Dentistry

Research Article Open Access

Treatment of Herpes Labialis: Repetition of a Study Comparing Two OTC Drugs and Untreated Controls and Comparing the Outcomes of Each Study

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Abstract

Statement of the Problem: In addition to the patient's pain and disfigurement, many dentists and hygienists are reluctant to treat a patient with an active oral herpes lesion. It is of mutual interest to both patient and the dental staff to find an effective treatment. We report the results of a repetition of a previously published study comparing the outcome of treatment using Abreva (Glaxo Smith Kline, Parsippany NJ) and Viroxyn Professional (Quadex Pharmaceuticals, Salt Lake City, UT) and using untreated cold sores as a control.

Methods and Materials: A cohort of people who were naïve to the first study (n=186)[a] were surveyed and asked to retrospectively report the amount of time their cold sores needed to heal without treatment and how long the pain lasted without treatment. These same questions were then asked of the participant's using a standardized outcome response form to report following treatment with Viroxyn Professional and Abreva. In addition there were participants who were naïve to Abreva (n=55). This cohort was analyzed separately for outcomes using Viroxyn versus untreated cold sores.

Results: Participants in both the Abreva and Viroxyn groups reported significant improvement in outcome versus untreated cold sores with Abreva offering a three day advantage over control and Viroxyn offering a seven day advantage over control (all t-tests; all $p<0.001$)[b].

Conclusion: When compared to untreated controls, both use of OTC drugs resulted in a significant reduction in time to healing and time to loss of discomfort. Additionally, Viroxyn offered a significant reduction in time to healing and time to loss of discomfort versus Abreva. When the study metric data were compared for the two separate studies, no differences were found. The outcome of the second study was the same as that of the first.

[a]n=number of participants in the study

[b]p=p-value. A p-value of < 0.05 is considered statistically significant. When p = 0.05 or less, there is a 5% chance, or less, that the observed outcome happened by chance.

Keywords: Herpes Labialis; OTC Drugs; HSV-1

Introduction

Recurrent herpes labialis (cold sores) usually caused by Herpes Simplex Type-1 (HSV-1) affects approximately 32% of those of school age and 44.6% of adult patients [1]. For the majority of those who suffer from recurrent disease, the outbreaks tend to be self-limiting, but for those with autoimmune disorder or neonates, the disease can be much more serious [1,2]. A new trend in behavior among the young has been identified in that over 70% of primary diagnosis of genital herpes is associated with HSV-1 [3].

For those with recurrent disease, four lesions per year is typical [4,5] with untreated lesions lasting on average about 10 days [6], but some unfortunate sufferers have been shown to experience 12 to 13 lesions per year [5]. The disease has 6 distinctive stages: 1) prodrome, 2) papule, 3) vesicle, 4) ulcer, 5) soft scab, 6) hard scab [5]. Soft and hard scab represent the healing stage and the physical discomfort has typically ended during healing [4,5]. Physical discomfort (pain, itching, burning) is most pronounced during the papule and ulcerative stage with discomfort at its peak during the ulcer stage [6-8].

During primary infection, the virus infects epithelial cells, reproduces, and causes symptoms that range from mild to much more clinically significant. Primary infection can result in fever, malaise, lymphadenopathy, and multiple and diffuse facial and oral cavity ulcers [2,8]. Recurrent ulcers are usually found on the lips or facial area, but can occur inside the oral cavity; typically on the gums or roof of the mouth [2,8]. Following primary infection, the virus enters a terminal sensory neuron, travels down the nerve axon, and then goes dormant in the nerve cell body [2,4,5]. A variety of stimuli have been shown to trigger recurrence. These include exposure to UV radiation, hormonal changes, febrile illness, and occasionally dental trauma [4,5].

Early and effective treatment of patients with active herpes lesions has the potential to impact dental patient care cancellations due to oral herpes. Many such patients fail to reschedule their appointments. Early treatment can be a useful tool in minimizing the risk of spread from patient to dental staff or the reverse. Spread of the disease can have unintended and dire consequences to dental staff. Herpetic Whitlow occurs with more frequency in dentists (2.4%) than in the general population (1.7%) [9].

