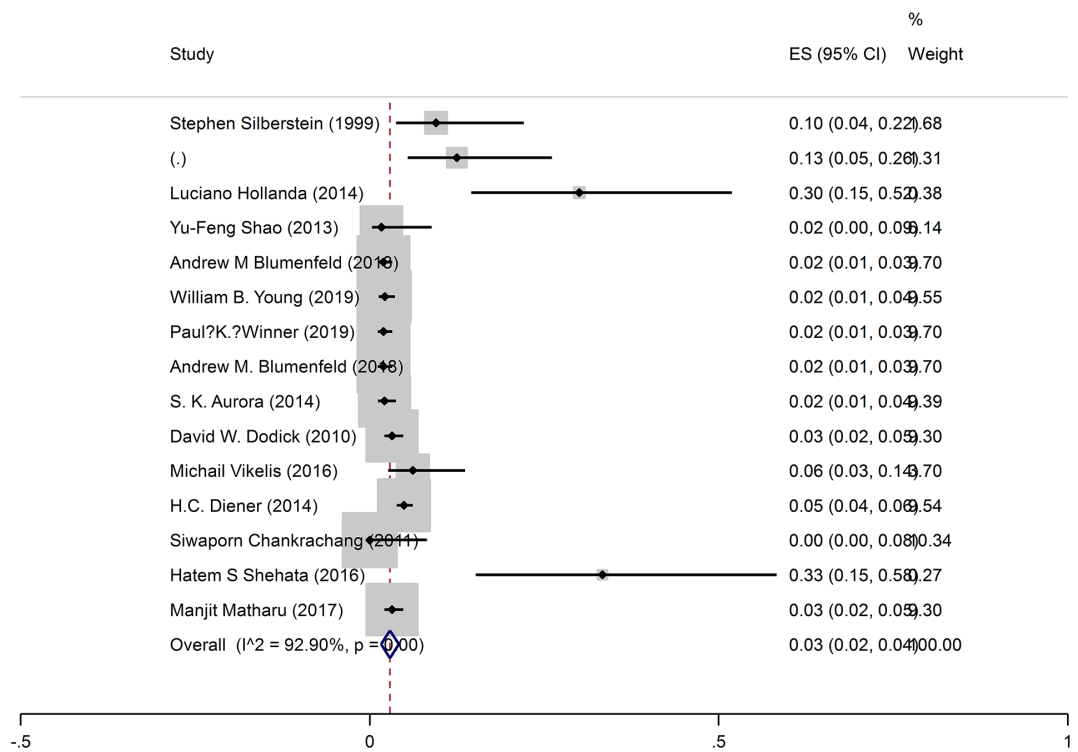

Figure 6. The pooled prevalence of injection site pain

Table 2. The Quality Assessment of the Included Studies

First Author and Year	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)	Other Potential Threats to Validity
Mathew (2009) (11)	LRB	LRB	URB	LRB	URB	LRB
Cady (2011) (12)	LRB	LRB	LRB	URB	LRB	LRB
Winner (2019) (24)	LRB	LRB	LRB	LRB	LRB	LRB
Petri (2009) (13)	LRB	LRB	LRB	LRB	LRB	LRB
Silberstein (2000) (14)	LRB	LRB	LRB	HRB	LRB	LRB
Hollanda (2014) (15)	LRB	LRB	HRB	URB	LRB	URB
Shao (2013) (16)	LRB	HRB	HRB	URB	LRB	HRB
Maasumi (2015) (17)	HRB	HRB	HRB	HRB	LRB	HRB
Blumenfeld (2019) (18)	HRB	HRB	HRB	LRB	LRB	URB
Young (2019) (19)	HRB	HRB	HRB	LRB	LRB	URB
Rothrock (2019) (20)	LRB	HRB	HRB	LRB	HRB	URB
Evers (2004) (21)	LRB	LRB	LRB	URB	URB	URB
Ali (2019) (22)	HRB	HRB	HRB	LRB	LRB	URB
Cernuda-Morollo´n (2015) (23)	HRB	HRB	HRB	LRB	LRB	HRB
Winner (2019) (24)	HRB	HRB	HRB	LRB	LRB	LRB
Blumenfeld (2018) (25)	HRB	HRB	HRB	URB	LRB	LRB
Ali (2019) (22)	HRB	HRB	HRB	URB	HRB	HRB
Aurora (2014) (26)	LRB	LRB	LRB	URB	LRB	LRB
Dodick (2010) (27)	LRB	LRB	LRB	LRB	LRB	LRB
Aurora (2010) (28)	LRB	LRB	LRB	LRB	LRB	LRB
Vikelis (2016) (29)	HRB	HRB	HRB	LRB	LRB	HRB
Ondo (2004) (30)	LRB	LRB	LRB	URB	LRB	URB
Diener (2014) (31)	LRB	LRB	LRB	LRB	LRB	LRB
Chankrachang (2011) (32)	LRB	LRB	LRB	LRB	LRB	LRB
Shehata (2016) (33)	LRB	HRB	HRB	URB	URB	HRB
Matharu (2017) (34)	LRB	LRB	LRB	LRB	LRB	LRB
Mazza (2015) (35)	URB	HRB	HRB	HRB	LRB	HRB
Lin (2014) (36)	HRB	HRB	HRB	URB	LRB	HRB
Brin (2018) (37)	HRB	HRB	HRB	HRB	LRB	HRB
Blumenfeld (2018) (18)	URB	HRB	HRB	URB	LRB	HRB
Chen (2010) (38)	LRB	LRB	LRB	URB	LRB	HRB
Freitag (2008) (39)	LRB	LRB	LRB	LRB	LRB	LRB
Christie (2010) (40)	HRB	HRB	HRB	LRB	LRB	URB
Khalil (2014) (41)	HRB	HRB	HRB	LRB	LRB	URB
Ornello (2020) (42)	HRB	HRB	HRB	LRB	LRB	LRB

