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Effectiveness of Botulinum Toxin Type A Injection on Moderate to Severe Glabellar Lines Systematic Review and Metaanalysis: Glabellar Line Scale Parameter Study

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ABSTRACT

Background: Glabellar lines have social and psychological implication since oftentimes generate negative facial expressions that could be misunderstood, such as anger, anxiety, fear or sadness, and others related to extrinsic aging signs. Botulinum toxin type A has been used for more than 20 years in aesthetic medicine and one of many options to improve dynamic facial lines on upper third of the face, including glabellar lines. On April 2009. FDA approved abobotulinum toksin A (Dysport) as the latest botulinum toxin type A, a purified complex diluted with human serum albumin and lactose.

Aim: The purpose of this study is to analyze the effectiveness of botulinum toxin type A (abobotulinum toxin A) as a therapy for moderate to severe glabellar lines.

Methods: searching the electronic database Pubmed-MEDLINE, Scopus, ProQuest, Cochrane library, ClinicalTrials.gov, and Google Scholar, found five articles (n=1.134) included in qualitative and quantitave analysis.

Result: Metaanalysis showed the value of Q statistic was z value = 9,079 (p=0,000). Glabellar lines improvement according to Glabellar Lines Scale were more prominent in botulinum toxin type A injection group compared to control group on the 30th day after botulinum toxin type A injection (relative risk 23,007; CI 95%,11,692 – 45,274). The result of the overall metanalysis showed that glabellar lines severity in the group with botulinum toxin type A injection was significantly improved compared to control group.

Conclusion: Botulinum toxin type A 50 U (abobotulinum toxin type A) is effective in significantly improving glabellar lines severity compared to placebo group

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Keywords: botulinum toxin type A, glabellar lines, Glabellar Lines Scale

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Introduction

Skin wrinkles is a condition due to aging process when collagen and elastin fibers responsible for flexibility undergo a change into being inflexible and rigid, thus the skin loses the elasticity, bones and muscles suffer atrophy, subcutaneous adipose decreases and skin layers become thinner, causing visible lines and skin folds and when facial muscle contractions are not followed with proper skin contractions, wrinkles around the mouth, eyes, and forehead are formed[1,2,3]. Glabellar lines have social and psychological implications due to negative facial expression that could be mistaken as anger, anxiety, fear or sadness, and related to extrinsic aging signs[4,5]. Moderate to severe glabellar lines are concerning because the patient may feel uncomfortable to the point of seeking alternative treatment to remove them.

Glabellar lines can be assessed with validated 4-point photographic scale to measure the severity of glabellar lines on baseline and maximum frown, known as Glabellar Line Scale (GLS) and Patient Frown Wrinkle Severity Scale (PFWS).

Glabellar lines can be treated effectively with muscle relaxant such as botulinum toxin type A by inhibiting acetylcholine thus weakening facial muscles contraction. Botulinum toxin type A has been used for more than 20 years in aesthetic medicine and one of many options to treat dynamic facial lines on upper third of the face[6]. On 2009, FDA approved abobotulinum toxin (Dysport) as the latest botulinum toxin type A to treat glabellar lines. Treatment with botulinum toxin injection is more popular since the result is proven tobe effective, satisfying, safe, and long-lasting to reduce fine lines, wrinkles, and facial rejuvenation. The treatment can be tolerated with high satisfaction from the subjects[7,8,9].

Material and Methods

Literature Search

Data collection was performed online on Pubmed-MEDLINE, Scopus, EBSCO, Cambridge Core, Elsevier Clinical Key, ProQuest, Springer Link, Cochrane library, ClinicalTrials.gov, Web of Knowledge, Web of Science, dan World Health Organization international clinical trials registry, followed with hand searching from Indonesian libraries within period of time until the data was analyzed. The following Medical Subject Headings (MeSH) was applied to create two subgroups of citations, (1) Botox; (2) glabellar line. Two subgroups was consolidated using Boolean's term 'OR' for each subgroup, also 'AND' to combine both subgroups in order to obtain a number of references relevant with research questions. Literature search was conducted based on PRISMA 2009 flowchart. Research samples are all randomized clinical trials regarding botulinum toxin type A injection therapy on moderate to severe glabellar lines which meet the criteria within research time period. Research inclusion criteria include botulinum toxin type A injection therapy on moderate to severe glabellar lines conducted until 2021, male and female aged 18 – 75 years old with median 43 years old, accompanied by moderate to severe glabellar lines. Exclusion criteria are case reports, case serials, editorial letters, systematical reviews, and literature reviews.