Treatment options and standard of care

Healthcare providers typically choose from a list of standard of care treatment options as found in the dental literature. The literature teaches both Rx and OTC drugs (Table 1).

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Received November 27, 2013; **Accepted** December 26, 2013; **Published** December 28, 2013

Citation: McCarthy JP, Browning WD, Bowman JP (2013) Treatment of Herpes Labialis: Repetition of a Study Comparing Two OTC Drugs and Untreated Controls and Comparing the Outcomes of Each Study. Dentistry 4: 185. doi:10.4172/2161-1122.1000185

Systemic use drugs	
Generic name (brand name)	Suggested dosage and duration (days)
Acyclovir (Zovirax) (Rx)	400 mg tid X 7
Famciclovir (Famvir) (Rx)	125 mg bid X 5
Valacyclovir (Valtrex)	500 mg bid X 5
Topical Use	
Generic name (brand name)	Suggested dosage and duration (days)
Penciclovir (Denavir) Cream, 1% (Rx)	Every 2 hours
Acyclovir (Zovirax) Ointment, 5% (Rx)	Every 2 hours
Docosanol (Abreva) Cream (OTC)	Every 3 hours
IPA tincture of BZK, 0.13% + 5% Benzocaine (Viroxyn Solution) (OTC)	Single Application
Reprinted with Permission from Essentials of Oral Medicine, Silverman S, Eversole R, Truelove E, 2001, BC Decker, Hamilton, ON – Table 13-2, p. 122	

mg=milligram
bid=twice daily
tid=three times daily

Table 1: Antiviral drugs for herpes simplex virus.

Prescription drugs see their maximum benefit only if prescribed very early, but only reduce lesion time by 1 to 2 days [6]. Drawbacks include: 1) only 10% reduction in time to healing, 2) undesired side effects, 3) expensive for the patient, and 4) the delay in seeing a provider may result in the drug being ineffective [6,7].

While the classic nucleoside drugs are Rx only, two drugs, Abreva (Docosonol, 5%) and Viroxyn (Isopropyl alcohol tincture of benzalkonium chloride, 0.13% plus Benzocaine, 5%) are over-the-counter. Abreva (docosanol) is a 22-carbon long chain fatty alcohol. Product advertising claims that the fatty alcohol acts to inhibit migration of the virus by providing hinderance. It is to be applied every 3 hours for the duration of the lesion. Viroxyn contains a quaternary ammonium compound which disrupts the lipid envelope of the herpes virus using a classical surfactant action [10]. Typically, only one application is required.

The purpose of this study is to learn if the results of a previous study can be duplicated. Three cohorts are studied: 1) untreated cold sores, 2) cold sores treated with Abreva, and 3) cold sores treated with Viroxyn. Participants reported on time to healing and on time to loss of physical discomfort including pain, itching, and burning. Differences between cohorts were examined at a significance level of 5% (p-value<0.05). Differences between the results of the two studies will likewise be tested using the null hypothesis where p-value is greater than 0.5.

Rationale for the study design

Since both Abreva and Viroxyn are taught in the dental literature as "standard of care" treatment options [2,7,11], it is important to the dental health professional to learn the relative effectiveness of each OTC treatment drug. Rx drugs are expensive and only provide a reduction in time to healing of about ten percent [6].

However, head-to-head evaluation of two OTC drugs which have been in the market for an extended period of time is rare and presents unique challenges. Abreva has the benefit of a multi-million dollar advertising campaign and is well known to sufferers of recurrent cold sores. Viroxyn is not as well known, but has been sold at retail to consumers and dispensed by dentists. Approximately 5 million doses have been dispensed by dentists or sold in retail drug stores to consumers. Thus, dropping in to the neighborhood drug store or a quick internet search would be all that is necessary to break the blind.

The primary purpose of the study was to learn whether the results of a previous study [7] could be duplicated in a different group of participants. Thus, the study design of the second study was identical to that used in the first. The design of both studies conforms to the recent FDA Guidance of Industry dealing with patient reported outcomes [12]. To meet the Guideline provisions, three key elements must be met. First, the participant must report the metrics being studied on a suitable instrument without input or filtering by a healthcare professional. Secondly, there must be a reasonable expectation that the participant will have a good memory of the outcome, and third, the metrics under study must be relevant to the disease and involve the ability for the lay person to accurately evaluate and report [13].

