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Is topical eflornithine an effective adjunctive therapy in reducing unwanted facial hair in women diagnosed with hirsutism?

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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 topical eflornithine is an effective adjunctive therapy in reducing unwanted facial hair in women diagnosed with hirsutism.

STUDY DESIGN: Systematic review of three randomized controlled trials (RCTs) from peer reviewed journals, published in 2006, 2007 and 2016.

DATA SOURCES: The studies analyze the effectiveness of eflornithine in women with hirsutism and were found using PubMed, Embase and Medline.

OUTCOMES MEASURED: Reduction of unwanted facial hair was measured through hair counts done at 0, 1, 3 and 6 months, Physician Global Assessment which considered hair length, density and darkening of skin, and Patient Self-Assessment.

RESULTS: Two of the randomized control trials suggested that the addition of topical eflornithine was statistically significant in the reduction of unwanted facial hair in women with hirsutism. The other study suggested that while eflornithine may initially be beneficial in the reduction of unwanted facial hair, it's utility decreases after 6 months.

CONCLUSIONS: On the basis of hair counts, Physician Global Assessments, and Patient Self-Assessment, it can be concluded that topical eflornithine is an effective adjunctive therapy in reducing unwanted facial hair in women diagnosed with hirsutism for at least the first 6 months.

KEY WORDS: topical eflornithine, hirsutism

INTRODUCTION

As humans, we are covered from head to toe with hair follicles that can stimulate the growth of three different types of hair: lanugo, vellus or terminal. Lanugo is the thin, soft unpigmented hair that covers newborns and disappears within the first few months.¹ Vellus is also soft and unpigmented hair, but it is a little thicker, generally 0.03 mm in diameter.¹ Terminal hairs are longer, coarse pigmented hairs that are at least 0.06 mm in diameter.¹ Hirsutism is defined as excessive terminal hair growth in women, typically in the androgen-dependent areas of the body such as the upper lip, chin, chest and abdomen. It is important that we distinguish hirsutism from hypertrichosis, which is characterized as generalized or localized vellus hair growth in a nonsexual distribution that is independent of androgens.²

Hirsutism is said to affect anywhere from 7-25% of women in the U.S.^{2,3} and is associated with a decreased quality of life and lower self-esteem.³ Every year, women in the U.S. spend billions of dollars on hair removal, which makes finding an exact number specific to hirsute women difficult, however, it has been estimated to be over \$600 million annually.² The most common cause of hirsutism is polycystic ovarian syndrome (PCOS) which affects roughly 5 million women of child bearing age.⁴ It is difficult to pinpoint exactly how many healthcare visits are made each year due to hirsutism. We know that between 2003-2008, there were 207,662 PCOS-related visits⁴ and up to 75% of women with PCOS have some degree of hirsutism, so we can estimate that up to 155,747 of those visits involved discussions about excessive hair growth.

Different cultures have different opinions about the appropriate amount of body hair, which again, makes calculating statistics difficult. While we know, hirsutism is associated with certain disorders such as PCOS, adrenal hyperplasia, thyroid dysfunction etc., it is difficult to

detect how many women are living with hirsutism by “our standards” because their cultural standards may say their hair distribution is normal. A proper work up of suspected hirsutism should include a history and physical, hormone profile, metabolic profile, ovulatory function tests and ultrasound evaluation.³ The gold standard for evaluation would be the modified Ferriman-Gallway score (mFG). The mFG score is calculated during physical examination of 11 body areas: upper lip, chin, chest, upper and lower back, upper and lower abdomen, arm, forearm, thigh, and lower leg.³ Each area is given a score 1 - 4 based on the amount of visible terminal hair; 11-15 is considered mild, 16-25 is moderate, and above 25 is severe. It is crucial to continue the extensive evaluation even after noting an androgen excess, because androgen excess does not correlate well with the actual severity.

Eflornithine hydrochloride, brand name Vaniqa, is an antiprotozoal most commonly used as a topical but can also be administered intravenously, brand name Priotto.⁵ The topical works by inhibiting ornithine decarboxylase (ODC)⁵, the enzyme that inhibits cell division and synthetic functions, and can thereby affect the rate of hair growth. It has been proposed that the combination of eflornithine with laser treatment is a safe and effective way to further reduce the growth and appearance of unwanted facial hair, thereby improving overall quality of life. This paper evaluates three blind, randomized controlled trials (RCTs) comparing the efficacy of topical eflornithine as an add on therapy for the reduction of unwanted facial hair.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not topical eflornithine is an effective adjunctive therapy in reducing unwanted facial hair in women diagnosed with hirsutism.

