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Is Juvederm Ultra Plus Effective For Treatment of Nasolabial Fold Wrinkles Over A One Year Period?

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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
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ABSTRACT

Objective: The objective of this evidence based medicine review is to determine whether or not Juvederm Ultra Plus is effective in treating nasolabial fold wrinkles over a one year period.

Study Design: Three blinded, randomized controlled trials were reviewed and selected based on their relevance to the clinical question and their inclusion of patient oriented outcomes (POEMS).

Data sources: Each study was obtained by searching Cochrane, PubMed databases, and product package insert.

Outcome measured: The outcomes measured were improvement in NLF wrinkle on a five point Wrinkle Assessment Scale compared to baseline.

Results: The studies by Lupo et al, Goodman et al, and Allergan found a statistically significant reduction in nasolabial fold wrinkles compared to baseline over a one year period after injection with Juvederm Ultra Plus.

Conclusions: The results showed Juvederm Ultra Plus is an effective treatment for nasolabial folds over a one year period, as evidenced by at least a one point reduction in severity of nasolabial fold wrinkles as well as low numbers needed to treat (NNT) for all three studies.

Keywords: “juvederm ultra plus” “nasolabial fold”

Introduction

Youthfulness is in large part what defines beauty. A key component in a youthful look, is the absence of wrinkles and folds.¹ It has been found that wrinkles and folds can lead to the perception of looking older than your age, less attractive, and as if you are tired.² Repeated sun damage, muscle use, gravity, loss of skin tone, and migration and loss of fat create and exaggerate the nasolabial fold wrinkle.³ The central location of this wrinkle, makes it quite obvious which can outwardly project an aged appearance as well as cultivate negative self-esteem.³

Collagen and elastin are main components in maintaining the structure of the dermis.⁴ Due to the aging process, collagen breaks down and is no longer able to provide support to the skin creating a wrinkle.⁴ With the advent of fillers and cosmetic surgeries, wrinkles and folds can be reduced and diminished, restoring the youthful look. Nonsurgical options include injections of autologous fat, bovine collagen, synthetic collagen, and hyaluronic acid based fillers.⁵ Juvederm Ultra Plus (JUP), a 2006 FDA approved cross-linked hyaluronic acid filler, is one of the top alternatives to the surgical alternative of a facelift.⁶ Hyaluronic acid (HA) is produced by *Streptococcus equi* bacteria and is naturally occurring in the extracellular matrix of all adult animal tissue, with half of it located in the dermis.⁷ HA is crucial in maintaining tissue strength and regulation of tissue moisture.⁷ Allergan, the producers of JUP, have formulated JUP as a 24 mg/ml HA that resists degradation, is safe and cost effective for correcting moderate and severe facial folds, such as the nasolabial fold.⁶

Along with an aging population and increased life expectancy, the desire for a youthful appearance is apparent by the increase in rejuvenating surgeries and cosmetic procedures.¹ In 2014 in the US alone, almost 8.9 million nonsurgical cosmetic procedures were performed with

almost 1.7 million being hyaluronic acid procedures.⁸ HA procedures ranked #2 in the top five nonsurgical procedures only behind Botox injections.⁸

It is also apparent from the data that the population prefers to spend less money on noninvasive procedures to see a faster correction of their wrinkles and folds.⁹ A study in 2015 showed 1.7 million HA injections were performed compared to 126, 713 facelifts, the surgical alternative to correcting nasolabial folds and wrinkles.⁸ Allergan reports, “The typical volume of JUP to achieve optimal correction is 1.6 mL per treatment site”, and injected by trained healthcare providers costs around \$1,300/1.6 mL.⁶ The average cost of a facelift in 2014 not including anesthesia, operating room costs, or other related expenses was \$6,550.⁸

One thing patients consider when deciding to undergo a filler treatment is the efficacy of the product over time. Synthetic, collagen and hyaluornic acid based fillers have been proven to last up to 6 months for the majority of patients.¹⁰ Juvederm Ultra Plus is the first engineered macromolecule filler that may last up to one year.⁶ Allergan advises “touch-up” treatments of JUP may be needed to maintain optimal correction, and found 0.7 mL to be effective at each treatment site.⁶

Objective

The objective of this selective EBM review is to determine whether or not “Juvederm Ultra Plus is effective in treating nasolabial fold wrinkles over a one year period.”