The protocols for both the first and second study were submitted to FDA for a 30-day review. Likewise, the protocols were reviewed by an Institutional Review Board (Western Institutional Review Board, Columbus, OH) who told the investigators that no IRB was needed as both drugs are OTC, the study was retrospective in nature, and the only labeling was the OTC Drug Facts Panel. Finally, a Study Report was submitted to FDA for both studies. Still, retrospective studies have a potential for design bias, but such potential biases were identified and addressed in the study design and subsequent study reports. These are fully revealed and discussed in the Discussion section.

Methods and Materials

The participants were sent a survey and asked to report the outcome of their untreated cold sores (Control), the outcome using Abreva (Comparator) and their outcome using Viroxyn (Treatment). Both Abreva and Viroxyn are legally marketed OTC drugs labeled for the treatment of cold sores.

The primary outcome metrics were:

1. Time to healing (loss of hard scab and return to intact skin) and
2. Time to persistent loss of discomfort (pain, itching, burning)

A list of possible participants was generated from a list of consumers who had purchased Viroxyn online. The list was compared to those who participated in the first study to insure that no participants in the first study would be sent a survey. To encourage participation in the study, they were offered either a complimentary tube of Abreva or a complimentary 3-pack of Viroxyn as they saw fit.

As was expected, some participants had not used Abreva. Their data was analyzed separately. All surveys returned to the Investigators were left unopened until the data entry team was assembled. The data entry team consisted of one Investigator who opened and read the data aloud, and a second Investigator who keyed in the data. The first person then verified the data had been correctly entered, and then an independent Certified Public Accountant (Savas, Green & Company, Cottonwood Heights, UT) also verified that the data entered matched the source document. After each data entry session, the CPA would burn the data to a disk and store it off-site at his offices. The CPA verified the final data set before sending it to the statistician who performed an analysis using the latest version of SAS (Version 9.3, SAS Institute, Carry, NC).

Survey

The first page of the survey asked for minimal participant demographics such as initials, age, gender, and ethnicity. Participants were then asked how many cold sores they got per year. This number was entered as a whole number. Where a range was given, the lowest number in the range was used. They were then asked to rate their untreated cold sores using the scale devised and validated by Boon et

al. [13]. The scale consisted of none, mild (I hardly notice it), moderate (I am very aware of the discomfort), and severe (I find it hard to concentrate, work, or sleep.)

For time to healing of cold sores treated with the study drug (Viroxyn) or comparator drug (Abreva), whole number one-day intervals were presented in a "check the box" format. The highest value was 10 days or more. Likewise, they were asked to rate the time to loss of discomfort in a "check the box" format as follows:

2 minutes (0.00139 days)

10 minutes (0.0069 days)

1 hour (0.042 days)

12 hours or less (0.5 days)

1 day or less (1 day)

2-4 days

4-6 days

More than 6 days

Number of participants (n)	First Study (n=180)	Second Study (n=186)
Males	69	68
Females	111	117
No gender provided		1
p-value (d)	p=0.829 (b)	
Age		
Mean Age	41.0	44.0
Number of respondents	176	183
No age data provided	4	3
p-value (a)	p=0.024 (c)	
Number of Cold Sores per year		
Mean	4.7	3.9
Median	4.0	3.0
Number of respondents	176	184
p-value (a)	p=0.011 (c)	
Time to Healing – Loss of hard scab –Duration of Untreated Cold Sores	First Study	Second Study
Mean	11.5 days	11.3 days
Median	11.0 days	10.0 days
Number of respondents	175	180
p-Value (a)	p=0.500 (b)	
Viroxyn Time to Healing		
Mean	4.0 days	3.5 days
Median	3.0 days	3.0 days
Number of respondents	180	184
p-value (a)	p=0.054 (c)	
Abreva Time to Healing		
Mean	7.6	7.6
Median	7.0	7.0
Number of Respondents	178	184
p-value (a)	p=0.910 (b)	
Untreated time to loss of discomfort		
Mean	6.7 days	6.6 days
Median	6.0 days	7.0 days
Number of respondents	171	179
p-value (a)	p=0.807 (b)	
Viroxyn Time to loss of discomfort		
Mean	0.6 days	0.5 days
Median	0.042 days	0.0069 days
Number of respondents	180	183
p-value (a)	p=0.235 (b)	
Abreva Time to loss of discomfort		
Mean	2.8	2.8
Median	3.0	3.0
Number of respondents	177	182
p-value (a)	p=0.950 (b)	
p-value Viroxyn vs. Control (a)	p<0.001 (c)	
p-value Abreva vs. Control l(a)	p<0.001 (c)	
p-value Viroxyn vs. Abreva (a)	p<0.001 (c)	

