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Do submental deoxycholic acid injections reduce submental fat in adult patients enough to create a significant increase in patient satisfaction?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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Abstract

Objective: The objective of this selective EBM review is to determine whether or not “Submental deoxycholic acid injections reduce submental fat in adult patients enough to create a significant increase in patient satisfaction”

Study Design: Review of 3 double blind, randomized control trials that were selected based on their relevance to the clinical question.

Data Sources: All three peer-reviewed articles were found using PubMed and Cochrane Database. The keywords “ATX-101”, “submental fat”, and “deoxycholic acid” were used.

Outcomes Measured: Satisfaction with appearance in association with face and chin evaluated by a patient reported subject self-rating scale (PR-SSRS), a numeric scale with values from 0-6.

Results: All three trials recorded significant improvement in subject satisfaction compared to placebo with a p-value <0.001. The REFINE-1 study showed had an NNT value of 2 with 82.8% of the treatment group showing improvement compared to 31.0% of the placebo group. Ascher et al had an NNT of 3. 64.8% of the treatment group showed improvement with only 29.3% of the control group showing improvement. Finally, Rzany et al reported an NNT of 3. The treatment group had an improvement rate of 66.1% and the control group’s rate was only 28.7%.

Conclusion: Deoxycholic acid injections to the submental region resulted in a consistent improvement in patients’ satisfaction with the appearance of their submental region. The NNT values are low proving these injections to be effective in improving satisfaction.

Introduction

Submental fat is considered by many to be aesthetically unappealing and its' origin is multifactorial; stemming from obesity, genetics, and aging. The increasing fullness underneath the chin is almost always visible and can cause individuals significant social and psychological stress. The presence of submental fullness is associated with all races, genders, and has an increasing prevalence with age. Because of this trend, it is seen as a sign of aging and obesity. Blunting of the cervicomental angle produces a less pronounced jawline. These issues can cause a decrease in self-esteem.¹⁻³

Currently there are a few options to decrease the fat below the chin. Surgical interventions, such as platysmaplasty (neck lift) and liposuction procedures currently exist. In addition there are also injectable treatments that are also available, however, these are currently unregulated and can be unsafe.¹⁻³ In a 2015 survey by the American Society for Dermatologic Surgery 67% of the population reported to be extremely bothered by the excess fat under their chin/neck⁴. In 2015 the number of neck lifts performed in the United States was 32, 695 per the Interanational Society of Aesthetic Plastic Surgery. This does not include consultation visits and post-procedure visits . There were 119,470 procedures of non-surgical fat removal but this was not differentiated into body area. In addition, there were 1,805,895 injection procedures but again, this was not differentiated by injection site⁵.

The exact cost for money spent on reduction of submental fat is not statistically available, however, the American Society for Aesthetic Plastic Surgery reports that total expenditures for surgical chin augmentation in 2012 was \$26,623,143. This is not including the costs for

liposuction and other non-surgical injectables. Overall in 2012 Americans spent over \$10 billion for cosmetic procedures in 2012.⁶

Deoxycholic acid is a substance that causes adipocytes to lyse by disrupting their membrane. This method is seen to be much safer than surgical interventions that can lead to long recovery times and increased rate of infections. The surgical procedures can also leave an aesthetic deformity. The currently used injectables have no documented efficacy, so deoxycholic acid has been proposed as a safe, effective way to reduce submental fat^{1,2,3}.

Objective

The objective of this selective EBM review is to determine whether or not “submental deoxycholic acid injections reduce submental fat in adult patients enough to create a significant increase in patient satisfaction”

Methods

The population of patients used in the studies in this review was adults aged 18-65. All of the adults were dissatisfied with the appearance of their submental region (0-3 on the patient reported submental fat rating scale) and they all were rated moderate to severe submental fat (2-3 on the clinician reported submental fat rating scale). All of the studies tested the efficacy and the safety of deoxycholic acid injections into the submental region. Each individual injection was 0.2mL with a max dose of 10mL per patient per treatment. Some of the studies included two treatment groups, one with a concentration of 1.0mg/cm², and another with a concentration of 2.0mg/cm². A 1.0cm x 1.0cm grid was used to assure equal spacing of the injections. All trials compared the treatment group with a placebo injection group. The measured outcome that I have

reviewed from the trials is patient satisfaction of their submental appearance. All three articles were phase III, randomized, double-blind, placebo controlled clinical trials.