Study Selection

Three researchers managed to look for literature independently while examining all references, primary articles, and latest literature reviews to identify missing articles. Every dispute in determining papers and data extraction was settled with consensus.

Data Extraction

Data was extracted independently by three researchers with data extraction forms prepared beforehand. The form was designed based on data collection forms that have been modified from Cochrane Library. The recorded data included every action using botulinum toxin injection with placebo injection, and Glabellar line score.

Assessment of Risk of Bias

Risk of bias assessment was performed independently by three reviewers using The

Cochrane Collaboration data collection forms specifically for RCT and The Cochrane Collaboration tools to assess risk of bias in randomized clinical trials.

Data analysis

Systematic review and metaanalysis of subject proportion differences between the groups with glabellar lines improvement and control groups will be analyzed using Software Comprehensive Metaanalysis version 3.0.

Result

The search for research articles was conducted based on the 2009 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flowchart (Figure 1)

Study Characteristics

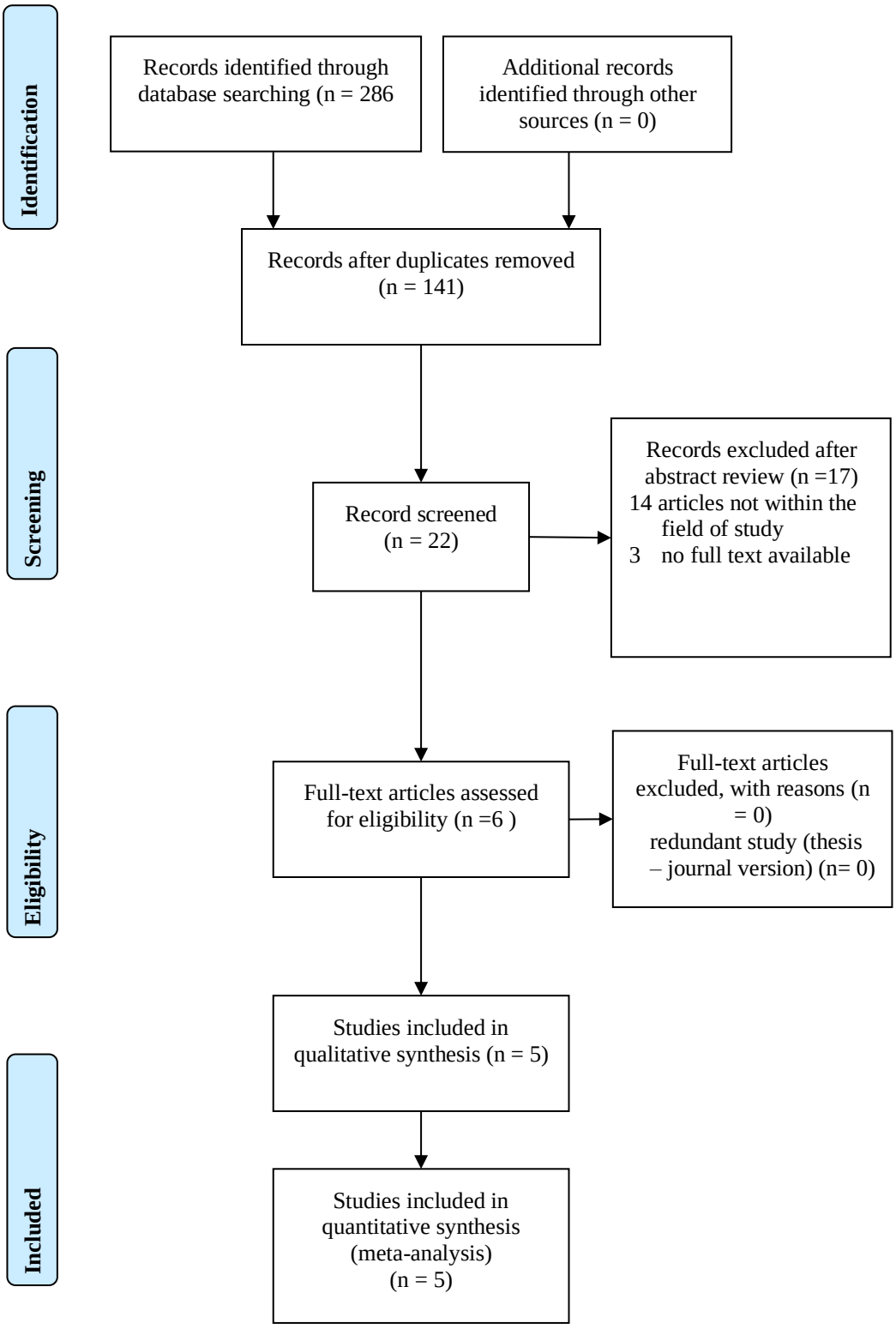
The majority of the research locations were carried out in United States of America (n=3), followed by Texas (n=1) and France (n=1) in 2009 – 2021. All studies used a randomized clinical trial design. The total sample from 5 studies were 1,134 people. All studies appointed moderate to severe glabellar lines as research subjects. All 5 studies selected samples based on sex categories into 142 males dan 992 females. Three studies have similar age group between 18 – 65 years old, one study has group of age 21 – 71 years old, and another one with group of age 19 -75 years old. All studies compared botulinum toxin type A injection with placebo control[10,11,12]. Study characteristics are written in Tabel 1