a. Two tailed independent T-test
b. Confirms the null hypothesis of no difference between studies
c. Statistically significant difference between studies
d. Fishers Exact Test

Table 2: Results of Analysis – Have used Abreva group.

Statistical analysis plan

Participants who sent in a survey with at least one data point showing an outcome metric for Viroxyn or Abreva were considered as having triggered "intent to treat" and were included in the analysis. Demographic information was analyzed using simple summary statistics (mean, median, standard deviation). Differences in age between male and female patients were analyzed using t-test. Differences between the ages of study participants in the first and second study were analyzed using t-test with the null hypothesis of no difference (5% test or p-value of 0.05 or less).

Analysis of study metric data was done using t-test. Since it was expected that the data would not be normally distributed, an additional analysis using an analysis of variance (ANOVA) on ranks procedure was performed to insure that the test choice did not influence the outcome. The analysis method (t-test) did not influence the outcome results (ANOVA and signed rank tests; all results p-value<0.01 for comparison between study drug, comparator drug, and control). Differences in outcomes of the first study and the second study were compared using the null hypothesis and t-test. To satisfy the null hypothesis, all p-values must be >0.05.

Data from participants who had used Viroxyn but not Abreva were analyzed separately in the same manner described above. With respect to simple descriptive statistics, most scholarly papers present the outcome as the median value. This is done to minimize the effect of outlying data or because the data are not normally distributed. In both the first study and this study the outcome data were not normally distributed due to design ceilings on time to healing and time to loss of discomfort. Thus, to be transparent, the data are presented as both median and mean.

Results

Participant reported outcome results

Four hundred eighty six surveys were sent out and of these survey instruments, over 45 were returned as undeliverable. The study was left open for 6 months and in that time data from 241 usable surveys was entered into the database. One survey was returned with no information at all on it. This second study had a lower response rate (54.6) than the first study (71%). Of those who returned a survey, 186 (77.2%) had used both Viroxyn and Abreva compared to the first survey (75.6%). These numbers are sufficiently similar to conclude that both studies resembled each other in participant responses. Table 2 provides information on the number of cold sores per year and compares the basic study demographics for each study.

While it is interesting to note that there are differences in age and number of cold sores between the participants who used both Viroxyn and Abreva in the first study compared to those in the second study, it does not seem to have had an effect on the study metric outcomes which are presented in Table 2. Likewise in the participants who only used Viroxyn, the difference in the age of participants is seen, but not the difference in number of cold sores. The study participants consisted of more women (63.3%) and more Caucasians (87.3%) than non-whites (Table 3).

Participants experienced with both viroxyn and abreva – primary outcome results: The number of cold sores per year in both studies is consistent with the literature [2,5,6] and the demographic data are similar as well (Table 2). Time to healing untreated cold sores is consistent with literature values as well.

Median and mean values for time to healing are shown in Table 2. The use of either product enjoyed a benefit over untreated cold sores used as a control, but the use of Viroxyn resulted in a faster time to healing than when using Abreva (All results of t-test; all p-value<0.001).

Median and mean values for time to loss of discomfort (pain, itching, burning) are also shown in Table 2. The use of either Viroxyn or Abreva showed a benefit when compared to the untreated controls, but time to loss of discomfort when using Viroxyn was significantly less than when using Abreva (All results of t-test; all p-value<0.001). The differences were both statistically and clinically significant.