Methods

The studies used in this systematic review include three blinded, randomized controlled trials, which were selected based on specific criteria. The population studied includes both males and females, any race, any Fitzpatrick skin phototype, 26-74 years old, who had severe, symmetric nasolabial folds (NLF). The intervention in all three studies was Juvederm Ultra Plus

(JUP) 24 mg/mL. The Goodman et al study was a split face study comparing the intervention to Perlane, a hyaluronic acid filler.⁷ The Lupo et al and Allergan studies conducted a split face study comparing the intervention side to Zyplast, a bovine collagen filler.^{10,6}

In all three studies, Goodman et al, Lupo et al, and Allergan, the outcome measured was the NLF severity at 48 wks using a validated, static, five-point Wrinkle Assessment Scale with a photographic guide to score the folds as 0 (no wrinkle), 1 (mild, shallow, just perceptible wrinkle), 2 (moderately deep wrinkle), 3 (severe, deep wrinkle, well-defined edges but not overlapping), 4 (extreme, very deep wrinkle, redundant fold, overlapping skin).^{6,10,7} In the Lupo et al study, the evaluating investigator as well as the subject were blinded and rated their NLF, while only the investigator had a photonumeric scale.¹⁰ In the Goodman et al study, only the subject was blinded.⁷ The Goodman et al study had the subject and the physician rate the NLF, while only the physician had a photonumeric scale.⁷ In the Allergan study, both the independent expert reviewer and subject were blinded and rated their NLF, while only the independent expert reviewer had a photonumeric scale.⁶

The Lupo et al and Goodman et al studies were published in English in peer reviewed journals and found by searching Pubmed with keywords “Juvederm Ultra Plus” and “Nasolabial fold”. The Allergan study was found on the Allergan website, published in English, without published data. Studies were chosen based on relevance to the question, the inclusion of patient orientated outcomes, and publication dates after 2005. Exclusion criteria included studies that allowed more than the initial two repeat treatments before scoring the NLF at one year. Investigators at multiple different research centers conducted the research collected by all three studies. Statistical analysis for this review include p-values, numbers needed to treat (NNT), relative risk reduction (RRR), and absolute risk reduction (ARR), and number needed to harm

(NNH) which were calculated by the author using dichotomous data found in each study. The demographics and characteristics of the three studies can be found in Table 1.

Table 1: Demographics of included studies

Study	Type	# pts	Age (yrs)	Inclusion criteria	Exclusion criteria	W/D	Interventions
Lupo et al ¹⁰ (2008)	RCT, double blind, within subject	16	26-74	-Severe NLF (Wrinkle Assessment Scale grade 3) -Fully visible b/l NLF that were severe at the deepest part and were symmetrical and of equal severity of each facial side.	-Hypersensitivity to bovine collagen or hyaluoronic acid -History of atopy, anaphylaxis, multiple severe allergies, or allergy to meat or lidocaine -Current immune therapy or history of autoimmune disease -Tendency for hypertrophic scarring -Use of PO retinoids or, in the NLF -Use of OTC or rx anti-wrinkle txs, microdermabrasion, or chemical peels in the 4wks before randomization -Any cosmetic procedure or tissue augmentation at the NLF in the 6 mo before study entry	71	JUP 24 mg/mL in one NLF with up to 2 touch-up treatments, two weeks apart
Goodman et al ⁷ (2011)	RCT, single-blind, within subject	77	33-69	-Fully visible and symmetrical NLFs of a severe presentation, defined as a score of 3 on a five-point validated Physician's Wrinkle Assessment/ NLF Photonumeric Rating Scale	-Pre-existing condition that might affect efficacy and/or evaluation of response, including visible scars, active inflammation, infection, cancerous or precancerous lesions, and prior surgical cosmetic procedures in the trtmt area -History of dermal filler or fat injections within 9 mo of randomization -Botox treatment or mesotherapy within 6 mo of randomization -History of permanent or semipermanent facial implants in the lower 2/3 of the face. -History of HA hypersensitivity, CT dz, bleeding d/o, concomitant anticoagulant or antiplatelet therapy -Use of ASA during the week preceding the study treatment -During the study use of antiwrinkle therapies in the area of the NLF or around the mouth were not permitted, with the exception of topical skincare products. -Females needed a (-) urine pregnancy test and to use contraception during the study	3	Up to two syringes of JUP in one NLF. No touch ups.
Allergan ⁶ (2014)	RCT, double-blind, within subject	23	26-74	N/A	N/A	123	JUP injections with up to 2 touch-up treatments, 2 wks apart, until

