

2019

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Recommended Citation

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Is there a greater statistically significant difference in the clearance or partial clearance of anogenital/genital warts when it comes to combination therapies that include cryotherapy versus cryotherapy alone?

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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

June 13, 2019

ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine if there is a statistically significant difference in using combination therapies that include cryotherapy vs. cryotherapy alone in the clearance of genital/anogenital warts.

STUDY DESIGN: Systematic review of three peer reviewed primary studies that were published between 2009-2014.

DATA SOURCES: Review of a double-blind placebo-controlled study, a single-blinded randomized controlled study, and a randomized clinical comparative study from 2011. All sources were selected from PubMed based on the applicability to the clinical question and how accurately they answered the question regarding the patient population

OUTCOMES: The outcomes of investigation were POEMs (Patient-Oriented Evidence that Matters) that measured the overall level of clearance and partial clearance of warts.

RESULTS: On et al., showed that after 17 weeks of therapy, the combination therapy of sinecatechins 15% ointment plus cryotherapy achieved 71% partial clearance vs. 52% on cryotherapy alone with a p-value of 0.2037. Gilson et al., at week 4, saw a 60% clearance with the combination of podophyllotoxin cream plus cryotherapy vs. 45% clearance of cryotherapy alone; although, these results weren't considered statistically significant and by week 24 the clearance rate of either therapy was the same. Mi et al., showed a 32% clearance of anogenital warts with both the ALA-PDT plus cryotherapy and cryotherapy alone. It also showed a 94% clearance of genital warts with the combination therapy and a 50% clearance with the cryotherapy alone.

CONCLUSIONS: In two of the three studies, it showed that there is a statistically significant improvement when using the combination therapies, specifically the combination of sinecatechins 15% ointment plus cryotherapy and the combination of ALA-PDT plus cryotherapy.

KEYWORDS: anogenital warts, genital warts, cryotherapy

INTRODUCTION

Human papilloma virus (HPV) is a sexually transmitted disease that only infects humans and has a 50% chance of causing an infection at least once in a person's lifetime.¹ Although the body has the capability to clear HPV on its own, when this does not occur there are adverse physical manifestations that arise. One of the manifestations of HPV is genital/anogenital warts; this is the most common sexually transmitted disease and affects a large majority of the population. This type of infection is caused by a low-grade HPV with a high rate of disease regression, which rarely advance towards cancer.¹ About 40 subtypes out of more than 120 HPV subtypes are directly linked to anogenital warts.² These warts increase in size over time becoming increasingly visible and can interfere with everyday life if there is no treatment intervention.

The number of people affected has been growing over the years and as it increases so does the financial burden. The number of new cases can range anywhere from 500,000-1,000,000 per year. As of 2012, there are as many as 20 million infected in the United States, and this number continued to increase.² As new patients seek treatment there is also an increase in office visits, follow-up visits, and trial and error of medication combination. Chesson et al. summarized that the overall cost of prevention and care of HPV in 2010 was \$8 billion, of which \$300 million was directed towards genital warts.³ Beyond treatment for established infections, HPV vaccines, including Gardasil and Cervarix, can be given to protect against this disease. In patients that are HPV naïve, Gardasil has shown to be 99 percent effective in genital wart prevention and long-term studies have shown that it doesn't seem to have waning immunity.³

When a person has been infected, the symptoms may not always be severe enough to seek treatment. Visible symptoms present 2-3 months after first contact² and can include but

aren't limited to itching, burning, tenderness, and/or discomfort. Warts can present as flat/sessile/lobular papules and can be symptomatic or asymptomatic.⁴ The treatment has become disproportionately centered around the removal of visible warts rather than the actual cure of the underlying cause. Consequently, there are no definitive treatments, but current therapies are individualized to each patient.² Because of this method, reoccurrence is high and depending on the size and number of warts present, it may take several office visits to get this condition under control.⁵ Without an absolute cure, the rate of persons infected will continuously increase.

There are two different approaches to the treatment of genital/anogenital warts: surgical and non-surgical. Surgical therapies include cryotherapy, excision, electrosurgery, and laser ablation. Non-surgical methods include podophyllin resin, podophyllotoxin cream, interferons, ALA-PDT, trichloroacetic acid, topical photodynamic therapy using aminolevulinic acid, sinecatechins 15% ointment, and cryotherapy. While there are many treatments that can halt the growth or reduce the chances of reoccurrence, the therapies available can be inadequate or have limitations that cannot treat the underlying cause. Cryotherapy alone has shown to be ineffective against latent lesions and limited to removal of visible lesions.⁶ Albeit some of these modalities only affect visible lesions, others have a stronger effect on latent infections or can reduce the amount of sessions needed for clearance. Although there are some benefits to using cryotherapy, the limitations from a single modality have caused the need for further research into combination treatments. Combination therapies have been demonstrated to affect latent lesions, can be used as at-home treatment, and have been shown to have an earlier onset of action.^{4,5,6} With so many possible methods for treatment, patients have a variety of options that can cater to their specific type of infection.