Overall n	First Study (n=58)	Second Study (n=55)
Males	26	26
Females	32	29
p-value (d)	p=0.851 (b)	
Mean age (years)	43.3	49.6
Number of respondents	58	54
p-value (d)	p=0.0180 (c)	
Cold Sores per year		
Mean	4.2	4.9
Median	4.0	3.0
Number of respondents	58	54
p-value (a)	p=0.488 (b)	
Untreated Cold Sore Duration – Loss of hard scab		
Mean	11.1 days	11.5 days
Median	10.0 days	11.0 days
Number of respondents	58	54
p-value (a)	p=0.588 (b)	
Viroxyn Time to healing		
Mean	4.0	4.0
Median	3.0	4.0
Number of respondents	58	55
p-value (a)	p=0.966 (b)	
Untreated Time to loss of discomfort		
Mean	6.2 days	6.2 days
Median	5.0 days	6.0 days
Number of respondents	57	51
p-value (a)	p=0.991 (b)	
Viroxyn Time to loss of discomfort		
Mean	0.53 days	0.73 days
Median	0.007 days	0.042 days
Number of respondents	58	54
p-value	p=0.412 (b)	
P-value Viroxyn v. Control (a)	<0.001 (c)	

a. Two Tail Independent t-test
b. Confirms the null hypothesis of no difference between studies
c. Statistically significant difference between studies
d. Fishers exact test

Table 3: Results of Analysis - Abreva Naïve Group.

Participants experienced with viroxyn, but who have never used abreva: Median and mean values for time to healing and time to loss of discomfort are presented in Table 3. The number of cold sores per year for both studies is consistent with the literature and the demographic data are similar as well (Table 3). Time to healing of untreated cold sores is consistent with the literature values as well [4-6,13].

Time to healing and time to loss of discomfort when using Viroxyn is consistent across the two studies and showed substantial benefit versus control. The benefit in time to healing and benefit in time to loss of discomfort is both clinically and statistically significant.

Discussion

Unmanageable study bias associated with a prospective study

As previously mentioned, both Viroxyn and Abreva are currently readily available in the OTC marketplace and thus achieving an effective blind for the investigators and participants is impracticable due to the substantial differences in form (cream vs. liquid), odor (mild oil odor vs. alcohol odor) and dispenser (tube vs. ampoule). Institutional Review Boards would require that information about each active ingredient be given at the time of enrollment and thus a quick trip to the neighborhood drug store or a minute or so on the internet would result in the blind being broken. There can be no way to insure that participants were not unduly biased by advertising claims or the non-professional reviews of lay persons who offer their unsolicited opinions of either product online. Again, the very nature of the drugs and their appearance, odor, and dispensers would not allow of even a very clever blinding scheme to be effective. Thus, after considering all the potential for bias in a prospective study, it was clear that a retrospective study, conducted using the Guidance for Industry published by the US Food & Drug Administration (FDA), would be the most credible way to proceed.

Weaknesses of a retrospective study

Memory bias, or the strength or weakness of a memory, is a potential weakness, but memory bias should affect all groups equally. It is important to note that the potential for memory bias in recollection of time to healing and time to loss of discomfort in the Control group did not materialize as their values are consistent with the literature [2,4-6].

It was noted that the participants were primarily Caucasian, but the authors are unaware of any scholarly papers that document a racial difference in response to HSV-1. Any concerns that the participants may have represented a unique subset of those who suffer from HSV-1 are answered in that this was a repeat of a previously published study [7]. Any significant subset of those who suffer from HSV-1 would have resulted in potential differences in study outcome. This did not happen and the Null Hypothesis (of no difference) was validated.

Study design-induced bias favors the less effective drug

To address any concerns regarding the weakness of retrospective studies, the Study Protocol introduced a design bias to strongly favor the less effective drug. The literature value of 10 days [4-6] for a cold sore to heal untreated is typically the median value and thus, many suffer longer than 10 days before their cold sores heal. In these two studies, the participants entered their time to healing for untreated cold

sores in whole number days without regard to the value. However, their time to healing using each drug was entered in a uniform fashion with a maximum value of 10 days or longer (assigned a value of 10) for time to healing and 6 days or longer (assigned a value of 6) for time to loss of discomfort.

