

Efficacy of Kybella Injection in the Treatment of Sub-Mental Fat: A Systematic Review

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Abstract: weather Kybella injection VS other technique in double chin patients is more effective in getting rid of sub-mental fullness.

Objectives: To conduct a systematic review of the efficacy and adverse events (AEs) of Kybella injection in sub-mental fat reduction.

Background: Deoxycholic acid, also known as Kybella is a new injectable treatment that melts away the excess fat that causes double chins. The most common side effects of Kybella include swelling, bruising, pain, numbness, redness, and areas of hardness in the treatment area. Weather Kybella is really effective in treating submental fullness is true or not that's the goal of this paper.

Design: Systematic Review

Methods: We conducted literature searches in PubMed, Cochrane, and EMBASE searching for descriptive and comparative studies evaluating the efficacy and safety of Kybella injections, which met predefined inclusion criteria.

Study selection: studies with information Kybella VS no Kybella procedures. Only randomized clinical trials and comparative studies were included.

Data extraction: data of trial design, weight (pre and post treatment), dose of Kybella, frequency of Kybella injection, duration of treatment, assessment method for double chin, sample size, total number of female and male, studies limitation and side effects.

Main Outcomes and Measures: sub-mental fullness improvement according to measurement scale or self-assessment scale, patient satisfaction and adverse events (AEs).

Results: Overall there was improvement in the grade of sub-mental reduction and patient satisfaction in all the studies. The primary efficacy endpoint, a reduction in sub-mental fat was assessed using ≥ 1 grade improvement on Clinician- Reported SMF Rating Scales [CR-SMFRS] for 2 mg/cm^2 .

Conclusions: In this systematic review, the effect of Kybella in the treatment of sub-mental fat was reviewed. Overall there was improvement in the grade of sub-mental reduction and patient satisfaction.

Keywords: Cosmetic Techniques, Cosmetic treatment, Kybella, and Deoxycholic Acid.

1. INTRODUCTION

Americans spend more than 13.5 billion dollars on combined, surgical and nonsurgical procedures in 2015, according to the American Society for Aesthetic Plastic Surgery (ASAPS). (1) This suggests people are investing in their appearance and are turning to cosmetic procedures in order to do so. According to a survey performed by the American Society for Dermatologic Surgery (ASDA) in 2014, up to **65%** of people said they have dissatisfaction with sub-mental fat. (2) There has been a rapid growth in nonsurgical procedures; physicians and patients are seeking less invasive, nonsurgical options to reduce sub-mental fat. Deoxycholic acid injections (Kybella) are quickly taking over the top five most sought out nonsurgical procedures. (1)

The shape of the neck plays an important role in the appearance of an individual. A wide variety of chin structures exist. Double chin, also known as sub-mental fat (SMF), is the accumulation of fat in the deep and superficial layer of the platysma muscle, causing the appearance of another chin. (4)(13) Loss of neck definition due to the accumulation of sub-mental fat is associated with aging, low self-esteem, discomfort and distress for individuals. (3,4) Also, SMF can be associated with diseases like periodontal disease and sleep apnea. There are many factors in the development of SMF, such as weight gain, diet, aging and genetics. (7)(13). Treatment options include surgical and non-surgical procedures. Surgical options include, Neck lift surgeries, submentoplasty and liposuction. Liposuction is the most common procedure used. (5) It maybe performed alone or with neck lift surgeries. (5)(9) Although, they have a high efficacy rate, they are associated with complications; such as injury of nerve, perforation of larynx, trachea, and scaring and complication of anesthesia. (6) Making them unpopular for many. Non-surgical procedures include, laser, thermage and ultratherapy, which uses focused ultrasonic energy to lift the skin. (13) (15)(16) however, limited evidence is available about their efficacy and safety.

