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Role of Botulinum Toxin Type A in Management of Vocal Fold Contact Granuloma Meta-Analysis Study

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ABSTRACT

Background: granulomas of the vocal process of the larynx are benign lesions of the posterior glottis generally centered over the tips of the cartilaginous vocal processes. Clinically they are associated with odynophagia, throat clearing, globus, and otalgia.

Aim of the Work: this meta-analysis study aimed to know the role of botulinum toxin type A in management of vocal fold contact granuloma.

Materials and Methods: this study strictly followed the recommendation of referred reporting items for systematic reviews and meta-analyses (PRISMA) statement. It was done in the following steps: target determination, identification the location of articles, screening and evaluation, data collection, data analysis and finally reporting and interpretation. **Results:** there was acceptable complete response rate of contact granuloma to botulinum toxin injection with event rate of 85.422% while rate of improvement among selected cases was 92.962%. Concerning to complications the most common complication was hoarsness of voice with rate of 52.737% while dysphagia was 21.125% among cases. **Conclusion:** botulinum toxin is a safe and effective therapy in resolving vocal process granulomas. Complete response and partial response are significant in our study also decreased Valsalva effort, failure rate and relapse rate are all significant outcomes. While temporary post injection hoarsness of voice, dysphagia, local pain at injection sites and fluid aspiration considered non significant outcomes.

Keywords: botulinum toxin type A, vocal fold contact granuloma.

INTRODUCTION

Vocal fold granulomas (VFGs) are areas of chronic inflammation, usually located near the vocal process of the arytenoids caused by a variety of conditions such as intubation, gastroesophageal reflux disease, and vocal abuse [(1)]. Management of VFGs remains a controversial topic for the laryngologist and head& neck surgeon. Their etiology varies, treatment is difficult, and there is a high recurrence rate. They were first described as "contact ulcers" in **1928** by **Jackson** [(2)] who reported a superficial ulceration along the posterior aspect of the larynx. At that time their etiology was thought to be voice abuse. Further application of endotracheal anesthesia led to a theory that VFGs can be a result of trauma secondary to prolonged intubation. Since then, several other factors have been implicated in their etiology including voice abuse and gastroesophageal reflux disease (GERD). Although these lesions are rare, recurrence rates of up to 90% have proven their management to be challenging [(3)]. The ENT surgeon is often the first specialist consulted by a patient with a voice disorder. More than half of these patients will have benign vocal fold changes and their treatment is often a combination of conservative and interventional measures. To this end, ENT surgeons with an interest in voice disorders rarely work alone, and a multidisciplinary team consisting of, amongst others, speech and language therapists allows for the best possible patient care [(4)]. Botulinum toxin, one of the most poisonous biological substances known, which is a neurotoxin produced by the bacterium Clostridium botulinum. C. Botulinum elaborates eight antigenically distinguishable exotoxins (A, B, C_1, C_2, D, E, F and G).

All serotypes interfere with neural transmission by blocking the release of acetylcholine, the principal neurotransmitter at the neuromuscular junction, causing muscle paralysis. The weakness induced by injection with botulinum toxin A usually lasts about three months. Botulinum toxins now play a very significant role in the management of a wide variety of medical conditions, especially strabismus and focal dystonias, hemifacial spasm, and various spastic movement disorders, headaches, hypersalivation, hyperhidrosis, and some chronic conditions that respond only partially to medical treatment [(5)].

In **1995**, **Nasri *et al.*** [(6)] introduced a new therapy in the treatment of laryngeal granulomas, Botulinum toxin type A was injected into one or both vocal folds to induce temporary vocal fold paresis allowing resolution of granulomas. The injectable sites are thyroarytenoid muscle, lateral cricoarytenoid muscle, interarytenoid Muscle and aryepiglottic muscle. The success of this therapy was confirmed by **Orloff *et al.*** [(7)] who noted

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resolution of granulomas in eight patients treated with botulinum toxin although voice therapy and anti-reflux therapy probably play significant roles in the overall treatment of laryngeal granulomas, the recovery period enabled by the paresis may be essential in order to prevent rapid recurrence.

AIM OF THE WORK

This meta-analysis study aimed to know the role of botulinum toxin type A in management of vocal fold contact granuloma.

MATERIALS AND METHODS

The study strictly followed the recommendation of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. It was done in the following steps:

1- Target determination

To detect the efficacy and safety of BTA injection in case of vocal fold contact granuloma.