The key words used in searches were “ATX-101”, “Deoxycholic Acid”, and “Submental fat”. All articles were published in English and were found on PubMed and Cochrane databases. Inclusion criteria for my search were studies that were randomized, controlled, and double blind. Exclusion criteria included individuals younger than 18, individuals with minimal submental fat, and individuals who were already satisfied with their submental appearance. The statistics used in the trials included NNT, CER, EER, ABI, and RBI.

Outcomes Measured

The outcome that was measured in all the studies that I focused on was the subject self-satisfaction rating (SSRS). I chose this outcome because it directly relates to how the patient felt about the treatment making it a POEM. The SSRS is a numeric scale from 0-6. The value of 0 was used for extremely dissatisfied, 1 for dissatisfied, 2 for slightly dissatisfied, 3 for neither satisfied nor dissatisfied, 4 for slightly satisfied, 5 for satisfied, and 6 for extremely satisfied. In these trials a person had to rate themselves 0-3 to be included. After treatment a value of 4-6 was considered a success. The studies also followed adverse effects reported by the study participants. The three most commonly reported adverse effects were bruising, anesthesia, and pain. Patients reported when these effects were experienced after each treatment.

Results

The REFINE-1 study included 506 participants with 256 being randomized to the treatment group and the other 200 to placebo injection. All 506 participants were included in the

Table 1. Study Demographic

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W /D	Interventions
Ascher (2013) ⁶	Double Blind RCT	360	46±9.87	Men and non-pregnant, non-lactating women under medical birth control if of reproductive age were required to be 18-65 years of age. Patients with moderate to severe (2-3) submental fat according to the clinician-reported submental fat rating scale (CR-SMFRS) who were dissatisfied (0-3 on the subject self-rating scale) with their submental appearance were eligible.	Individuals with a BMI >30kg/m ² . Individuals with any significant abnormality in their clinical and laboratory evaluations. Patients with any of the following: previous submental fat treatments or recent aesthetic facial treatments; loose skin or previous trauma in the neck or chin area, prominent platysmal bands, any cause of enlargement in the submental area other than submental fat; patients currently on or considering starting a weight-reduction regimen, or sensitive to any components of the study.	26	A maximum of 10mL of deoxycholic acid injected with 0.2mL injections injected 1.0cm apart using a grid to provide even coverage.
Jones (2015) ⁴	Double Blind RCT	506	49.5±9.3	Men and women age of 18-65 years. Patients with moderate to severe (2-3) submental fat according to the clinician-reported submental fat rating scale (CR-SMFRS) who were dissatisfied (0-3 on the subject self-rating scale) with their submental appearance were eligible. Patients also need a BMI ≤40kg/m ² and had a stable body weight for ≥6 months	Subjects were excluded if they had excessive skin laxity or allergy/ hypersensitivity to the components of the study drug or topical/ local anesthetics; received treatment previously for submental fat or were treated in the neck/chin area with radiofrequency, lasers, chemical peels, or dermal fillers ≤12 months or botulinum toxin injections ≤ 6 months before randomization; or previously participated in ATX-101 trials	0	A maximum of 10mL of deoxycholic acid injected with 0.2mL injections injected 1.0cm apart using a grid to provide even coverage.
Rzany (2013) ⁵	Double blind RCT	363	46.4±10.29	Men and women age of 18-65 years. Patients with moderate to severe (2-3) submental fat according to the clinician-reported submental fat rating scale (CR-SMFRS) who were dissatisfied (0-3 on the subject self-rating scale) with their submental appearance were eligible. Patients also need a BMI ≤30 kg/m ² .	Previous intervention to treat submental fat, anatomical features or previous trauma; evidence of any cause of submental enlargement other than submental fat;. Patients with a history of sensitivity to any components of the study material or topical or local anesthetics were also excluded	34	A maximum of 10mL of deoxycholic acid injected with 0.2mL injections injected 1.0cm apart using a grid to provide even coverage.

final analysis. Using the SSRS as the measured variable, those in the treatment group had a success rate of 82.8% compared to the placebo success rate of 31.0% (p -value <0.001). The NNT for this trial was 3. This study used a maximum of 6 different treatments spaced out 28 ± 5 days. In the treatment group 164 individuals received all 6 treatments and 92 received less than six. The three biggest reasons that were given for withdrawal were insufficient submental fat (33), adverse effects (19), and withdrawal of consent due to subject convenience (14). In the control group 213 received all 6 treatments and 37 received less than 6.¹