In 2015, FDA has approved Deoxycholic acid (Kybella) injections for contouring the neck and jawline. Deoxycholic acid is a secondary bile acid involved in dietary fat emulsification that causes irreversible adipocyte lysis when injected into subcutaneous fat tissue. (10) After adipocyte lysis, macrophages and phagocytes are recruited causing cellular debris clearance. (12) Although, they cause lipolysis they are not recommended for treatment of fat in other areas. (11) They are available in a variety of formulas; the most common is phosphatidylcholine and sodium deoxycholate. (13) (17)(18) According to the FDA, patients may receive up to 50 injections or 10 ml in a single treatment, with up to six single treatments spaced a month apart. The number of treatments and injections should be specifically tailored to each individual and the degree of SMF. Injections should be spaced 1 cm from each other. (11) All patients must be screened for other cause of sub-mental fullness, such as thyromegaly and cervical lymphadenopathy before receiving injection. (11) The most serious adverse event is mandibular nerve injury, causing asymmetric smile. (8) However, local side effects in the treatment area, such as bruising, swelling and hematoma are the most common adverse event. Kybella injection is contraindicated if there is infection. The effect and desirable outcome of these injections is administration dependent. (7)(11)

2. RATIONALE ⁽²⁾

From searching the literature and clinical exposure from recurrent complain about sub-mental fat there is no ideal treatment of choice. There are many surgical options. Although surgical treatments proved its efficacy in treating sub-mental fat but it's costly and has side effects and not appropriate for everyone. As for non-surgical treatment options, the FDA has recently approved them and there is no sufficient data about their efficacy. The cheapest non-surgical treatment that is getting attention worldwide is Kybella, that's why its time either to prove its efficacy or not in getting rid of sub-mental fat. Since many are seeking Kybella injections to reduce the appearance of sub-mental fat. In this systematic review, we will review the efficacy of Kybella in reduction of sub-mental fat.

3. METHODS

We conducted literature searches in PubMed, Cochrane, and EMBase. We did not apply any date or language restrictions. Hence, we obtained articles from all over the world, describing samples collected from people of different ethnic backgrounds. We conducted searches on the databases using the following keywords: Cosmetic Techniques, Cosmetic treatment, Cosmetic Technique, Kybella, and Deoxycholic Acid. Using an advanced search builder (((("Cosmetic Techniques"[Mesh]) OR Cosmetic treatment) OR Cosmetic Technique)) AND (((Kybella) OR "Deoxycholic Acid"[MeSH]) OR "Deoxycholic Acid"). With different combinations of these keywords, we obtained 65 articles from PubMed, 0 from Cochrane library, 35 from EMBase.