2- identification the location of articles

From January to April 2017, ten electronic search engines/libraries were systematically searched for relevant publications, including:

1. PubMed,
2. Google Scholar,
3. Web of Science,
4. Scopus,
5. WHO Global Health Library (GHL),
6. Virtual Health Library (VHL),
7. System for Information on Grey Literature in Europe (SIGLE),
8. New York Academy of Medicine (NYAM).
9. POPLINE,
10. Clinical Trials (the Laryngoscope Journal, Otolaryngol Head and Neck Surgery, Acta Oto-Laryngologica Journal of Voice, the Journal of Laryngology and Otology).

Except for Google Scholar, the search term for all other libraries was as follows:

- Botulinum OR botox OR BOTOX
- Vocal cord OR
- Contact granuloma OR
- Laryngeal granuloma

For Google Scholar, we used the advanced setting in which:

- Vocal cord was filled in "with all of the words
- Botulinum toxin A for "with at least one of the words" and
- Contact granuloma" was filled in "with all of the words".

Additionally, we conducted a manual search by reviewing the citations within the included publications and reviewing the related references presented in PubMed.

3- Screening and evaluation

Among results from the ten aforementioned search engines / libraries, only papers fulfilling the predetermined eligibility criteria were included in further steps of data collection, analysis and reporting.

The inclusion criteria were:

(i) Studies reporting efficacy, complications and safety of botulinum toxin in treatment of contact granuloma.
(ii) Studies conducted on human subjects.
(iii) Articles published in English.

The exclusion criteria were:

(i) Studies lacking sufficient raw data.
(ii) Studies conducted on animals and pregnant or breast feeding women.
(iii) Review articles and case reports.
(iv) Studies that lacked reporting about outcomes.

4- Data collection

After screening of articles data were collected from relevant articles including:

- Characteristics of patients (gender and age),
- Duration of treatment,
- Duration of follow up,
- Incidence of post injection complications (hoarseness of voice, dysphagia, local pain, fluid aspiration or decreased valsalva effort),
- Rate of response (complete or partial),
- Rate of failure,
- Rate of relapse.

5- Data analysis

Statistical Methods

Statistical analysis was done using MedCalc© version 15.8 MedCalc© Software bvba, Ostend, Belgium.

6- Reporting and interpretation (results)

Testing for Heterogeneity

Studies included in meta-analysis were tested for heterogeneity of the estimates using the following tests:

1. Cochran Q chi square test: A statistically significant test (p-value <0.1) denoted heterogeneity among the studies.
2. I-squared (I^2) index which is calculated as follows: $I^2 = \left(\frac{Q-df}{Q}\right) * 100\%$. The I-squared is interpreted as follows:

0% to 40%: might not be important

40% to 60%: may represent moderate heterogeneity
50% to 90%: may represent substantial heterogeneity
75% to 100%: considerable heterogeneity

Effect Size Estimation

Event rates were expressed as proportion with its 95% confidence limits (95% CI).

Pooling of Estimates

In absence of significant heterogeneity, the Mantel-Haenszel fixed-effects method (FEM) was used for pooling of estimates from individual studies. The random-effects method (REM) was used if there was significant heterogeneity.

Examination of Publication Bias

Publication bias was assessed by examination of funnel plots. A funnel plot is a plot of the estimated effect size (rate) on the horizontal axis versus the standard error (SE) for the effect size as a measure of study size on the vertical axis. Large studies appear toward the top of the graph, and tend to cluster near the mean effect size. Smaller studies appear toward the bottom of the graph, and (since there is more sampling variation in effect size estimates in the smaller studies) will be dispersed across a range of values. By contrast, in the presence of bias, it is expected that the bottom of the plot would show a higher concentration of studies on one side of the mean than the other. This would reflect the fact that smaller studies (which appear toward the bottom) are more likely to be published if they have larger than average effects, which makes them more likely to meet the criterion for statistical significance.

Level of Significance

- A two-sided p-value <0.05 denoting statistical significance regarding heterogeneity.
- Our type of study is descriptive meta-alalysis proportion and the level of significance of outcomes is considered through the incidence rate and presense or absence of publication bias.

RESULTS

Literature search

A total number of 267 articles were retrieved from six search engines/libraries. SIGLE, POPLINE, NYAM, and Clinical Trials generated no results. After the initial title and abstract screening of the 267 articles, 32 articles were selected for full-text reading. Two independent reviewers performed the full-text screening after which 24 articles were excluded due to: 1- inappropriate study design; 2- unreliably extracted data; 3- *in vitro* or animal study and 4- posters. Finally, a total of eight studies, with a total of 713 patients with vocal fold cord granuloma, were included for data extraction and final analysis (**Table 1**).