							the level of correction was achieved
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Outcome Measured

The outcome measured in all three studies was improvement in nasolabial fold wrinkle since baseline. All three studies considered a one-point or more improvement in score (reduction in wrinkle) on the five-point Wrinkle Assessment Scale to be significant.^{6,7,10} This scale used by investigators in all three studies had a photonumeric guide.^{6,7,10} The Goodman et al study reported both investigator’s and subject’s scores at 12 months. The subjects used the same five-point Wrinkle Assessment Scale without a photonumeric guide.⁷ The Allergan study did not have one year as a specific scoring date, but rather reported scores from at least one year or more since treatment date.

Results

All three studies were randomized controlled trials looking at the effectiveness of Juvederm Ultra Plus (JUP) in nasolabial folds (NLF) over a one year period. All studies provided dichotomous data that could be used for calculation of RRR, ARR, and NNT at 6 months after treatment. The study by Goodman et al provided data to make these calculations at 12 months as well. The studies by Lupo et al and Allergan report p-values and mean change from baseline at 12 months. The study by Lupo et al reports that because the NLF severity at 12 months was statistically similar to the data collected at 6 months that the data from 6 months is representative of 12 month results.

In the Lupo et al study, 87 adult subjects were given a baseline NLF score then injected with as much JUP to correct the wrinkle on one side of the face, and injected with bovine collagen to the other side, by a blinded investigator.¹⁰ Up to two touch-up treatments within two

weeks of initial treatment were allowed for optimal correction.¹⁰ For the purpose of this review, only the NLF injected with JUP will be analyzed. 82% of the subjects were lost to follow up and did not complete the 12 month study.¹⁰ 16 subjects had their NLF wrinkles scored at 12 months.¹⁰ Statistical data was calculated on the intent-to-treat population.¹⁰ The study found that at 12 months 81% of the subjects had a statistically significant ($p < 0.05$) improvement in NLF score, reported as a one point or more reduction in score (improvement in wrinkle) (Table 2).¹⁰ It was found that the mean improvement in NLF score at 12 months was 1.3 points.¹⁰ Lupo et al reports that subjects also scored their NLF on a five-point Wrinkle Assessment scale without a photonumeric guide and that the results were similar to those of the investigator.¹⁰ The data at 6 months after treatment demonstrated a relative risk reduction (RRR) of 1.34% and an absolute risk reduction (ARR) of 0.55 %. The number needed to treat (NTT) is 2, meaning that 2 patients needed to be treated with JUP in order for one more patient to have a one point or more improvement in NLF score than those injected with bovine collagen at 6 months after treatment (Table 2).

In the study by Goodman et al, 80 subjects were enrolled in the study and were given a baseline NLF score on the 5-point Wrinkle Assessment Score and photonumeric guide by an unblinded physician.⁷ Subjects also rated their NLF on the NLF severity scale without a photonumeric guide.⁷ The subjects were then randomly injected into either the right NLF or left NLF with JUP, and the opposite side was injected with Perlane.⁷ Enough product to achieve optimal correction, up to two syringes, was used and no touch-up treatments were permitted.⁷ 96% of subjects completed the study, two were lost to follow-up and one was lost to unrelated depression.⁷ Physicians and subjects scored their NLF at 12 months.⁷ For the purpose of this review, scores of NLF injected with Perlane were excluded. The physicians found that 70% of

the subjects had at least a one point improvement ($p < 0.002$) in NLF score at 12 months and 62.5% patients thought they had a one point or more improvement ($p < 0.01$) in NLF score (Table 2).⁷ The data at 12 months after treatment with JUP demonstrated a relative risk reduction (RRR) of 55% and an absolute risk reduction (ARR) of 25%. The number needed to treat (NTT) was 4, meaning that 4 patients needed to be treated with JUP in order for one more patient to have a one point or more improvement in NLF score than those injected with Perlane at 12 months after treatment (Table 2).