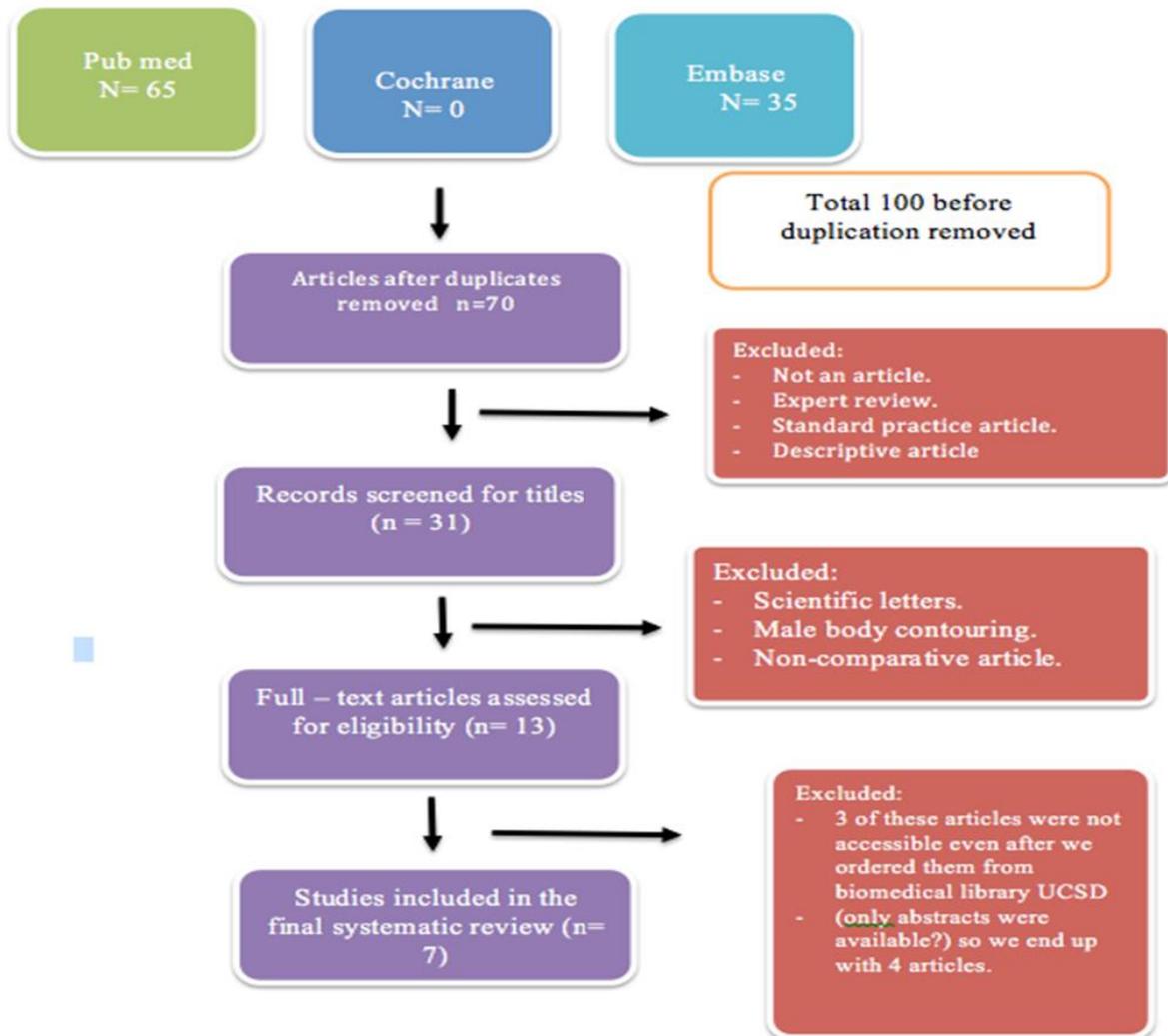


Diagram 1: methodology flowchart

Inclusion Criteria:

Inclusion and Exclusion Criteria

I. Patient Cohorts:

All studies that reported human clinical trials in adult patients with double chin were included in our review. Patients with any stage of double chin, studies describing preclinical animal work were excluded.

II. Assessment of Treatment:

Assess the efficacy of Kybella injection in removing and improving the grade of double chin. To evaluate the efficacy of treatment, Kybella injection should be compared to other treatments.

III. Types of Studies

Only clinical trials and longitudinal studies will be included and reviews will be excluded. As the goal of this systematic review is to understand the directionality of the field as a whole, all stages of clinical trials will be allowed.

Search and Data Extraction:

Two reviewers independently evaluated the results from entering the keywords into the numerous databases. Titles and abstracts were first evaluated preliminarily for their relevance to the criteria above. Articles from each database that met the criteria were extracted and checked further independently for further adherence to the criteria. Then we deleted the duplicate articles. In the end, 7 articles were selected for further qualitative studies. Three of them were published in

abstract forms only. We ordered the full text from biomedical library by university California San Diego but it came again with abstract only as available data for these articles and nothing more.

Table1: selection criteria

Inclusion Criteria	Exclusion Criteria
1. Published peer reviewed Articles	1. Non-Human Studies
2. English Language	2. Case reports
3. Clinical Trials	3. Retrospective studies.
4. Human Subjects.	4. Non English articles
5. Comparative study	

4. RESULTS

Study Selection:

We identified 100 articles in the database searches, after removing duplicates we were left with 70 articles. After exclusion of ineligible studies, 31 articles were selected for further detailed review. After applying inclusion and exclusion criteria, we selected 7 research papers for review and analysis.

Study Designs:

There were four clinical trials. (4)(8)(13)(14)

Description of Patients:

The age range of the participants enrolled was 18-65, except for one study only enrolling from 25 years and older. In the studies reviewed, the total number of participants was 1,271, of these the total male participants was 277 and the total number of female participants was 994 (M/F ratio 277/994). The majority of participants were Caucasian (n=714). The mean BMI <40 kg/m².

Kybella Dose and Schedule:

The intervention group (n= 782) was sub-divided into participants receiving Kybella dose of 1 mg/cm² (n=241), participants receiving 2 mg/cm² (n=527) in two studies and participants receiving Kybella with phosphatidylcholine (n=14) in one study. Participants received up to 4 treatments with an interval of 28 days between each session. Post-treatment follow-up was assessed in 3 of the 4 studies, occurring at an interval of 4weeks, 12 weeks and 24 weeks.