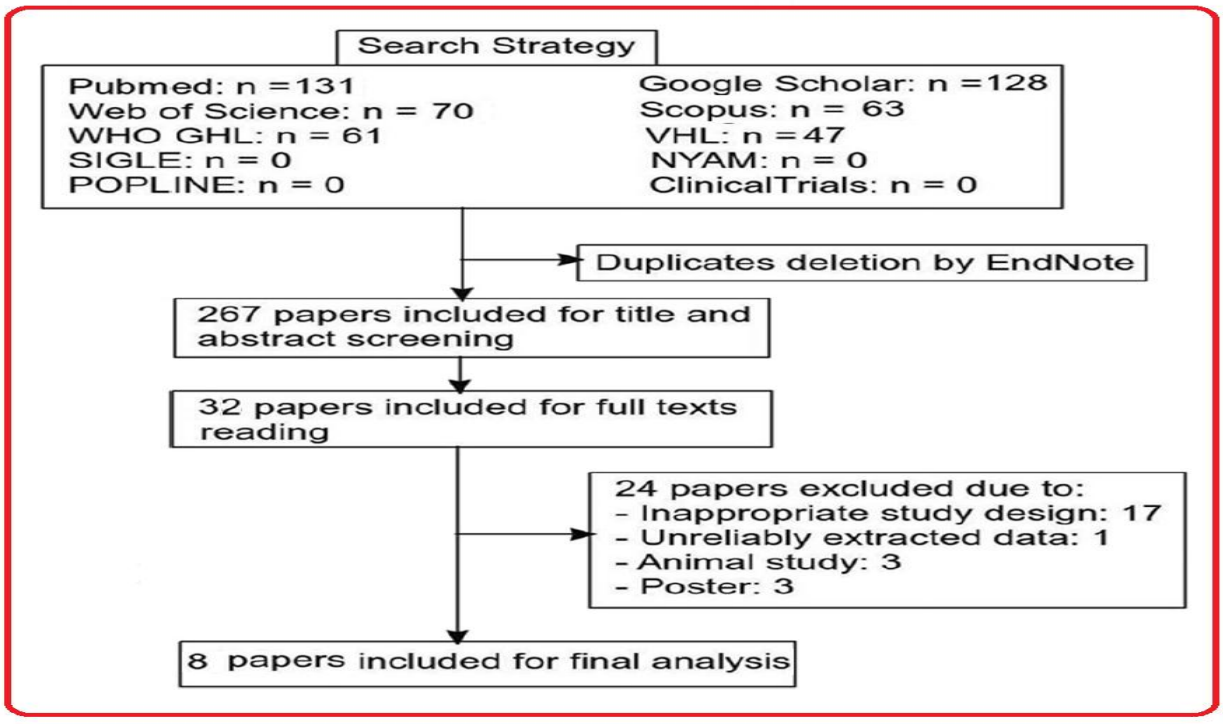

Figure 1: flow diagram of studies' screening and selection

Table 1: summary of excluded papers

Author (year)	Cause of exclusion
Allam *et al.* [8]	in appropriate study design
Aurora *et al.* [9]	in appropriate study design
Beerens *et al.* [10]	in appropriate study design
Bohluli *et al.* [11]	in appropriate study design
Boutsen *et al.* [12]	in appropriate study design
Brin *et al.* [13]	in appropriate study design
Cannito *et al.* [14]	in appropriate study design
Costa *et al.* [15]	in appropriate study design
Denglehem *et al.* [16]	in appropriate study design
Lundih *et al.* [17]	in appropriate study design
Jankovic *et al.* [18]	in appropriate study design
Lei *et al.* [19]	in appropriate study design
Mendes *et al.* [20]	in appropriate study design
Novakovic *et al.* [21]	in appropriate study design
Pham *et al.* [22]	in appropriate study design
Ruiz *et al.* [23]	in appropriate study design
Gassner *et al.* [24]	in appropriate study design
Ma *et al.* [25]	Un reliable extracted data
Halum *et al.* [26]	Animal study
Rontal *et al.* [27]	Animal study
Zalvan *et al.* [28]	Animal study

Descriptive analysis of all studies:

The eight selected papers were published from years 1995 to 2015.

Of these eight included papers, a total of 713 patients were included in the analysis with mean age of 51.25 years. 608 males and 105 females with male predominance (85.3% vs 14.7%).

The average follow up time was (19.62 months) with longest follow up time of 6 to 100 months in **Yilmaz *et al.*** [30] study and shortest follow up time of 2 to 7 weeks in **Damrose *et al.*** [29] study.