In both studies, about 35% of Abreva respondents checked the 10 days or longer box for time to healing while about 1% of Viroxyn users did. Likewise, for time to loss of discomfort, 13-15% respectively, checked the 6 days or longer for time to loss of discomfort using Abreva while less than 1% of Viroxyn users checked this box. This had the effect of lowering the time to healing outcome and time to loss of discomfort outcome for the Abreva cohort. Absent this planned bias to favor the less effective drug, the benefits of Abreva would have been shown to be substantially reduced.

Bias related to price, availability and advertising

Participants went to a convenient local drug store and paid %16-$18 for a tube of Abreva. However, those who purchased Viroxyn either did so from a dental healthcare professional and paid over $40 or went online, paid over $40 for the drug, and had to wait for it to be delivered in the mail. In addition, Abreva enjoys a nation-wide advertising campaign in print and on TV and proclaims itself to be the "Number One Cold Sore Medication Recommended by Pharmacists". The price difference and massive multi-million dollar advertising campaign tend to show Abreva in a more positive light than Viroxyn. Abreva is better nationally recognized and accepted. For Viroxyn to show superiority despite these biases that favor Abreva and the previously discussed design-induced bias that favor Abreva is indeed noteworthy.

In the first study, compensation was in the form of a complimentary 3-pack of Viroxyn. In retrospect, this may have discouraged participants who naturally favored Abreva and thus did not participate. In the second study, this concern was addressed by offering either a complimentary 3-pack of Viroxyn or a complimentary tube of Abreva. Thus, if anyone favored Abreva and wanted to be heard, they could send in a survey and receive a free tube of Abreva. Only two persons favored Abreva and in the first case, the outcome data supported that Abreva worked better for that participant. The other person who requested Abreva checked the box that he had never used Abreva. It is reasonable to assume that he wanted to try it for free.

That upon analysis, the first study outcome metrics did not differ from the second, in which participants had a choice of Abreva or Viroxyn tends to indicate that the concern mentioned above had little influence on the outcome of the first study.

Conclusions

Both studies have demonstrated, within the limits of their design, that the use of Viroxyn for the treatment of herpes labialis (cold sores/fever blisters) significantly improves time to healing versus untreated control and versus Abreva. The Control Group had a median 10.0 days for time to healing in the first study and a median 11.0 days for time-to-healing in the second study. The use of Abreva lowered the time to healing in both studies to a median 7.0 days or a 3 or 4 day improvement depending on the study. In both studies, use of Viroxyn lowered time to healing to a median 3.0 days or a 7.0 or 8.0 day improvement over Control and a 4.0 day improvement over Abreva.

Both studies also demonstrated, within the limits of their design that the use of Viroxyn for the treatment of cold sores also significantly improves the time to loss of discomfort versus Control and versus Abreva. The control group had a median time to loss of discomfort of 6.0 days in the first study and 7.0 days in the second study. Abreva improved time to loss of discomfort with a median 3.0 days in both studies or a 3.0 or 4.0 day improvement respectively. Viroxyn demonstrated a time to loss of discomfort of 1 hour in the first study and 10 minutes in the second study representing a 6.0 or 7.0 day improvement over Control and a 3.0 day improvement over Abreva.

For this conclusion to be reached despite all the design and study induced bias against Viroxyn and benefiting Abreva makes the study conclusions all the more credible.

Disclosures and Acknowledgements

The authors would like to disclose the following duality of interest. James P McCarthy , the first author, works for the company that initiated both of the studies and developed one of the drugs compared, Quadex Pharmaceuticals LLC. None of the authors have any potential for financial gain from publication. This study was funded by Quadex Pharmaceuticals.

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Citation: McCarthy JP, Browning WD, Bowman JP (2013) Treatment of Herpes Labialis: Repetition of a Study Comparing Two OTC Drugs and Untreated Controls and Comparing the Outcomes of Each Study. Dentistry 4: 185. doi:10.4172/2161-1122.1000185