Table 1. Research Characteristics[10,12,13,15]

	Researcher and Year	Country	Age Range (year)	Sample quantity	Treatment		Research Outcomes	Observation Time	Research design
					Treatment group (botulinum toxin 50 U)	Control group (placebo)			
1.	Ascher, et al. 2019	United States of America	18-65	185	125	60	ILA/GLS, SSA, FACE-Q	6 months	Randomized, double-blind, placebo-controlled trial
2.	Schlessinger et al 2021	Texas	18-64	301	224	77	ILA/GLS,SSA FACE-Q	6 months	Randomized, double-blind, placebo-controlled
3.	Kestemont, et al 2021	French	18-65	190	125	63	ILA/GLS, SSA, FACE-Q	3 months	Randomized, double-blind, placebo-controlled and open label
4.	Monheit, et al, 2019	America	21-71	300	200	100	ILA/GLS, SSA, FACE-Q, TAEAs	5 months	Randomized, double-blind, placebo-controlled
5.	Brandt, et al, 2009	America	19-75 years and over	158	105	53	GLS, SSA, TAEAs	6 months	Randomized, double-blind, placebo-controlled

Table 2.Proportion of subjects with reduced/improved GLS 2 treatment and control groups

NO	Study Name	Control Type	Treatment		Control	
			30 Days	N	30 Days	N
1	Ascher,2019	Placebo	110	125	1	60
2	Schlessinger, 2021	Placebo	147	224	0	77
3	Kestemont, 2021	Placebo	105	126	2	64
4	Monheit, 2019	Placebo	178	200	0	100
5	Brandt, 2009	Placebo	94	105	4	53



Result of Qualitative Data Analysis (Systematic Review)

1.Ascher, et al, 2019[13]

This study was conducted on 25 males and 160 females with moderate to severe glabellar lines, who had never received botulinum toxin type A injection therapy before the study, comparing the use of botulinum toxin type A injection therapy with placebo. Administration of a single dose of botulinum toxin type A injection therapy with 183 days of observation. The selection of research subjects into the treatment and

placebo groups was done by randomization. Randomization was performed using a computer-generated randomization list. Allocation concealment did not mentioned in the paper. Patient blinding of study subjects was not anonymized for the benefit of the coordinating investigator when accessing electronic case reports. The age range of the research subjects was 18-65 years, with the age of the subjects in the treatment group being 47.7 ± 9. 75 and the placebo group 48.0 ± 9.09. The standard treatment for patients is to give botulinum toxin type A injections in a dose of 50 units and placebo divided into 5 injection points.The primary outcomes assessed in this study were the validated glabellar lines scores by investigator's live assessment (ILA) with a 4 point 0 photographic scale not present; 1 light; 2 medium; 3 weights were measured by the researcher at the maximum lines that was assessed on day 29 after treatment. The secondary outcomes assessed were the proportion of ILA on the 8th day visit, 15, 57, 85, 113, 148, 183, the proportion of SSA at each visit the proportion of patients with a decrease of 2 scores of GL severity ILA per visit, the SSA was the assessment carried out by research subjects with a score of 0: no lines, 1: mild lines, 2: moderate lines, 3: severe lines. The tertiary outcome assessed was the change in the baseline FACE-Q results and each visit. Patients rated their satisfaction using a 4-point scale, namely 0: very satisfied, 1: satisfied, 2: dissatisfied, 3: very dissatisfied.