The average dose of botox in all patients was (10.43 units) with lowest average dose of 2-5 units in **Lee *et al.*** [31] study and highest average dose of 10-25 units in **Damrose *et al.*** [29] study (**Table 2).**

Table 2: data collected from articles included in the meta-analysis.

study	Nasri *et al.* [6]	Orloff *et al.* [7]	Emami *et al.* [32]	Damrose *et al.* [29]	Fink *et al.* [33]	Yilmaz *et al.* [34]	Lee *et al.* [31]	Yılmaz *et al.* [30]
No.of patients	6	8	52	7	8	20	590	22
Mean age	60.83	48.4	47	52.58	52.3	47	52.9	49
Male/female	6/0	8/0	42/10	7/0	8/0	18/2	501/89	18/4
Dose of botox injections in units	10 to 15	1.25 to 20	10 to 12	10 to 25	5 to 25	2.5 to 10.0	2 to 5	5 to 10
Numbers of injections	1 or 2	1,2 or 3	2	1	1 or 2	4	2	2
Follow up period	60-90days	11- 41 months	2 - 30 months	2 to 7 weeks	1.5-16 months	11 - 88 months	3 months	6 - 100 months
Complete response	6	8	40	7	5	20	438	17
Partial response	0	0	6	0	2	0	114	0
Non response	0	0	6	0	1	0	38	5
hoarsness	6	8	0	7	4	0	0	22
dysphagia	6	8	0	4	0	0	0	0
Local pain	6	8	0	0	0	0	0	0
Fluid aspiration	0	8	0	0	0	0	0	22
Decreased valsalva	0	1	0	0	0	0	0	0
Period of complication	3 months	4 months	0	4 weeks	4 weeks	0	0	2 weeks
relapse	0	0	0	0	0	0	38	1
Timing of relapse	0	0	0	0	0	0	26.8 months	1 year

Results of metaanalysis for incidence of post botulinum toxin injection hoarsness of voice:

All patients included in **Nasri *et al.* [6], Orloff *et al.* [7], Damrose *et al.* [29]** and **Yilmaz *et al.* [30]** studies and 50% of patients in **Fink *et al.* [33]** study, complained from post injection hoarseness of voice. While, other patients in other series didn't develop post injection hoarseness of voice.

I squared (I^2) index was 98.06% denoting significant heterogeneity between studies ($p < 0.0001$).

Pooling of estimates via random effects method (REM) was chosen to assess incidence of post injection hoarseness of voice and showed event rate of 52.737% (95% CI for I^2 = 13.312 to 90.182). Funnel plot of hoarseness of voice rate on botox use showed that publication bias was highly significant so hoarseness of voice rate of 52.7% was not considered a significant reliable result (Table 3).

Table 3: meta-analysis for the incidence of hoarseness of voice

Study	Number of patients	Event rate (%)	95% CI
Nasri *et al.* [6]	6	100.000	54.074 to 100.000
Orloff *et al.* [7]	8	100.000	63.058 to 100.000
Emami *et al.* [32]	52	0.000	0.000 to 6.848
Damrose *et al.* [29]	7	100.000	59.038 to 100.000
Fink *et al.* [33]	8	50.000	15.701 to 84.299
Yilmaz *et al.* [34]	20	0.000	0.000 to 16.843
Lee *et al.* [31]	590	0.000	0.000 to 0.623
Yilmaz *et al.* [30]	22	100.000	84.563 to 100.000
Total (fixed effects)	713	1.629	0.837 to 2.844
Total (random effects)	713	52.737	13.312 to 90.182
Test for heterogeneity			
Q	361.2347		
Significance level	P < 0.0001		
I^2 (inconsistency)	98.06%		
95% CI for I^2	13.31 to 90.18		

Q= Cochran Q statistic, DF = degree of freedom.

Results of meta- analysis for incidence of post botulinum toxin injection dysphagia:

The incidence of post injection dysphagia was 100% in **Nasri *et al.* [6], Orloff *et al.* [7]** and 57.14% in **Damrose *et al.* [29]** studies respectively. While, other patients in other series didn't develop post injection dysphagia.

I squared (I^2) index was 94.90% denoting significant heterogeneity between studies ($p < 0.0001$).

Pooling of estimates via random effects method (REM) was chosen to assess incidence of post injection dysphagia and showed event rate of 21.125% (95% CI for I^2 = 3.997 to 46.847).