Response to Kybella:

The primary efficacy endpoint, a reduction in sub-mental fat was assessed using ≥ 1 grade improvement on Clinician-Reported SMF Rating Scales [CR-SMFRS] for 2 mg/cm². Only 3 out of the 4 studies used this as the primary efficacy endpoint (table 4). However, patient satisfaction was assessed using different scale among these studies, which made it difficult to compare the overall between all the studies. One study used Patient-Reported SMF Rating Scales PR-SMFRS](8), while the others used Subject Self-Rating Scale (SSRS) Patient-Reported Sub-mental Fat Rating.

Table 2: ≥ 1 grade improvement for 2 mg/cm²

Endpoint	Derek H. Jones, 2016	B.Ascher, 2014	B. Rzany, 2014
1-Grade Composite Response	70%	62.2%	65.3%

Table 3: ≥ 1 grade improvement for 1mg/cm²

Endpoint	B.Ascher, 2014	B. Rzany, 2014
1-Grade Composite Response	58.3%	59 2%

Table 3. Demographic Characteristics					
Study	Population	Intervention	Comparison	Outcome	Result
ADAM M. ROTUND A, 2009	N=42 Intervention=28 Control=14 Ethnicity= Caucasian (86%)	Kybella 1 mL	Kybella with phosphatidylcholine	Double chin was assisted by patient self-assessment questionnaire	Deoxycholate alone is as efficacious in fat ablation as formulations containing deoxycholate with phosphatidylcholine. Treatment of the submental area with both formulations produced minimal aesthetic improvement overall.
Derek H. Jones, 2016	N=506 Intervention=256 Control=250 Ethnicity= Caucasian, Black, Asian, Hispanic	Kybella (2 mg/cm ²)	Placebo	Double Chin was evaluated using validated Clinician-Reported and Patient-Reported SMF Rating Scales [CR-SMFRS and PR-SMFRS], MRI	Treatment resulted in high levels of subject satisfaction and was well tolerated. Results support the utility of Kybella as an effective and minimally invasive treatment option for SMF reduction.
B.Ascher, 2014	N=360 Intervention=121 (1 mg/cm ²) +122 (2 mg/cm ²) Control=117 Ethnicity= Caucasian (92.9%). Other (7.1%)	Kybella	Placebo	Double Chin was evaluated using Clinician-Reported Sub mental Fat Rating Scale (CR-SMFRS) Subject Self-Rating Scale (SSRS) Patient-Reported Sub mental Fat Rating, Scale (PR-SMFRS) and changes in the Patient-Reported Sub mental Fat Impact Scale (PR-SMFIS), Subject Global Questions,	Treatment resulted in a statistically significant reduction in the submental convexity and amount of SMF, a significantly improved visual appearance of the submental area. Treatment had a positive impact on psychological quality of life/well-being, resulting in significant patient satisfaction with treatment and appearance in association with their face and chin.
B. Rzany, 2014	N=363 Intervention=120(1mg/cm ²) +121(2 mg/cm ²) Control=122 Ethnicity= Caucasian (94.8%), other (5.2%)	Kybella	Placebo	Double Chin was evaluated using 5-point Clinician-Reported Sub mental Fat Rating Scale (CR-SMFRS)] and patients satisfied with their face and chin appearance on the Subject Self-Rating Scale (SSRS).	Resulted in significantly reduced SMF severity and increased patient satisfaction with the appearance of the face and chin, evaluated using primary efficacy outcome.

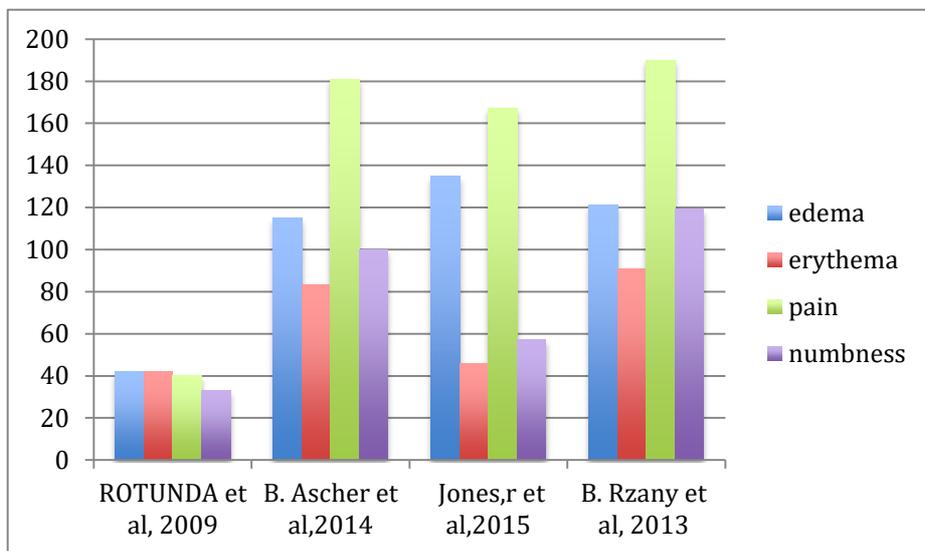
Table 4: Scales used to measure response	
Scales	Description
CR-SMFRS*	Sub mental convexity evaluated by clinician on a 5-point ordinal scale (0–4) with 0 = absent 1 = mild 2 = moderate 3 = severe 4 = extreme Photo numeric guide included (See Supplemental Digital Content 7, Figure E6, http://links.lww.com/DSS/A37)