As previously mentioned, genital/anogenital warts can have a negative impact on a person's intimate life. Although the main concern is the visibility of the wart, accompanying symptoms such as itching, pain/bleeding with intercourse, and the possibility of warts in the mouth/throat when in contact with an infected person⁴ are reasons to look for an alternative treatment.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not there is a greater statistically significant difference in the clearance or partial clearance of genital/anogenital warts when it comes to combination therapies that include cryotherapy vs cryotherapy alone.

METHOD

All sources were searched and selected from PubMed. The three studies used in this review were 3 randomized, single/double blinded and comparative studies comparing combination therapies that included cryotherapy vs. cryotherapy alone in the complete/partial clearance of genital/anogenital warts. The patient population consisted of males and females ages 18 and above that had either anogenital or genital warts. The interventions included sinecatechins 15% ointment plus cryotherapy, podophyllotoxin plus cryotherapy, and photodynamic therapy plus cryotherapy. All these interventions were in comparison to the control group, cryotherapy. The outcomes of these EBM studies were focused around the overall level of clearance and partial clearance of warts.

The key words that were used in the selection of these articles through PubMed included: cryotherapy, genital warts, and anogenital warts. These peer-reviewed articles were published in

English and publication took place within the last 10 years. The selection was based on their applicability and how accurately they answered the question regarding the patient population. The statistics reported consisted of Chi-square, Fisher's exact test, ANCOVA model, Cochran, and the Mantel-Haenszel test. A more described inclusion and exclusion criteria is explained below in Table 1.

Table 1. Demographics and characteristics of included studies

Study	Type	# of pts	Age (yrs)	Inclusion criteria	Exclusion criteria	W/D	Interventions
On, 2014	RCT	42	>18	2 or more clinically typical, visible warts; negative pregnancy tests and use of approved method of birth control throughout duration of study	Hx of herpes genitalis, HIV, hepatitis B and C, hx of organ allograft, and/or internal warts requiring tx. Recent tx, within 90 days, or dermatologic procedures that could interfere with the evaluation of current tx	9	Sinecatechins 15% ointment plus cryotherapy vs cryotherapy
Gilson, 2009	RCT	149	18-70	At least 2 external anogenital warts that could be appropriately treated	HIV positive, concurrent internal anogenital warts, warts > than 4 cm ²	13	Podophyllotoxin cream plus cryotherapy vs cryotherapy
Mi, 2011	randomized clinical comparative study	109	18-54	At least 3 (max of 30) anogenital warts or one larger than 0.5 cm (max: 2 cm)	Infected with other sexually transmitted ds, had immunosuppression, were pregnant or breast feeding, or had concurrent intra-anal or intra-vaginal warts	29	Photodynamic therapy plus cryotherapy vs cryotherapy

OUTCOMES MEASURED

The outcomes were patient oriented (POEMs) and were determined based on the reoccurrence of warts, and the comparison between complete vs. partial clearance. On et al., used chi-squared test to compare partial. Gilson et al., used observed data and last observation carried forward (LOCF) in patients that didn't follow-up according to their schedule. Mi et al., used Cochran and the Mantel-Haenszel test to evaluate the recurrences of warts and number of completed responses.

RESULTS

All three studies tested methods that would decipher whether a combination therapy or cryotherapy alone would result in a better outcome in genital/anogenital warts. Each systematic review consisted of either a double-blind placebo-controlled study, a single-blinded randomized controlled study, or a randomized clinical comparative study. About 20% loss to follow up was experienced in the study consisting of podophyllotoxin cream plus cryotherapy. In the study including sinecatechins 15%, only 2 patients were lost to follow-up. In all three studies, all the patients were randomly placed into either the experimental or control group and all evaluators remained blinded during examination of the lesions. Adverse effects were limited to erythema, scaling, irritation, mild to moderate pain, hypopigmentation, soreness, and in no study did patients withdrawal due to severity of adverse effects.^{4,5,6}

Table 2. Treatment effect comparison in ITT population regarding partial clearance⁴

	sinecatechins 15% ointment plus cryotherapy (n=21)	Cryotherapy alone (n=21)	*P-value
Week 1 n (%) cleared	7 (33.3%)	6 (28.6%)	p = 0.7385
Week 9 n (%) cleared	15 (71.4%)	9 (42.9%)	p = 0.0614
Week 17 n (%) cleared	15 (71.4%)	11 (52.4%)	p = 0.2037

* p-values calculated using Chi squared

On et al. conducted a study where 42 patients underwent cryotherapy treatment as a baseline and after one week two groups were divided between the experimental group, sinecatechins 15% ointment, and the control group, cryotherapy alone. Both groups had an average range of 8.3 – 9.8 lesions. Subjects were to have at least 2 or more visible warts and were expected to continue treatment for 17 weeks or until complete clearance of warts.⁴ On et al., defined complete clearance as having zero lesions and partial clearance was defined as having 50% reduction from baseline. At the end of week 17, the resulting $p > 0.05$ indicated the outcome regarding partial clearance was not statistically significant even though the trend favored the combination therapy.