Abbreviations: LRB, Low risk of bias; HRB, High risk of bias; URB, Unclear risk of bias.

Diener et al. pooled data from 4 trials by evaluating 1997 patients with migraines and found that AEs happened in 73%, and almost all were mild/moderate (31). It was also demonstrated that patients who received 150-200 units per cycle experienced fewer AEs than those receiving more than 200 units per cycle of botulinum toxin. Most AEs were mild, lasted for one week, and were resolved between 8 to 9 weeks.

By enrolling 254 patients with chronic migraines in the Hull Migraine Clinic, Khalil et al. found injection-site pain, neck stiffness, ptosis, headache exacerbation, and dysphagia as common AEs after onabotA injection, respectively (41).

Dominguez et al. followed up on 725 patients with chronic migraine up to one year after administration of onabotA and showed AE incidence in 12.3% after the first dose, while 82.3% were mild/moderate and only 0.7% discontinued onabotA due to AEs (45).

Matharu et al. followed up on 1160 patients with chronic migraines from 58 European centers, 41.2% of which reported AEs, 5.3% were serious, and 4.4% discontinued treatment (46).

The present study had some strengths and limitations. First, we included most of all trials in this field. Second, we analyzed all related AEs.

The limitation was the difference in the dose of botulinum toxin in different studies.

5.1. Conclusions

The results of this systematic review and meta-analysis show that the most common AEs following botulinum toxin injection for migraine headache prophylaxis are neck pain followed by musculoskeletal weakness and injection site pain.

Footnotes

Authors' Contribution: E. R.: Conceiving and designing the evaluation and drafting the manuscript; H.: Participating in designing the evaluation, performing parts of the statistical analysis, and helping draft the manuscript; W.M.: Re-evaluating the clinical data, revising the manuscript, and performing the statistical analysis; A. and GH.: Collecting and interpreting the clinical data, and revising the manuscript; V.: Re-analyzing the clinical and statistical data and revising the manuscript. All authors read and approved the final manuscript.

Conflict of Interests: The authors declared no conflict of interest.

Data Reproducibility: The dataset presented in the study is available on request from the corresponding author during submission or after publication.

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Table 1. Data Extracted from Studies