METHODS

The studies selected for this systematic review included a randomized split-face single blinded controlled trial⁶ and two randomized double-blinded controlled trials^{7,8}. They were selected based on their population, intervention, and comparison. The population for this review includes women over the age of 18 years who have hirsutism. The intervention is topical eflornithine used in conjunction with laser hair therapy. All the women were treated with some form of laser therapy, applied eflornithine cream to one half of their face and either a placebo vehicle cream or nothing to the other half of their face. Right to left comparisons were then made by the participants themselves in addition to the physicians leading the study. Before and after hair counts were also used to aid in the comparison process.

All three of the articles included were published in peer reviewed journals and found using the following databases: PubMed, Embase and Medline. The articles were chosen using the keywords “hirsutism” and “eflornithine” then selected based on their relevance to each other, the clinical question and the presence of patient oriented evidence that matters (POEMs). Articles were excluded if they were published greater than ten years ago, included pregnant or lactating women or were not blinded controlled trials. Additional inclusion and exclusion criteria for each individual article can be found in Table 1, as well as their specific demographics. Each article was published in the English language. Significance of the results was determined through evaluation of the calculated p-value, relative benefit increase (RBI), absolute benefit increase (ABI) and number needed to treat (NNT). Safety of the medication was also monitored.

Table 1 – Demographics and characteristics of included studies

Study	Type	# of Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Vissing ⁶ (2016)	Single blinded RCT	18	26-46	>18 years, moderate to severe facial hirsutism	Pregnant, lactating, immunosuppressant medication, unable to follow protocol	4	Topical eflornithine initiated 2 days after IPL (laser)-treatment Applied BID x 6 months
Hamzavi ⁷ (2007)	Double blind RCT	31	22-65	>18 years, carried out upper lip hair removal of any kind at least twice a week, predominantly dark facial hair, willing to discontinue all hair removal modalities for 2 weeks before study	Presence of tattoos over or near the upper lip, photosensitivity, severe acne vulgaris, pregnancy, lactating, immunosuppression	2	Apply thin layer of eflornithine to one half of upper lip and placebo cream to other half of lip BID in addition to 6 laser treatments of the entire lip at 4 week intervals
Smith ⁸ (2006)	Double blind RCT	54	26-80	Fitzpatrick skin types I-IV, bilaterally symmetric facial hirsutism of the lip and chin, predominantly brown/black terminal hairs, hair density of 5 hairs/cm ²	Pregnant, lactating, recent use of laser photoepilation or electrolysis, systemic medications that affect hair growth	10	Apply topical eflornithine on one side of face and vehicle on the contralateral side for 34 weeks and receive laser therapy to both sides at weeks 2 and 10

OUTCOMES MEASURED

The outcome measured in all three studies was the effectiveness of topical eflornithine in reducing the amount of unwanted facial hair. This was measured via hair counts at 0, 1, 3 and 6 months, Physician Global Assessment and Patient Self-Assessment. Photographs would be taken and digitized to a 1324 x 1024 pixel image⁷ and all visible hairs would be manually counted, right and left sides separately. The physician global assessment was a 0 – 3 grade scale that considered changes in hair length, hair density and darkening of the skin (see Table 2).

Table – 2 Physician Global Assessment of facial hair response.^{7,8}

Grade 0	No improvement / worse – no decrease or increased visibility of terminal hair and darkening of skin due to terminal hair is worse or not improved
Grade 1	Improved – clinically apparent decrease in visibility of terminal hair and noticeable lightening of facial skin due to terminal hair
Grade 2	Marked improvement – considerable decrease in visibility of terminal hair and minimal darkening of facial skin due to terminal hair
Grade 3	Clear / almost clear – no or nearly no visible terminal hair or darkening of facial skin due to terminal hair

RESULTS

In the study conducted by Vissing et al., 32 women were assessed for eligibility, 22 were deemed eligible and 18 completed the 6 month protocol. Of the 22 that were eligible and included in the trial, one withdrew, one was lost to follow up and two were excluded due to deviation from the treatment protocol. A sample size of 18 was determined to detect a minimal 20% difference in hair counts. Each participant received 5-6 rounds of photoepilation with laser and intense pulsed light (IPL) treatments of their face and neck prior to the study. Two days after the final IPL-treatment was considered baseline and this is when the topical eflornithine was initiated. A nurse did the first application and then instructed each woman to apply a thin layer over half of their face, either right or left, twice daily, at least 8 hours apart, for 6 months.