Research subjects who experienced ≥ 2 levels in the severity of lines in the treatment group with botulinum toxin type A injection on the 29th day of observation were 88.3% while in the placebo group it was 1.4% (P<0.0001). SSA on day 29 in the treatment group was 76.0%, while in the placebo group it was 2.2% (P<0.0001). Patient satisfaction on day 29 in the treatment group was 80.9%, in the placebo group patient satisfaction ranged from 4.9%-12.3% at each visit.

2. Schlessinger, et al, 2021[14]

This study was conducted on 37 males and 264 females with moderate to severe glabellar lines who had never previously received botulinum toxin type A injection therapy. 180th day after therapy. The selection of research subjects into the treatment and placebo groups was carried out randomly based on the research center. Allocation concealment and Blinding are not described in the journal. The age range of the subjects was 18-64 years with the average age of the treatment group 44.7, SD 11.43, the mean age of the placebo group 44.1, SD 11.56. The standard treatment for subjects was to give 50 units of botulinum toxin type A injection and a placebo which was divided into 5 injection points each. 1 injection in the procerus muscle and 2 injections in each corrungator muscle. The placebo is a liquid that does not contain botulinum toxin type A.

Outcome in this study was proportion of patients with a reduction of 2 levels of glabellar lines severity at the investigator's maximum frown ILA, the subject's self-assessment (SSA) and the subject's satisfaction rating (FACE-Q) at day 30. The ILA score was 0 : none 1 : mild, 2 : moderate 3 : severe, SSA score was 0 : no lines, 1: light lines 2: moderate lines, severe lines, the subject's satisfaction score was scored 0 : very satisfied 1 : satisfied, 2: dissatisfied 3: very dissatisfied.

Research subjects who experienced a decrease in glabellar lines severity 0 to 1 on the 30th day of observation in the botulinum toxin type A group were 65.8% (CI: 59.49 – 72.03), while in the placebo group it was 0.0%. (CI : 0.00 – 4.68) with P value < 0.01. ASS on day 30 in the treatment group was 72% while in the placebo group it was 16% P < 0.001. Patient satisfaction on day 30 the majority (73%) of patients felt younger after treatment.

3. Kestemont, et al, 2021[15]

The study was conducted on 190 patients consisting of 17 males and 173 females with moderate to severe glabellar lines severity who had never previously received botulinum toxin type A injection therapy. The study compared the use of botulinum toxin type A injection with placebo. This research was conducted by DBPC

(double blind placebo controlled). Subjects who have completed the observation at the DBPC stage and meet the requirements will continue in the open label study, by giving 4 cycles of botulinum toxin type A. The DBPC stage will last for 85 days and continue with the open label stage for 12 months of observation after DBPC.

Subjects were selected randomly in blocks based on a computer-generated randomization list, randomization rates were grouped by gender and score of glabellar lines. The randomization list is stored in a secure location.

The age range of the research subjects was 18-65 years, the subjects in the treatment group were 21-65 years, and the control group was 25-65 years. The treatment of patients was given botulinum toxin type A injection dose of 50 units and placebo which was divided into five injection points in the glabellar area. The placebo is a solution that does not contain botulinum toxin.

The outcome of this study was the investigator's assessment, on a 4-point scale (ILA/GLS), the subject's assessment (SSA) on day 29 which was defined as a subject who had no lines or mild lines during the DBPC cycle observation.

Subjects in the treatment group experienced a decrease 0 to 1 level of lines severity on day 29 based on the investigator's assessment of 81.6% and the placebo group of 0.8% ($p<0.0001$), based on the assessment of the subject of the treatment group of 68.1 % and placebo 2.3% ($p<0.0001$).