Funnel plot of dysphagia rate on botox use showed that publication bias was significant so dysphagia rate of 21% was not considered a significant reliable result **(Table 4).**

Table 4: meta-analysis for the incidence of dysphagia

Study	Number of patients	Event rate (%)	95% CI
Nasri *et al.* [6]	6	100.000	54.074 to 100.000
Orloff *et al.* [7]	8	100.000	63.058 to 100.000
Emami *et al.* [32]	52	0.000	0.000 to 6.848
Damrose *et al.* [29]	7	57.143	18.405 to 90.101
Fink *et al.* [33]	8	0.000	0.000 to 36.942
Yilmaz *et al.* [34]	20	0.000	0.000 to 16.843
Lee *et al.* [31]	590	0.000	0.000 to 0.623
Yilmaz *et al.* [30]	22	0.000	0.000 to 15.437
Total (fixed effects)	713	0.501	0.125 to 1.337
Total (random effects)	713	21.125	3.997 to 46.847
Test for heterogeneity			
Q	137.3727		
Significance level	P < 0.0001		
I^2 (inconsistency)	94.90%		
95% CI for I^2	3.99 to 46.847		

Q= Cochran Q statistic, DF = degree of freedom.

Results of meta analysis for incidence of post botulinum toxin injection local pain:

The incidence of post injection local pain was 100% in **Nasri *et al.* [6]** and **Orloff *et al.* [7]**

studies. While, other patients in other series didn't develop post injection local pain. I squared (I^2) index was 94.08% denoting significant heterogeneity between studies ($p < 0.0001$).

Pooling of estimates via random effects method (REM) was chosen to assess incidence of post injection local pain and showed event rate of 14.904% (95% CI for I^2 = 1.915 to 36.998).

Funnel plot of local pain rate on botox use showed that publication bias was significant so local pain rate of 14.9% was not considered a significant reliable result **(Table 5).**

Table 5: meta-analysis for the incidence of local pain

Study	Number of patients	Event rate (%)	95% CI
Nasri *et al.* [6]	6	100.000	54.074 to 100.000
Orloff *et al.* [7]	8	100.000	63.058 to 100.000
Emami *et al.* [32]	52	0.000	0.000 to 6.848
Damrose *et al.* [29]	7	0.000	0.000 to 40.962
Fink *et al.* [33]	8	0.000	0.000 to 36.942
Yilmaz *et al.* [34]	20	0.000	0.000 to 16.843
Lee *et al.* [31]	590	0.000	0.000 to 0.623
Yilmaz *et al.* [30]	22	0.000	0.000 to 15.437
Total (fixed effects)	713	0.402	0.0800 to 1.190
Total (random effects)	713	14.904	1.915 to 36.998
Test for heterogeneity			
Q	118.2464		
Significance level	P < 0.0001		
I^2 (inconsistency)	94.08%		
95% CI for I^2	1.91 to 36.998		

Q= Cochran Q statistic, DF = degree of freedom.

Results of meta analysis for incidence of post botulinum toxin injection fluid aspiration:

The incidence of post injection fluid aspiration was 100% in **Orloff *et al.* [7]** and **Yilmaz *et al.* [30]** studies. While , other patients in other series didn't develop post injection fluid aspiration.

I squared (I^2) index was 97.18% denoting significant heterogeneity between studies ($p < 0.0001$).

Pooling of estimates via random effects method (REM) was chosen to assess incidence of post injection fluid aspiration and showed event rate of 18.787% (95% CI for I^2 = 0.671 to 52.917).

Funnel plot of fluid aspiration rate on botox use showed that publication bias was highly significant so fluid aspiration rate of 18.7% was not considered a significant reliable result. (Table 6).

Table 6: meta-analysis for the incidence of fluid aspiration

Study	Number of patients	Event rate (%)	95% CI
Nasri *et al.* [6]	6	0.000	0.000 to 45.926
Orloff *et al.* [7]	8	100.000	63.058 to 100.000
Emami *et al.* [32]	52	0.000	0.000 to 6.848
Damrose *et al.* [29]	7	0.000	0.000 to 40.962
Fink *et al.* [33]	8	0.000	0.000 to 36.942
Yilmaz *et al.* [34]	20	0.000	0.000 to 16.843
Lee *et al.* [31]	590	0.000	0.000 to 0.623
Yilmaz *et al.* [30]	22	100.000	84.563 to 100.000
Total (fixed effects)	713	0.907	0.351 to 1.904
Total (random effects)	713	18.787	0.671 to 52.917
Test for heterogeneity			
Q	248.2283		
Significance level	P < 0.0001		
I^2 (inconsistency)	97.18%		
95% CI for I^2	0.671 to 52.91		

Q= Cochran Q statistic, DF = degree of freedom.

Results of meta analysis for incidence of post botulinum toxin injection decreased valsalve effort:

The incidence of post injection decreased valsalva effort was 12.5% in **Orloff *et al.* [7]** study. While, other patients in other series didn't develop post injection decreased valsalva effort.