Table 3. Anogenital wart clearance; ITT analysis using LOCF⁵

	Podophyllotoxin combination (n=70)	Cryotherapy alone (n=70)	Unadjusted OR (95% CI) ----- P-value	Adjusted OR (95% CI) ----- P-value
Week 4 n (%) cleared	42 (60.0)	32 (45.7)	1.78 (0.91 to 3.48) p = 0.09	1.99 (0.91 to 4.36) p = 0.085
Week 12 n (%) cleared	42 (60.0)	32 (45.7)	1.78 (0.91 to 3.48) p = 0.09	1.94 (0.95 to 3.97) p = 0.069

Gilson et al. conducted a multicentre, randomized, double-blind, placebo-controlled study with patients stratified by sex and history of anogenital warts. Patients were divided into two groups of 70. The experimental group was composed of podophyllotoxin plus cryotherapy, and control group was composed of cryotherapy alone. The effectiveness of podophyllotoxin was investigated by percentage of clearance and exploratory analysis regarding wart history and wart type.⁵ There were two major endpoints, at 4 and 12 weeks, when studying podophyllotoxin cream plus cryotherapy. While the most research is evaluated by these two endpoints, there were still data collected until 24 weeks on a voluntary basis. Even though the overall clearance was higher (60%) with the combination therapy at both endpoints than cryotherapy alone (45.7%) it wasn't enough to be considered statistically significant due to the p-value being greater than 5%. During the 4th week there was a higher clearance rate in patients that had warts before ($p = .009$) vs. those who have never had warts before although there was no significant finding between the two groups at the 12-week mark.⁵ Between the keratotic and non-keratotic warts, there was no difference in clearance at week 4 or 12. The adjusted odds ratio takes into account the baseline number and area of warts, history and treatment center.⁵

Table 4. Difference in the clearance or partial clearance of anogenital/genital warts when it comes to combination therapies that include cryotherapy versus cryotherapy alone

Study	Control event rate (CER)	Experimental event rate (EER)	Absolute benefit increase (ABI)	Numbers needed to treat (NNT)
On et al. complete clearance	.286	.286	0	N/A
On et al. partial clearance	.429	.714	.190	4
Gilson et al. complete clearance	.457	.600	0.143	7

On et al. study showed there is no increased therapeutic outcome in using the combination treatment over the monotherapy regarding complete clearance. This study also showed that for every 4 patients treated with sinecatechins plus cryotherapy, one more will have clearance of at least 50% than if treated with cryotherapy alone. Gilson et al. showed that for every 7 patients treated with combination therapy, one more person will have overall clearance than if treated with cryotherapy alone.

Table 5. Response rate in patients after 1 and 2 treatments of cryotherapy plus ALA-PDT or cryotherapy⁶

	Cryotherapy plus ALA-PDT	Cryotherapy plus placebo-PDT
Number of lesions in the anal area	111	132
Response rate after one treatment	18.9%	18.2%
Response rate after two treatments	32.4%	32.6%
Number of lesions in the external genitals	137	111
Response rate after one treatment	73.7%	38.7%
Response rate after two treatments	94.2%	50.5%

Mi et al. conducted a randomized clinical comparative study with 40 patients that received the combination of ALA-photodynamic therapy (PDT) plus cryotherapy and 40 patients that received cryotherapy alone. ALA-PDT disrupts the target cell by the build-up of ALA-induced protoporphyrin IX in cells that are increasing in number.⁶ Mi et al. states based on the Pearson chi-squared test and the t-test there was no statistically significant differences in the initial number of warts between the experimental and the control group. Table 5 shows a higher response rate in the treatment of genital warts with the combination therapy and the response rate

of anogenital warts clearance is about the same with both, cryotherapy alone and the combination therapy. Table 5 shows that after multiple treatments the clearance is higher in genital warts with the combination of cryotherapy plus ALA-PDT and no statistically significant improvement in the treatment of anogenital warts. Anogenital warts resulted in a $p > 0.05$ after both treatments and a $p < 0.05$ in external genital area after both treatments.⁶ The response rates of genital/anogenital warts regarding each treatment utilized is explained in tables 5.