In the Allergan study, 146 patients were enrolled and were randomly assigned a side of the face for JUP to be injected in the NLF and Zyplast was injected into the other side.⁶ For the purpose of this review, the NLF injected with Zyplast will not be included in analysis. A blinded reviewer scored baseline NLF severity and severity at 12 months using a photonumeric 5-point NLF severity score.⁶ 84% of the patients were lost due to follow-up.⁶ The average baseline NLF severity was 2.6, and the average NLF severity score at ≥ 12 months was 1.6 ($p < 0.0001$).⁶ The mean improvement in NLF score at 12 months was 1.1 points.⁶ Data was not presented on the NLF injected with Zyplast at 12 months, so the calculation for NNT was done on data collected at 6 months. The data demonstrated at 6 months after treatment, a relative risk reduction (RRR) of 125% and an absolute risk reduction (ARR) of 50% (Table 2). The numbers needed to treat for this study was 2 meaning that 2 patients needed to be treated with JUP in order for one more patient to have a one point or more improvement in NLF score than those injected with Zyplast at 6 months after treatment (Table 2).

Table 2. Percent of subjects who saw at least a one point improvement in NLF score at the designated time, scored by the investigator, and NNT.

Study	Other filler event rate	JUP event rate	P-value	(RRR)*	(ARR)*	(NNT)*
Lupo et al (2008) at 6 mo	41%	96%	N/A	134%	55%	2
Lupo et al (2008) at 12 mo	N/A	81%	<0.05	-	-	-
Goodman et al (2001) at 6 mo	65%	90%	<0.0001	38%	25%	4
Goodman et al (2001) at 12 mo	45%	70%**	<0.002	55%	25%	4
Allergan (2014) at 6 mo	40%	90%	<0.0001	125%	50%	2
Allergan (2014) at 12 mo	N/A	78%	<.0001	-	-	-

* Relative risk reduction, Absolute risk reduction, Numbers needed to treat

** 62.5% of blinded patients recorded a one point or more improvement in NLF score (p <0.01).

The Lupo et al study reported minor adverse events to the injections of JUP and Zyplast limited to injection site reactions such as erythema, induration, pain, edema, nodule, bruising, pruritus, and discoloration, that lasted no longer than 7 days.¹⁰ The Goodman et al study reported both JUP and Perlane were well tolerated and adverse events were related to the same injection site reactions as the Lupo et al study.⁷ Bruising after the Perlane injection into the NLF resulted in bruising for seven days for 11.3% of the subjects, and 28.8% of the subjects injected with JUP (Table 3).⁷ The numbers needed to harm for this study is 6, meaning that for every 6 patients that are treated with JUP, one more patient would experience the adverse effect than if they were injected with Perlane (Table 3). The Allergan study reported the same adverse events limited to injection site reactions, for both JUP and Zyplast.⁶ 20% of subjects injected with Zyplast and 22% of subjects injected with JUP reported bruising for seven days after injection (Table 3).⁶ The numbers needed to harm for this study is 50, meaning that for every 50 patients that are

treated with JUP, one more patient would experience the adverse effect than if they were injected with Zyplast (Table 3).

Table 3. Percent of subjects with bruising at injection site at day 7 and NNH.