I squared (I^2) index was 20.86% denoting non significant heterogeneity between studies (P = 0.2640). Pooling of estimates via fixed effects method (FEM) was chosen to assess incidence of post injection decreased Valsalva effort and showed event rate of 0.157% (95% CI for I^2 = 0.00578 to 0.802). Funnel plot of decreased valsalva effort rate

on botox use showed that; publication bias was not significant so decreased Valsalva effort rate of 0.1% was considered a significant reliable result. (**Table 7).**

Table 7: meta-analysis for the incidence of decreased valsalva effort

Study	Number of patients	Event rate (%)	95% CI
Nasri *et al.* [6]	6	0.000	0.000 to 45.926
Orloff *et al.* [7]	8	12.500	0.316 to 52.651
Emami *et al.* [32]	52	0.000	0.000 to 6.848
Damrose *et al.* [29]	7	0.000	0.000 to 40.962
Fink *et al.* [33]	8	0.000	0.000 to 36.942
Yilmaz *et al.* [34]	20	0.000	0.000 to 16.843
Lee *et al.* [31]	590	0.000	0.000 to 0.623
Yilmaz *et al.* [30]	22	0.000	0.000 to 15.437
Total (fixed effects)	713	0.157	0.00578 to 0.802
Total (random effects)	713	0.605	0.0101 to 2.107
Test for heterogeneity			
Q	8.8450		
Significance level	P = 0.2640		
I^2 (inconsistency)	20.86%		
95% CI for I^2	0.0057 to 0.802		

Q= Cochran Q statistic, DF = degree of freedom.

Results of meta analysis for rate of complete response to botulinum toxin injection:

There was acceptable complete response rate of contact granuloma to botulinum toxin injection among selected cases. Of eight series, four papers achieved 100% of complete response [6, 7, 29,34]. While ,complete response of others ranged from 62.5% to 77.27%.

I squared (I^2) index was 73.13% denoting highly significant heterogeneity between studies (P = 0.0005).

Pooling of estimates via random effects method (REM) was chosen to assess incidence of complete response and showed event rate of 85.422% (95% CI for I^2 = 75.173 to 93.296).

Funnel plot of complete response rate on botox use showed that publication bias was not significant so complete response rate of 85% was considered a significant reliable result. (Table 8).

Table 8: meta-analysis for the rate of complete response

Study	Number of patients	Event rate (%)	95% CI
Nasri *et al.* [6]	6	100.000	54.074 to 100.000
Orloff *et al.* [7]	8	100.000	63.058 to 100.000
Emami *et al.* [32]	52	76.923	63.160 to 87.468
Damrose *et al.* [29]	7	100.000	59.038 to 100.000
Fink *et al.* [33]	8	62.500	24.486 to 91.477
Yilmaz *et al.* [34]	20	100.000	83.157 to 100.000
Lee *et al.* [31]	590	74.237	70.508 to 77.722
Yilmaz *et al.* [30]	22	77.273	54.630 to 92.179
Total (fixed effects)	713	76.345	73.070 to 79.403
Total (random effects)	713	85.422	75.173 to 93.296
Test for heterogeneity			
Q	26.0474		
Significance level	P = 0.0005		
I^2 (inconsistency)	73.13%		
95% CI for I^2	75.173 to 93.296		

Q= Cochran Q statistic, DF = degree of freedom.

Results of meta analysis for the rate of inprovement to botulinum toxin injection.

Rate of improvement means all cases responded totally or partially to botulinum toxin injection.

There was acceptable rate of improvement of contact granuloma to botulinum toxin injection among selected cases. Of eight series, four papers achieved 100% of improvement rate [6, 7, 29,34]. While

improvement rate of others ranged from 77.2% to 93.5%.

I squared (I^2) index was 36.18% denoting non-significant heterogeneity between studies (P = 0.1400).

Pooling of estimates via fixed effects method (FEM) was chosen to assess incidence of rate of improvement and showed event rate of 92.962% (95% CI for I^2 = 90.843 to 94.719).

Funnel plot of rate of improvement on botox use showed that publication bias was not significant so improvement rate of 92.9% was considered a significant reliable result. (Table 9).

Table 9: meta-analysis for the rate of improvement

Study	Number of patients	Event rate (%)	95% CI
Nasri *et al.* [6]	6	100.000	54.074 to 100.000
Orloff *et al.* [7]	8	100.000	63.058 to 100.000
Emami *et al.* [32]	52	88.462	76.559 to 95.646
Damrose *et al.* [29]	7	100.000	59.038 to 100.000
Fink *et al.* [33]	8	87.500	47.349 to 99.684
Yilmaz *et al.* [34]	20	100.000	83.157 to 100.000
Lee *et al.* [31]	590	93.559	91.267 to 95.402
Yilmaz *et al.* [30]	22	77.273	54.630 to 92.179
Total (fixed effects)	713	92.962	90.843 to 94.719
Total (random effects)	713	91.934	86.900 to 95.833
Test for heterogeneity			
Q	10.9677		
Significance level	P = 0.1400		
I^2 (inconsistency)	36.18%		
95% CI for I^2	90.84 to 94.7		

Q= Cochran Q statistic, DF = degree of freedom.