Ref.	Year	Country	No. of Patients in Botox Group	No. of Controls	Dose of Botox or Type of Control	Age[a]	Disease Duration[a]	Age at Onset[a]	Duration of Taking Botolinum	Muscular Weakness	Neck Pain	Blepharoptosis	Myalgia	Skin Tightness	Injection Pain	Headache	Musculo-Skeletal Pain	Dental Pain	Dizziness	Migraine	Facial Paralysis	Musculo-Skeletal Stiffness	Influenza-Like
(11)			30		42.2U			14.9 (7.2)	3		6	13							2				
	2009	USA		30	Topiramate			20.0 (9.2)															
(12)	2010	USA	29		200U				3									13					
				30	Topiramate													6					
(10)	2020	USA	45		155U	15.1 (1.4)	4.1 (2.9)	10.7 (3.0)	3		3						1		3	1			
			43		74U	15.0 (1.5)	4.2 (2.7)	10.4 (2.9)			5						3		0	3			
				37	Placebo	15.2 (1.5)	4.5 (3.4)	10.3 (3.8)			0						0		1	1			
(13)	2009	Germany	31		210U	42 (12)	23 (14)		3		8	2											
			29		80U	49 (11)	29 (13)																
				62	Placebo	47 (11)	27 (12)				1												
(14)	1999	USA	42		25 U	42.8	23.4		3			6			4								
			40		75 U	42.4	16.9					7			5								
				41	Placebo	46.8	27.4					0			1								
(15)	2014	Brazil	20		100U	44.8 (12.6)			3						6	2							
				18	Placebo	45.8 (14.2)									2	1							
(16)	2013	China	60		25U	40.25	5.7		4			2			1								
(17)	2016	USA	359		155U	45.1 (13.2)			12	3	3	5				5		1				4	3
(18)	2018	USA	716		155U	43.0 (11.3)			27	17	29	18	10	7	14	12				7	9		
(19)	2019	USA	641		155U	43.1	12.8	32.3	27	10	28	17		6	14	10			3	6	7	17	3
(20)	2019	USA	140		200U	40.2 (11.7)			8		10							1	6	6			
				142	Topiramate	39.4 (12.6)					3							19	18	2			
(21)	2004	Germany	20		100U	37 (14)	21 (14)		3		3	2	2								0		
			20		16U	41 (9)	23 (11)				1	4	2								2		
				20	Placebo	37 (9)	22 (2)				5	0	1								1		
(22)	2019	USA	30		185U	16.5 (1.83)			12-24									1					
(23)	2015	Spain	132		155-195U	46.3 (12.3)	10.5 (8.4)		12		6	7											
(24)	2019	USA	716		155U	43.0 (11.3)			27	10	29	18		7	14	12				7	9	17	

Continued on next page

Table 1. Data Extracted from Studies (Continued)

(25)	2018	USA	716		155U	43.0 (11.3)	10.6 (11.0)	32.5 (13.7)	27	10	29	18		7	14	12				7	9	17	
(22)	2018	India	30		185U	16.5 (1.8)			3									1					
(26)	2014	USA	513		195U	41.4 (10.2)	19.6 (12.4)		6	8	22	10			11								
				492	Placebo	42.3 (10.7)	19.3 (12.6)																
(27)	2010	USA	688		155U	41.1			6	38	46	28	18		22	20	15					16	
				696	Placebo	41.5				2	15	2	2		14	11	5					5	
(28)	2010	USA	341		155U	41.2	20.3		6	20	20												
				338	Placebo	42.5	20.6																
(29)	2016	Greece	81		155U	43.5 (9.8)			9			5			5		3						
(30)	2004	USA	30		200U	46.3 (9.4)			6			1											
				30	Placebo	47.7 (12.7)																	
(31)	2014	Germany	1384		163U	42.1 (10.34)	20.1 (12.55)	21.0 (11.09)	6	127	191	63	43		68	111		51	33	53	109	99	35
				1052	Placebo	42.3 (10.89)	19.8 (12.89)	21.6 (11.79)		3	25	5	3		28	58		29	17	25	1	14	31
(32)	2011	Thailand	43		120U	38.9 (9.8)	4.3 (4.7)		3		2	0			0			1	2			1	
			43		240U	38.1 (9.8)	5.4 (6.3)				0	2			0			0	1			0	
				41	Placebo	38.7 (10.2)	4.7 (6.6)				1	0			1			0	0			0	
(33)	2016	Egypt	15		155-195U	32.81 (7.64)	5.12 (2.98)		3			1			5								
				14	RTMS	31.98 (8.12)	5.61 (3.20)																
(34)	2017	UK	688		155U	41.1 (10.4)	19.4 (12.4)	21.2 (11.0)	6	38	46	23	18		22	20	15					16	
				696	Placebo	41.5 (10.7)	19.0 (12.7)	21.9 (11.9)															
(35)	2015	Italy	24		NR				6		7	4											
(36)	2014	Taiwan	8		75U	47.6 (13.6)	8.1 (8.3)		3		2	0											
			59		100U						3	3											
			27		155U						0	1											
(37)	2018	USA	716		155U	43 (11.3)			27		1	0			0	3						1	
(18)	2018	USA	715		155U	43 (18-73)			27		29	18			14							17	
(38)	2010	Taiwan	688		155U				6	38	60												
				696	Placebo																		
(39)	2008	USA	20		100U	42.2 (19-64)			4		1								0				

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Table 1. Data Extracted from Studies (Continued)

				21	Placebo	42.4 (25-55)					1								1				
(40)	2010	Canada	53[a]		95-130 U	46.5 (8.4)			6	2		5											
(41)	2014	UK	254		155U	45.04 (19-91)	1.4 (0.8-3)		1		37	28			38	11							
(42)	2020	Italy	115		155U	50 (44.5-54)	5.2 (2-12)		15	11					12								

[a] Values are presened as mean.