Assessments were made at baseline, 1, 3, and 6 months and included hair counts, patient satisfaction scores (0-10) and patient evaluated efficacy (0-3). Evaluators were blind to which side of the face was being treated, patients however were not blinded to treatment.

Based on hair counts, topical eflornithine reduced hair regrowth by 14% after 1 month ($P = 0.007$), 9% after 3 months ($P = 0.107$) and 17% after 6 months ($P = 0.048$) with a 95% confidence interval (CI).⁶ RBI was calculated to be 0%, ABI was calculated to be 72% and NNT was 2. This suggests that for every two hirsute women treated with topical eflornithine for six months, one more will have a statistically significant reduction in hair regrowth. Patients' satisfaction was consistently recorded at a moderate level at every visit, with a median of 5/10 at months 1 and 3 and 6/10 at month 6.⁶ Patient evaluated efficacy of eflornithine improved with treatment. At every assessment, there was always more patients favoring eflornithine treatment than no treatment. After 1 month, only three patients saw a significant difference in hair counts compared to six patients after six months.⁶ This study reported topical eflornithine to have a 17% additive effect on hair reduction compared to no additional treatment.⁶ Vissing et al. also mentions that it is important to note that half of the participants experienced greater than a 17% effect. In the end 72% of participants (13/18) did take benefit from the topical eflornithine treatment.

In the study conducted by Hamzavi et al., 33 females enrolled but only 31 participated in the 26 week study. One withdrew after experiencing hyperpigmentation after the second treatment and one was lost to follow up. Patients were scheduled to undergo six treatments with a long pulsed alexandrite laser at four week intervals while simultaneously using two different topical creams twice daily for two weeks after their final laser treatment. The creams were in color coded tubes, one contained the topical eflornithine, while the other was a simple vehicle

placebo cream. This allowed both the patients and the investigators to be blinded throughout the study. It is important to note that hand washing was mandatory after each application to prevent the risk of cross contamination. Assessments were conducted at baseline, at four week intervals in conjunction with the laser treatments and two weeks after the final treatment and involved hair counts, patient self-assessments and investigator global assessments.

It should be noted that of 31 women who participated in the study, only 19 underwent all six laser treatments.⁷ Five patients did not require the final treatment because hair regrowth was not apparent and the other seven missed one of their scheduled appointments along the way. Hair counts always favored the eflornithine treated side and were statistically significant throughout the study with a maximum difference of 17% seen after the second treatment ($p < .0001$, 95% CI).⁷ The assessment made two weeks after the final treatment showed hair counts on the eflornithine treated side were 7.9% lower than the placebo side ($p < .01$, 95% CI). At the conclusion of the study 41.9% (13/31) of participants thought the eflornithine cream provided better hair reduction while the remaining 58.1% (18/31) of participants thought there was no overall difference ($p = 0.029$).⁷ Investigators gave a hair removal grade 3 (see Table 2) to 93.5% (29/31) of participants on the eflornithine treated side compared to 67.9% (21/31) of participants on the vehicle cream side ($p = 0.021$).⁷ The following values were calculated using the investigator global assessment data: RBI of 38%, ABI of 25.6% and NNT of 4 (see Table 3). This suggests that for every four hirsute women treated with topical eflornithine in conjunction with their laser therapy, one will see a statistically significant reduction in hair regrowth.

In the study conducted by Smith et al., 2 campuses were used, 64 women were enrolled and 54 completed the 34-week trial. Two women voluntarily withdrew, four were lost to follow up and four violated protocol. Participants were given topical eflornithine and a vehicle cream

and were instructed to apply each cream to a specific side of their face twice daily for 34 weeks. Assessments were made at weeks 2, 6, 10, 16, 22, 28 and 34 using a physician global assessment (see Table 2) of changes from baseline, physician comparison of right to left and a subject self-assessment comparing right to left. The upper lip area and chin were evaluated separately. After evaluations were made at weeks 2 and 10, each patient underwent a laser therapy treatment.