DISCUSSION

Genital/anogenital warts is a sexually transmitted disease caused by HPV that infects the body through a break in the skin or the mucosa when there is skin-to-skin contact or mucosa-to-mucosa contact.¹ Cryotherapy has long been a common modality in the treatment of warts. Unfortunately, its limitations cause researchers to look for alternative treatments with better results. Ideal alternatives would treat the underlying condition.

Each research study described several ways to increase accuracy in their results. Sinecatechins 15% ointment could have been better reviewed with a larger sample size. Outcomes could have been affected by participants practicing unsafe sex or they may have not reported all sexual partners.⁴ Gilson et al., also expressed a larger sample size could determine whether or not the effects of podophyllotoxin cream with cryotherapy was actually superior to cryotherapy alone. Factors that could've affected the outcome include patients being able to self-assess and more patients in the podophyllotoxin combination arm stopped blinded study medication than in cryotherapy alone⁵. Mi et al. described a major limitation in the follow-up time. Follow-up was limited to 12 weeks and reoccurrence can be known to occur up to a year out.⁶ One of the limitations of the cryotherapy plus photodynamic therapy vs. cryotherapy is part of their exclusion criteria did not include those that were recently treated, if applicable. In two of

the studies, it was not made clear if they had tested for latent lesions. The study including podophyllotoxin cream plus cryotherapy was done in the United Kingdom and the combination was shown to have increase pain/soreness, so patient compliance would come into question.⁵ Even with addressing these limitations there are always going to be uncontrollable factors such as patient compliance and reaction to medication that will inevitably cause meeting accuracy challenging.

This EBM review was meant to evaluate 3 studies comparing different combination therapies that included cryotherapy vs. cryotherapy alone in the complete/partial clearance of genital/anogenital warts. Even though the results were favoring the combination therapy of sinecatechins 15% ointment plus cryotherapy, the data stated that the results were not statistically significant regarding partial clearance based on the p-value reported. In the review of podophyllotoxin cream plus cryotherapy, the results remained constant with slightly favorable results with the combination therapy, although not statistically significant even when adjusted for baseline number and area of warts, history and treatment center differences between the groups.⁵ In the review of photodynamic therapy plus cryotherapy, the clinical results favored the combination therapy response rate over cryotherapy alone in the treatment of external genital warts after both treatments.

CONCLUSION

All three studies have shown both combination therapies and cryotherapy alone have the capability of clearing anogenital/genital warts to an extent. The results in the study involving photodynamic therapy and cryotherapy favored the combination treatment. The studies involving sinecatechins 15% plus cryotherapy and podophyllotoxin plus cryotherapy favored cryotherapy alone. Although one portion of one of the studies favored combination therapy, there is not

enough evidence to ultimately conclude that combination therapies have a greater statistical difference in the clearance or partial clearance of anogenital/genital warts. Further research needs to be done since this is the first time the combination of photodynamic therapy plus cryotherapy has been studied and would benefit from expanding the exclusion criteria such as recent treatment and dermatological treatments that could interfere with results. All three of these combination therapies have not been properly evaluated before^{4,5,6} and with decreased limitations in future research, better outcomes can be achieved.

REFERENCES

1. Brianti P, De Flammoneis E, Mercuri SR. Review of HPV-related diseases and cancers. *New Microbiol.* 2017 Apr;40(2):80-85.
2. Yanofsky VR, Patel RV, Goldenberg G. Genital warts: a comprehensive review. *J Clin Aesthet Dermatol.* 2012;5(6):25-36.
3. Chesson HW, Ekwueme DU, Saraiya M, Watson M, Lowy DR, Markowitz LE. Estimates of the annual direct medical costs of the prevention and treatment of disease associated with human papillomavirus in the United States. *Vaccine.* 2012 Sep 14;30(42):6016-9. doi: 10.1016/j.vaccine.2012.07.056.
4. On SC, Linkner RV, Haddican M, et al. A single-blinded randomized controlled study to assess the efficacy of twice daily application of sinecatechins 15% ointment when used sequentially with cryotherapy in the treatment of external genital warts. *J Drugs Dermatol.* 2014;13(11):1400-1405. doi: S1545961614P1400X [pii].
5. Gilson RJ, Ross J, Maw R, Rowen D, Sonnex C, Lacey CJ. A multicentre, randomised, double-blind, placebo controlled study of cryotherapy versus cryotherapy and podophyllotoxin cream as treatment for external anogenital warts. *Sex Transm Infect.* 2009;85(7):514-519. doi: 10.1136/sti.2009.038075
6. Mi X, Chai W, Zheng H, Zuo YG, Li J. A randomized clinical comparative study of cryotherapy plus photodynamic therapy vs. cryotherapy in the treatment of multiple condylomata acuminata. *Photodermatol Photoimmunol Photomed.* 2011;27(4):176-180. doi: 10.1111/j.1600-0781.2011.00592.x