4. Monheit, et al, 2019[10]

This study was conducted on 300 subjects consisting of 40 male and 260 female with moderate to severe glabellar lines who had never previously received botulinum toxin type A injection therapy. The study compared the use of botulinum toxin type A injection with placebo. Botulinum toxin type A therapy and placebo were given as a single dose for 150 days of observation. Subject selection was done by randomization. Methods of randomization, allocation concealment and blinding were not years, the subject in the treatment group was 24-67 years, and the age range for the placebo group was 19-75 years. The treatment of the described in the journal. The age range of the research subjects was 21-71 years with the age range of the treatment group being 21-71 years, the average was 44.7 years. The age range for the placebo group was 21-71 years, the mean was 44.2 years.

Outcome in this study was the patients proportion with a lines severity score of 0 or 1. After treatment assessed by ILA, the subject's satisfaction rating (SSA) was on day 30. Subject satisfaction was assessed on day 14, treatment effect, duration of treatment effect. The ILA score uses a validated glabellar line severity scale, namely: 0: none 1: mild 2: moderate 3: severe. SSA score 0 : no lines, 1: light lines, 2: moderate lines 3: severe lines.

Subjects in the treatment group experienced a decrease in severity of line measured by ILA 0 to 1 level on day 30 by 89% of subjects compared to 0% placebo ($p< 0.01$). SSA on day 30 in the treatment group was 85% subjects, placebo group was 2% subjects ($p< 0.01$). Subject satisfaction with the appearance of glabellar lines was achieved maximally on day 14 in 93% of subjects in the treatment group and 2% of subjects in the placebo group.

5. Brandt et al, 2009[12]

This study was conducted on 158 subjects consisting of 23 male and 135 female with moderate to severe glabellar lines who had never previously received botulinum toxin type A injection therapy. The study compared the use of botulinum toxin type A injection with placebo. Botulinum toxin type A injection and placebo given in a single dose were observed 180 days after therapy.

Subjects were selected randomly using a unique code. The bottle of botulinum toxin type A and placebo could not be identified apart from a unique sequence number known only to the researcher. Allocation concealment is not described in the journal. The age range of the research subjects was 19-75

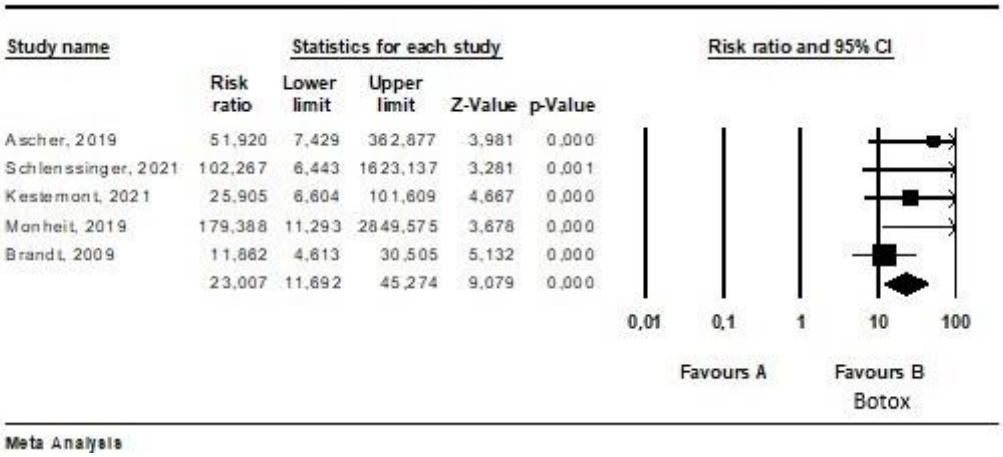
patients was given botulinum toxin type A injection at a dose of 50 units and a placebo which was divided into 5 injection points in the

glabellar area. Placebo is saline solution with lactose and albumin that does not contain botulinum toxin type A.

The outcome of this study was a 4-point photographic glabellar wrinkle score validated (GLS) by the researcher, a static 4-point category scale assessed by the research subject (SSA) on day 30. The GLS score uses a glabellar line severity scale, namely 0: none, 1: mild, 2: moderate, 3: severe, SSA score 0: no lines 1: light lines 2: moderate lines 3: severe lines.