Study	Other filler event rate	JUP event rate	Numbers needed to harm (NNH)
Lupo et al (2008)	N/a	N/a	N/a
Goodman et al (2011)	11.3%	28.8%	6
Allergan (2014)	20%	22%	50

Discussion

The randomized controlled trials in this review examine Juvederm Ultra Plus (JUP) as an effective way to reduce the nasolabial fold (NLF) wrinkle over one year. All three studies, Lupo et al, Goodman et al, and Allergan showed with statistical significance ($p < 0.05$) that JUP is an effective treatment for NLF at one year. The subjects in the Lupo et al study and Goodman et al study started with a NLF of severity 3 (severe, deep wrinkle, well-defined edges but not overlapping) and 81% and 70% respectively saw at least a one point improvement in NLF score.^{10,7} At the end of the study patients either had a NLF of severity 2, a moderately deep wrinkle, or a score of 1 is a mild, shallow, just perceptible wrinkle.^{10,7} The subjects in the Allergan study started with an average NLF score of 2.6 and 78% of subjects saw at least a one point improvement.⁶

There are several limitations to this review. Lupo et al reports that they collected patient self-ratings of NLF, but did not record the data in their articles. It would be relevant and helpful to patients if they knew what subjects thought of the improvement in their NLF wrinkles.

The Goodman et al study was sponsored by Allergan Australia and was a single-blind study. Because the injector who was scoring NLF wrinkles at baseline and 12 months, was not blinded there is question of validity. The Goodman et al and Lupo et al study were funded by

Allergan, leading to questions in validity. Allergan did not reference the studies whose data is on their package insert, so the actual studies could not be found. This challenges the validity of the study and makes it unclear if there is overlap with the Lupo et al study.

The sample size was also a limitation in this review. Data from a total of 116 patients from the three studies was collected and analyzed. To increase the validity of the study, there should be a larger sample size. Lupo et al suggests that the data collected from NLF severity at 6 months was statistically significant to the data collected at 12 months and suggested the effectiveness at 6 mo can be extended to the overall population at 12 months.¹⁰ To validate this suggestion, the data from 12 months should have been included.

Another limitation on the study is the amount of JUP used in the NLF. The amount used was not consistent across studies and not clearly stated in all three studies. It is unclear whether JUP is a dose dependent treatment, where treating the area with more product will make the product last longer. Treatment of NLF wrinkles is an elective cosmetic procedure; therefore insurances will not cover the cost of JUP or cosmetic face-lifts. Prospective patients need to consider the amount of product they will be buying in order to achieve the effectiveness of JUP at one year.

A limitation the author experienced when searching for the studies, was there were not many articles published on JUP that looked at effectiveness over a year without repeat treatment at 6 months. Additionally, the full study printed on the Allergan package insert could not be found.

Hyaluronic acid fillers, such as Juvederm Ultra Plus, have become 13x more popular than facelifts as a treatment for facial folds and wrinkles.⁸ At nearly 1/12 the cost of a facelift, a patient can buy one 0.8mL syringe of JUP.⁸ JUP is a noninvasive, quick, cost effective treatment

for the midface nasolabial folds. The physical and chemical properties of the filler affect the ease of injection, degree of tissue filling, longevity, and adverse effects.⁵ JUP was engineered as a larger cross-linked molecule containing 24mg/mL of hyaluronic acid which allows it bind more water molecules contributing to its ability to be a robust filler and last longer.⁷ The cross-linked HA is also found to strengthen the extracellular matrix responsible for the production and functioning of collagen and elastin.⁴ Collagen, bovine and 20 mg/mL hyaluronic acid based fillers have not been proven to last beyond 6 months.¹⁰

The physiochemical properties of Juvederm Ultra Plus have no effect on the safety of the product.⁶ All the studies, found JUP to be well tolerated and adverse effects were limited to injection site reactions.^{6,7,10} Patients reported erythema, edema, bruising, pain, induration, pruritus, and discoloration at the site of injection.^{6,7,10} JUP is contraindicated in patients with severe allergies associated with anaphylaxis or allergies associated with gram-positive bacterial proteins.⁶ The use of JUP during pregnancy, breastfeeding, or patients under 18 years of age has not been studied.⁶

Conclusions

The three randomized controlled trials studied in this review provide statistically significant evidence that Juvederm Ultra Plus is an effective treatment for correction of nasolabial folds over a one year period. These results suggest that JUP is a safe and effective nonpermanent alternative to a facelift for patients wanting a more youthful appearance. Further studies should include larger sample sizes, no repeat treatments at 6 months, subject nasolabial fold assessments, and funding from sources other than Allergan. Future research studies should look at injections of JUP in mild NLF wrinkles for prevention of moderate to severe NLF wrinkles.

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