Results of meta analysis for the failure rate to botulinum toxin injection:

Failure rate effect of botulinum toxin on contact granuloma was 11.5%, 12.5%, 6.4% and 22.7% in **Emami *et al.*** [32], **Fink *et al.*** [33], **Lee *et al.*** [31] and **Yilmaz *et al.*** [30] studies respectively with mean failure rate 7.03%. Other series have no falure rate.

I squared (I^2) index was 36.18% denoting non-significant heterogeneity between studies (P = 0.1400).

Pooling of estimates via fixed effects method (FEM) was chosen to assess incidence of failure rate and showed event rate of 7.038% (95% CI for I^2 = 5.281 to 9.157).

Funnel plot of failure rate on botox use showed that publication bias was not significant so failure rate of 7% was considered a significant reliable result **(Table 10).**

Table 10: meta-analysis for the failure rate

Study	Number of patients	Event rate (%)	95% CI
Nasri *et al.* [6]	6	0.000	0.000 to 45.926
Orloff *et al.* [7]	8	0.000	0.000 to 36.942
Emami *et al.* [32]	52	11.538	4.354 to 23.441
Damrose *et al.* [29]	7	0.000	0.000 to 40.962
Fink *et al.* [33]	8	12.500	0.316 to 52.651
Yilmaz *et al.* [34]	20	0.000	0.000 to 16.843
Lee *et al.* [31]	590	6.441	4.598 to 8.733
Yilmaz *et al.* [30]	22	22.727	7.821 to 45.370
Total (fixed effects)	713	7.038	5.281 to 9.157
Total (random effects)	713	8.066	4.167 to 13.100
Test for heterogeneity			
Q	10.9677		
Significance level	P = 0.1400		
I^2 (inconsistency)	36.18%		
95% CI for I^2	5.281 to 9.15		

Results of meta analysis for the relapse rate to botulinum toxin injection:

The incidence of relapse rate was 6.4% and 4.5% in **Lee *et al.*** [31] and **Yilmaz *et al.*** [30] studies respectively. While other patients in other series have not shown incidence of relapse.

I squared (I^2) index was 21.35% denoting non-significant heterogeneity between studies (P = 0.2599).

Pooling of estimates via fixed effects method (FEM) was chosen to assess incidence of relapse

rate and showed event rate of 5.470% (95% CI for I^2 = 3.926 to 7.39).

Funnel plot of relapse rate on botox use showed that publication bias was not significant so relapse rate of 5.4% was considered a significant reliable result (**Table 11).**

Table 11: meta-analysis for the relapse rate

Study	Number of patients	Event rate (%)	95% CI
Nasri *et al.* [6]	6	0.000	0.000 to 45.926
Orloff *et al.* [7]	8	0.000	0.000 to 36.942
Emami *et al.* [32]	52	0.000	0.000 to 6.848
Damrose *et al.* [29]	7	0.000	0.000 to 40.962
Fink *et al.* [33]	8	0.000	0.000 to 36.942
Yilmaz *et al.* [34]	20	0.000	0.000 to 16.843
Lee *et al.* [31]	590	6.441	4.598 to 8.733
Yilmaz *et al.* [30]	22	4.545	0.115 to 22.844
Total (fixed effects)	713	5.470	3.926 to 7.390
Total (random effects)	713	3.904	1.695 to 6.971
Test for heterogeneity			
Q	8.9006		
Significance level	P = 0.2599		
I^2 (inconsistency)	21.35%		
95% CI for I^2	3.926 to 7.39		

Q= Q statistic, DF = degree of freedom.

DISCUSSION

Vocal fold contact granuloma is an uncommon disorder encountered by laryngologists. It is difficult to treat. It has high propensity to recur when removed surgically. It is of multifactorial origin. It arises from vocal process of arytenoid cartilage, and less commonly from the body of arytenoid cartilage. That is why it is also called arytenoid granuloma. It is thought to be caused by vocal abuse, habitual throat clearing, and laryngopharyngeal reflux. It has a high tendency for persistence despite many treatment alternatives [35].There are many treatment options available for contact granuloma. Such a high number of alternatives indicate lack of satisfaction from therapy modality alone [34]. Observation alone yields 81% remission rate within a mean of 30.6 weeks, which is about 7 months. High spontaneous remission rate is a characteristic of intubation granuloma, and contact granulomas rarely disappear without treatment [36]. Medical treatment has included antibiotics, steroids, histamine-2 receptor blockers, proton pump inhibitors, botulinum toxin injections [32]. Surgical excision is still commonly performed but had been shown to have a high incidence of recurrence. The method of choice in most centers is endoscopic removal with the carbon dioxide (CO2) laser [37].