Subjects in the treatment group who experienced a decrease in the score of glabellar lines 2 levels of ILA on day 30 were 89.5% subjects compared to 7.5% placebo (p<. 0.001) the assessment of severity of glabellar lines by subjects (SSA) in the treatment group was 75 .7% subjects, placebo group 9.8% subjects (p<. 0.01). This study showed that single-dose treatment with botulinum toxin type A in subjects with moderate to severe glabellar streaks was significantly higher than placebo.

Table 3. Results Meta-analysis of the effectiveness of botulinum toxin type A injection on glabellar lines



Quantitative Data result (Meta-Analysis)

The results of the meta-analysis of the effectiveness of botulinum toxin injection against GLS can be seen in table 3.

Results of a meta-analysis of the therapeutic efficacy of botulinum toxin type A injection against moderate to severe glabellar lines against GLS. The results of the heterogeneity the data was homogeneous. The Z value in the meta-analysis was 9.079 (p=0.000). This shows that the overall administration of botulinum toxin type A injection can reduce or improve the score of glabellar lines in patients with moderate to severe score of glabellar lines. The results of the analysis show that the risk ratio = 23,007 (95% CI = 11,692-45,274)

Risk of Bias from the included studies

The study of Ascher et al, 2019 had a high risk of bias for allocation concealment, Schlenssinger et al, 2017, Brandt et al, 2009 had test showed the value of Q = 5.829df = 4, P = 0.212, Tau2 = 0.334. This indicates that the data is homogeneous, in line with the results of the statistical Q test and heterogeneity analysis. The value of tau is obtained Tau2 = 0.334, this also shows that the data is homogeneous. The analysis was carried out using a fixed-effect model because

a high risk of bias for allocation concealment. In the study of Kestemont et al, 2021 all assessment categories have a low risk of bias. In the study of Monheit et al, 2019 had a high risk of bias in allocation concealment, blinding subjects. Four studies, namely Ascher et al, 2019, Schlenssinger et al, 2017, Monheit et al, 2019, Brandt et al, 2009 were categorized as moderate quality of evidence. The research of Kestemont et al, 2021 is categorized as good quality of evidence. Table 4.

Table 4. Risk of bias in studies used for systematic reviews and meta-analyses. Circle symbol of● with a positive sign indicating a lowrisk of bias, circle symbol of● with a question mark the risk of bias cannot be assessed, circle symbol of● with a negative sign indicates a high risk of bias.

	Random Sequence Generation	*Allocation Concealment*	*Selective Reporting*	*Other Bias*	*Blinding of Parpicipants and Personnel*	*Blinding of Outcome Assesment*	*Incomplete Outcome Data*	**Standard AHRQ**
Ascher dkk, 2019	+	−	+	+	+	+	+	*Fair*
Schlenssinger dkk, 2017	+	−	+	+	+	?	+	*Fair*
Kestemont dkk, 2021	+	+	+	+	+	+	+	*Good*
Monheit dkk, 2019	+	−	+	+	−	+	+	*Fair*
Brandt dkk, 2009	+	−	+	+	+	+	+	*Fair*

Discussion

This study is a meta-analytic observational study, a systematic review and a meta-analysis on the effectiveness of botulinum toxin type A injection on moderate to severe glabellar lines with GLS parameter. GLS score after botulinum toxin type A injection was reduced significantly on all 5 studies: Ascher et al., 2019; Schlenssinger et al., 2021; Kestemont et al., 2021; Monheit et al., 2019; Brandt et al., 2009. It is in accordance with hypothesis that botulinum toxin type A injection in patients with moderate to severe glabellar lines could reduce the lines severity.

In a study by Ascher et al., 2019, GLS score decreased remarkably on the group with botulinum toxin type A injection compared to the placebo group. The improvements can be recognized from the higher percentage of subjects with GLS score reduction in intervention group compared to placebo group. GLS score reduction of 88,3% was found on intervention group, meanwhile 1,4% reduction was found on placebo group ($p<0,0001$). Score reduction ≥ 2 on intervention group was turned into 0: none or 1: mild. This result is consistent with former studies that have been reported in the past. Response to glabellar lines improvements on respondents did not reach 100% due to several reasons such as the differences between size and activities in subjects' muscles. Standard dosage for each invidual was dissimilar, some patients may need higher dosage to undergo a change, thus when given research standard dosage they will not experience significant improvement and should be given botulinum toxin type A injection dosage adjustment in accordance with patient's muscle mass[11,12,16,17].