Adverse Events:

Among the 4 studies only patients experienced local adverse events, such as, pain, burning, swelling, bruising, bleeding, numbness, erythema and burning. Pain was managed using topical anesthetic preparations and cooling with ice. Analgesics were also prescribed.

Table 5:

Local-injection site	N. Of patients. (%)
Pain	577 (73.9%)
Swelling	413 (52.8%)
Numbness	308(39.5%)
Erythema	262 (33.5%)



Jadad scale:

After we did the assessment all of the studies score 3 out of 3 as all of them were randomized, blinded studies and the reasons of drop out were mentioned. (Table.4)

	Rotunda et al, 2009	B. Ascher et al, 2014	Jones, r et al, 2015	B. Rzany et al, 2013
Randomization	1	1	1	1
Blindness	1	1	1	1
Reasons of drop- out	1	1	1	1

5. DISCUSSION

Overall there was improvement in the grade of sub-mental reduction and patient satisfaction in all the studies. The efficacy measures used in three of these studies were ≥ 1 grade improvement validated Clinician- Reported and Scales [CR-SMFRS] at 2-mg/cm² (Table 4). However, two studies also assessed at the 1-mg/cm² dose. One major challenge we faced was to Asses the response to treatment for all the studies combined. Since no gold standard exists for evaluating response to treatment. Over all Patient satisfaction was not possible to asses between all the studies, as each study used a different scale. Additionally in one of these studies, changes in sub-mental fat was evaluated using magnetic resonance imaging (MRI).

One study showed minimal improvement of sub-mental fat reduction that could be due to the lack of an objective scale in their assessment, as they used a subjective scale. Also, they used photograph assessment, which could also contribute to the minimal improvement. Since the degree of the chin angle could differ when posing for the photo. In addition, Sample size was small (n=42) compared to the other studies.

We noticed in all these studies, pre- and post-treatment weight was not mentioned. It's important to mention this to exclude weight loss as a confounding factor. As weight loss could contribute to the reduction of sub-mental fat. Also, the different causes of sub-mental fat were not mentioned, as treatment would differ between a genetic cause and aging for example. In addition, the majority of participants were Caucasian and response of treatment would differ between the different ethnicity/races.

6. CONCLUSION

In conclusion, Kybella injection is a relatively new procedure; more studies need to be conducted to gather more data. Also, a standardized was of efficacy assessment should be utilized.

7. FUTURE STUDY

As more non-surgical treatment options for sub-mental fat reduction are being FDA approved. Further randomized clinical trial studies need to be conducted to compare between all non-surgical procedures i.e. Kybella, ultherapy, and thermage and surgical treatments. To show if non-surgical options are superior and cost effective. However, blindness will not be possible as there are completely different procedures to compare between. Variables should be considered in this study (causes and risk factors of double chin, weight before, through and after treatment, long term effect treatment, objective scale to assess double chin, race, and family history of double chin).

Study & literature limitations:

- Epidemiology of Sub-mental fat, i.e. (prevalence, male to female ratio)
- Small proportion of male genders were included
- Most ethnicity were Caucasians
- One study, used subjective assessment of double chin, not a validated method
- Studies didn't mention the cause of double chin
- Studies didn't not asses pre and post-treatment weight
- In one study, follow-up was limited.
- Adverse events were not mentioned in exact number or percentage only shown in diagram, which maybe in accurate when calculated.

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