Using the physician global assessment, a statistically significant treatment benefit can be seen at week 6 ($p = 0.007$), week 10 ($p < 0.001$), week 16 ($p = 0.015$) and week 22 ($p < 0.001$) for the upper lip and at week 6 ($p = 0.024$), week 10 ($p < 0.001$) and week 22 ($p = 0.48$) for the chin.⁸ At the final evaluation, 34 weeks, physician right to left comparison showed preference for the eflornithine treated side in 22.2% (12/54) of participants and preference for the vehicle treated side in 25.9% (14/54) of participants ($p = 0.845$).⁸ The remaining participants did not demonstrate a difference between sides at 34 weeks. RBI was calculated to be $< -1\%$, ABI was calculated to be -4% and the NNT was -25 (see Table 3). This suggests that for every 25 patients treated, one less will benefit compared to control. In their self-assessments, patients consistently preferred the eflornithine treated side to the vehicle treated side ($p = 0.017$).

All three studies also closely monitored their participants for adverse events. In general, topical eflornithine was found to be tolerated well with no serious or prolonged effects. Adverse events noted included the development of acne, dermatitis, redness, pigmentation, paresthesia and reactivation of herpes simplex.^{6,8} Most events resolved on their own under continued eflornithine treatment without the need for medical intervention.

Table 3 – Efficacy of Eflornithine and statistical significance

	RBI	ABI	NNT	p-value
Vissing (2016)	0%	72%	2	0.048
Hamzavi (2007)	38%	25.6%	4	0.021
Smith (2006)	$< -1\%$	-4%	-25	0.845

DISCUSSION

Eflornithine (Vaniqa) is a topical antiprotozoal agent used to reduce unwanted hair in women. The most common adverse reactions associated with the medication are acne vulgaris (11-21%) and pseudofolliculitis barbae (5-16%).³ Less likely (<10%) adverse events include headaches, tingling skin, dizziness, pruritus, rash, xeroderma, erythema, alopecia, dyspepsia and anorexia.³ These reactions are consistent with those identified in all three studies. There are currently no known drug interactions with eflornithine and it is considered to be a pregnancy Category C drug. Information related to its use in pregnant or lactating women is limited, so it is best to exercise caution and consult a medical provider before continuing or starting the drug. The safety and efficacy of eflornithine has also not been studied in children under 12.

Vaniqa is the first and only prescription hair reduction cream to be FDA approved. For a 45 gram tube the price is roughly \$199.20³ based on a single manufacturer. Unfortunately, most insurance policies will not cover this prescription leaving its recipients with an expensive bill. To help minimize patient costs, the company does offer a rebate program, however it is only available for those with private insurance or cash paying customers.

After analyzing the results of three RCTs, it is important that we discuss their limitations. The most glaring issue with the studies conducted by Vissing et al and Hamzavi et al are without a doubt their sample sizes, 18 and 31 respectively. While the population is relatively small, it is still expected to have a sample size of at least 50. Despite some limitations, all three RCTs are POEMs meaning they are relevant to the population. They are also all valid studies. The presence of p-values, confidence intervals, randomization and blinding are all factors that attribute to each of the studies validity.

CONCLUSION

The primary objective of this systematic review was to determine whether or not topical eflornithine is an effective adjunctive therapy in reducing unwanted facial hair in women diagnosed with hirsutism. Unfortunately, the evidence provided by these RCTs is conflicting so we are unable to confidently answer the question. Two of the studies showed statistically significant evidence that supports the effectiveness of eflornithine, however, the third study is unable to support its effectiveness. Smith et al had the largest sample size but they were unable to prove that topical eflornithine was an effective adjunctive therapy. In fact, their data, had it been statistically significant, would have proven the exact opposite. Due to its lack of significance, we cannot say for certain that this study counteracts the first two.

In order to improve future studies, it is important to establish a large sample size that would be more reflective of the population. It would also be interesting to compare groups of participants who use the topical eflornithine during their laser hair treatments to those who undergo laser hair therapy prior to starting the eflornithine. I would continue to do the split face trials and incorporate a placebo cream so both patient and physician were blind. I would also implement hair counts, physician scores and self-assessments. Being that this topic is about patient oriented evidence that matters, the self-assessment is arguably the most important aspect. If hair counts suggest that there is no difference between the placebo and the test cream, but the patient believes they see an improvement, they are going to keep using it.

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