Mechanism of action of botulinum toxin type A is by inhibiting acethylcoline on neuromuscular junction to induce flaccid paralysis. After the injection, botulinum toxin type A will diffuse into the tissue and bind selectively and irreversibly at neuromuscular junction pre-synaptic terminals, then attach to specific membrane protein responsible to acetylcholine excretion. This process induces local muscles relaxation reversibly until fine lines that are formed by continuous muscle contraction cease[16,18].

Botulinum toxin type A is targeting muscle activities primarily used for facial expressions. It is focused not on the capability of the muscles, but rather on the weakening of the muscles appearing asfacial lines that can be assessed with clinical scale[19].

The result of the study could be affected by subjects' sex, such as in male patients. According to the literature, male's muscle mass is bigger than female's, thus to obtain expected results, the dosage needed to be adjusted with subjects' muscle mass. Glabellar area anatomy, particularly the distances between left and right brow on male and female are different, therefore the distance between male's corrugator and lavator is shorter than in female's, with possibilty that drugs distribution and penetration into levator muscle is higher, is one of many factors why male should be given higher dosage of botulinum toxin type A compared to female patients[13].

In consideration with the results, it is compulsory to comprehend that subjects' mean age in each group is remarkably different based on intervention groups and proportion of moderate and severe glabellar lines since the beginning was not identical, although the differences are not significant statistically. Ethnicity is one of many factors determining the formation of glabellar lines, where the lines are more common to be found in white people (mostly skin color phototype I and II)[20].

Schlessinger et al., 2021, stated that GLS score improve significantly in intervention group with botulinum toxin type A injection compared to placebo group on the 30th day of follow up at maximum frown. The result can be perceived from how the subjects proportion with glabellar lines improvement in intervention group is more substantial than in control group after botulinum toxin type A injection administration. Subject was defined as patient with moderate (2) or severe grade of glabellar lines (3) on maximun frown at the beginning, and severity level of none (0) or mild (1)[12,21].

Glabellar lines improvement can be assessed with four-point photographic severity scale validated beforehand, Glabellar Lines Scale (GLS). GLS is a composite scoring system for clinical assessment in wrinkles and lines as follows: 0 (no wrinkles), 1 (mild wrinkles), 2 (moderate wrinkles), 3 (severe wrinkles) as the measurements. There is another parameter that can be used to evaluate glabellar wrinkles severity, FWS (*Frown Wrinkle Severity*). FWS is a 4-point scale validated into 0 = no muscle contraction, 1 = mild muscle contraction, 2 = strong muscle contraction, 3 = very strong muscle contraction causing skin discoloration[17,23].

Kestemont et al., 2021, Monheit et al., 2019, and Brandt et al., 2009 found similar results in which subject proportions with glabellar lines severity improvement in intervention group were bigger than in control group after botulinum toxin type A injection. Botulinum toxin type A injection in these 3 studies reduced GLS score ≥ 2 on 30th day follow up after treatment[10,12,15].

Results of this meta-analysis showed that proportion of subjects who experienced improvement in the Score of Glabellar Lines (GLS) in the treatment group was greater than the control group after botulinum toxin type A injection. The control group has a better result as a whole group within 30 days after injection (95% CI, 11,692-45,274). These results overall showed that of Score of Glabellar Lines, that a group receiving botulinum toxin type A injection was significantly lower than the control group overall (P=0.000). Higher quality of evidence for this outcome suggests, further research have an important impact to the possible effects and it could change the probability.

All the articles included in meta-analysis are articles without publication bias, usually data safety and efficacy from DBPC clinical trials are at the highest level of evidence without bias, showing there is no publication bias on severity lines improvement analysis with GLS parameter[24]. Total amount of subjects in meta-analysis is 1,1134 people comprised of 142 males and 992 females. Intervention group consists of 780 subjects while control group consists of 354 subjects, with varying ethnicities all around the world. The different results of each articles could be influenced by sex, race/ethnicity, subjects' mean age, relaxed glabellar lines severity, and lines severity at maximum frown from research subjects[25].

Conclusion

Botulinum toxin type A (abobotulinum toxin type A) 50 U is effective to significantly improve glabellar lines severity scale compared to placebo group.

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