Botulinum toxin A was suggested for the first time as a form of treatment for contact granuloma patients by **Nasri *et al.*** [6]. It's claimed to be safe and effective as multiple studies showed that botulinum toxin injections into the thyroarytenoid muscle have allowed recalcitrant granulomas to heal, generally at a rate faster than that was reported with medical therapy [33].

BTA is a neurotoxin which acts at the neuromuscular junction and interferes with the neurotransmission with acetylcholine causing temporary paresis in the vocal folds resulting in temporary hoarsness of voice which was reported in all patients by many authors [6,7,29,30] and 50% in **Fink *et al.*,** [33]. While other studies didn't report any post injection hoarsness of voice [30,31,32]. In our study event rate of postinjection hoarsness was 52.737% but because of the significant publication bias this outcome was considered non reliable.

Dysphagia may also be caused temporaily after BTA injection which was reported in all patients by many authors [6,7] and of 57.14% in [29] While other studies didn't report post injection dysphagia [30,31,32,33,34]. This agrees with our study that showed significant publication bias so dysphagia was considered non significant outcome.

Local pain after BTA injection for treatment of vocal fold granuloma was found in 100% of patients in **Nasri *et al.*** [6] and Orloff ***et al.,*** [7] studies. Other studies didn't report any local pain after BTA injection [29,30,31,32]. So according to our study local pain was considered non significant outcome due to presense of bias between studies.

Injection of BTA in vocal folds may affects the laryngeal muscles which leads to Weakening of the closing action of the larynx that results in fluids aspiration and this can be overcome by tilting the chin down during swallowing and swallowing more slowly.Fluid aspiration was reported in all patients in **Orloff *et al.*** [7] and **Yilmaz *et al.*** [30] studies while, others didn't report post injection fluid aspiration [6,29,31,32,33,34].

In our meta-analysis we found that temporarily post injection aspiration of fluids is non

significant outcome because of presense of bias between studies.

With injection of BTA in vocal folds the inability of arytenoids to be approximated firmly and larynx not tightly closed theoretically leads to uncontrolled blowing of air while the patient tries to valsalva. Although it theoretically sounds, this complication was only reported of 12.5% of patients in **Orloff *et al.*** [7] study with only one out of eight patients, while almost all authors reviewed didn't report this complication in the trials [6,29,30,31,33,34]. In our meta-analysis the event rate of decreased Valsalva effort post injection was 0.157% which is considered a reliable outcome due to absence of publication bias. All complications were temporary which lasted from 2 weeks to 3 or 4 months where they improved with the resolving of botox effect.

Many authors reported complete response to BTA injection in all the patients [6,7,29,34], while in other studies complete response to BTA injection was reported with range 62.500 to 77.237 % of the patients [30,31,32,33].

Concerning to the rate of improvement all patients in **Nasri *et al.*** [6], **Orloff** [7], **Damrose *et al.*** [29] and **Yilmaz *et al.*** [34] reported improvement while other studies show rate of improvement ranging from 77.273 to 93.559 % of the patients [30,31,32,33].

Despite the good response to BTA injection failure rate rangin from 6.4 to 22.7% was reported by **Yilmaz *et al.*** [30], **Lee *et al.*** [31] and **Fink *et al.*** [33], while other studies didn't report any failure rate [6,7,29,34]. In our meta-analysis complete response rate was 85%, improvement rate was 92.962% and failure rate was 7% all were considered significant outcomes because all their results are reliable results without significant publication bias.

Finally a relapse rate post BTA injection of 4.5% was reported by **Yilmaz *et al.*** [30] and of 6.4% by **Lee *et al.*** [31] while, other studies didn't report any relapse rate [6,7,29,32,33,34]. The relapse rate was 5.4% in our meta-analysis the absence of bias between studies show that the relapse rate is significant reliable outcome.

CONCLUSION

Botulinum toxin is a safe and effective therapy in resolving vocal process granulomas. Complete response and partial response are significant in our study also decreased Valsalva effort, failure rate and relapse rate are all significant outcomes. While temporary post injection hoarsness of voice, dysphagia, local pain at injection sites and fluid aspiration considered nonsignificant outcomes.

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