Ascher et al had 360 patients in the study. 117 patients were randomized to the placebo injection group. 122 were put into the treatment group with the concentration of $2.0\text{mg}/\text{cm}^2$. This is the concentration that was consistent throughout all of the trials; therefore it was used for the purposes of this study. The treatment group had success on the SSRS with a rate of 64.8% compared to a placebo success rate of 29.3% (p -value <0.001). The NNT in this study was 3. This study looked at four treatment sessions spaced 28 ± 5 days. In the injection group 32 of the 122 withdrew from the study early. The most common reasons were adverse effects (14), consent withdrawn (10), and early success (6). 16 of the 117 in the placebo group withdrew from the study early.²

The Rzany et al. study included 363 participants. There were 122 randomized to the placebo group. Another 121 were placed in the treatment group that received the $2.0\text{mg}/\text{cm}^2$ concentration. 66.1% of the individuals in the treatment group were a success on the SSRS compared to 28.7% in the placebo group (p -value <0.001). This study also had a maximum of 4 treatments spaced out 28 ± 5 days. 34 of the 121 discontinued the treatment before receiving all four treatments. The most common reason was early therapeutic success (13), followed by

adverse effects (10), and withdrawal (7). 14 of the 122 participants in the placebo group discontinued prematurely.³

Table 2. SSRS Results

Study	Control Event Rate (CER)	Experimental Event Rate (EER)	Absolute Benefit increase (ABI)	Relative Benefit Increase (RBI)	Numbers Needed to Treat (NNT)
REFINE-1 ¹	31.0%	82.8%	167.1%	51.8%	2
Ascher et al ²	29.3%	64.8%	121.1%	35.5%	3
Rzany et al ³	28.7%	66.1%	130.3%	37.4%	3

Safety outcomes were recorded in each trial as adverse effects. The REFINE-1 study used clinician visual and tactile assessments of the submental region, as well as reports of adverse effects, laboratory tests (U/A, Chemistry, Hematology, and thyroid function, and vital signs. The studies by Ascher et al and Rzany et al used clinical evaluations and patient reports of adverse effects before and after each treatment to record safety outcomes. They also used unspecified clinical laboratory parameters. The NNH for the most common adverse effects of pain, bruising, and anesthesia are displayed in table 3.

Table 3. Adverse Effects

Study	Bruising NNH	Anesthesia NNH	Pain NNH
REFINE-1 ¹	37	2	2
Ascher ²	10	2	2
Rzany ³	7	2	2

Discussion

The SSRS was chosen for this review because of its universal application in the studies and because it answers a simple question “did you go from unsatisfied to satisfied with the appearance of your submental region?” Using the SSRS all of the trials showed a statistically significant increase in the treatment groups compared to placebo. For the purposes of this review this variable was selected from all of the studies because it is patient oriented evidence that provides insight into exactly how the patients felt about the treatment. However, all of the studies had other outcomes that they measured. The other outcomes included a clinician evaluated submental fat convexity and patient evaluated submental fat rating. They also followed the psychological impact of submental fat appearance on feelings and perceived visual self-image using a standardized reporting scale.

Deoxycholic acid is currently being used under the brand name Kybella distributed by Kythera Biopharmaceuticals. This treatment is purely cosmetic and is an elective treatment; therefore virtually no insurance covers the cost. The actual out of pocket cost for patients varies due to the individualized nature of the treatment. Patients with more submental fat could require more injections per treatment and more treatments overall which could inflate costs. The cost of treatment varies between providers and also between geographic regions. It’s not unreasonable to expect to spend several thousand dollars for all of the required treatments.

These trials all compared the deoxycholic acid injections to a placebo injection. A more potent comparison could be made by comparing different forms of treatment such as liposuction; however, this would have to be a comparison between two different subjects as one person would not be eligible for both treatments.

The adverse effects were also reported significantly more in the treatment group compared to the control. All three trials however, reported that many of these effects were experienced during their first treatment and faded quickly. There were instances of dysphagia and facial paralysis reported by the trials, but they did not have a high enough incidence to be reported in the results (needed incidence $\geq 5\%$). The authors also reported that these effects were transient.

CONCLUSION

The trials all had a significant increase in SSRS in the treatment groups compared to placebo. Therefore deoxycholic acid injections did decrease submental fat in a way to improve satisfaction with the submental region. The comparison between these injections and other modalities of reducing submental fullness has not been fully explored. Further research could be conducted to show a superior treatment, if one exists. Currently there are studies that are being done to evaluate the long term effectiveness of deoxycholic acid injections. Currently, however, these injections seem to be an effective and relatively safe method of reducing submental fat in individuals who wish to do so.

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