Pediatric Infectious Diseases Society of the Philippines Journal
Vol 15 No. 2 pp.2-9 July –December 2014
Martinez, RE, Samson, J. Efficacy of Citronella Shampoo for Head Lice

ORIGINAL ARTICLE

A DOUBLE BLIND RANDOMIZED CLINICAL TRIAL ON THE EFFICACY OF CITRONELLA SHAMPOO VERSUS 5% PERMETHRIN LOTION IN THE TREATMENT OF HEAD LICE INFESTATION

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The authors declare that the data presented are original material and have not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all the authors, who have met the requirements for authorship.

ABSTRACT

Background: Resistance to standard permethrin lotion has been reported. There is a continuing search for more natural and safe remedies for head lice infestation among children. Citronella, a natural repellant, has been reported as a pediculocide.

Objective: To compare the efficacy of Citronella shampoo versus 5% permethrin lotion in controlling head lice (*Pediculosis humanus capitis*) among children between 5-15 years old.

Methods: A double-blind randomized clinical trial was performed at the community outpatient department of MPI-Medical Center Muntinlupa Foundation, PNR (Phil. National Railway) Site Bgy. Putatan, City of Muntinlupa. Children living in areas endemic for head lice were screened, and if found positive, were randomized equally to daily citronella shampooing (CS) or permethrin lotion (PL). Subjects were manually inspected for adult lice or nits and ova on the 2nd, 7th, and 14th day of treatment. Chi-Square test was used to compare proportions, which considered p-values less than .05 as statistically significant.

Results: Eighty-two children with head lice were included in the final analysis. Children in both groups were comparable in terms of age, sex, family size with head lice, anthropometric measures, frequency of bathing and shampooing and baseline severity of head lice infestation. Citronella shampoo was as effective as the standard 5% permethrin lotion in eradicating head lice in children. The cure rates were comparable for day 2 (CS=65.1% versus PL=72.1%, p=.76), day 7 (CS=65.1% versus PL= 79.1%, p=.30), and day 14 (CS=81.4% versus PL=90.7%, p=.33) of treatment. There were no re-infestations and adverse reactions noted for the use of Citronella and the fragrance was more acceptable.

Conclusion: Citronella is as effective as Permethrin lotion in the eradication of headlice and Citronella shampooing can be an alternative natural remedy for pediatric head lice.

KEYWORDS:

citronella shampoo, permethrin lotion, Pediculosis humanis capitis, head lice, Cymbopogon nardus, Cymbopogon winterianus

INTRODUCTION

Head lice infestation caused by *Pediculosis humanus var. capitis* is a worldwide public health concern that affects mostly school-aged children. In the Philippines, the burden of disease is high at 54.7% in a population of primary school children with female predilection (66.5% versus 42.3% in males).[1]

Citronella is a volatile oil derived from the leaves and stem of the plant *Cymbopogon winteratus or Cymbopogon nardus.* Citronella oil has therapeutic potential because it includes antiseptic, deodorant, insecticide, parasitic, tonic, and stimulant properties. However, it may irritate the very sensitive skin and cause dermatitis. [12]

There were no local studies made regarding the pediculocide properties of Citronella, however we found only one clinical trial done on 2003 in Israel for 103 elementary school children ages 6-14. The study of Mumcouglu showed that after two to four months of spraying Citronella , once a day for six days, statistical reduction was noted when compared with placebo.[13] However, Mumcouglu's trial did not possess a permethrin (positive control) arm to ascertain the superiority of the test drug.

This study aims to document the pediculocide properties of Citronella *in vivo.* Head lice is a widespread problem among children and its treatment is relatively difficult especially for those who are in the lower income groups. Thus, a therapeutic regimen that is safe and affordable should be sought for. This study will provide scientific evidence of the effects of both permethrin lotion and Citronella oil-based shampoo in treating head lice. The rising cost of medicines nowadays, will teach health care practitioners to consider effective and safe alternative treatments for head lice.

METHODOLOGY

Study Design, Setting and Participants

This is a double-blind randomized clinical trial of standard 5% permethrin compared to citronella shampoo (laboratory formulation). The study took place at the MPI-MCM foundation PNR (Philippine National Railway) Site, Bgy. Putatan, Muntinlupa City. The study participants were apparently healthy children between 5 to 15 years old.

The study included children with head lice/nymphs infestation and had parental consent. We excluded those with seborrheic dermatitis, eczema and other scalp dermatoses, tinea capitis, open wounds, conjunctivitis and other eye diseases other than strabismus, and systemic illness (hepatic, renal, GIT, hematologic, pulmonary and neurologic).

Sample Size Estimation

The sample size of 19 per arm is required in order to estimate the absence of a difference (equivalence) in the cure rate between permethrin and citronella shampoo, (based on a previous finding of 90% and 40% respectively). This estimation rejected the hypothesis of non-equality with a 0.05 level of significance that yields a type 2 error of 20% and generates a study power of 80%. The modified POCOCK formula was used to compute the sample size, which was in turn estimated using the data from Mumcouglu's study that used 12% as the effectiveness rate at 2-months. The present study utilized 41 subjects per arm.

Randomization and blinding

Once the preliminary requirements were met, the physician thoroughly examined the patients' heads and performed a routine physical examination. Each patient received a randomly generated code that identified the patient until completion of the clinical trial.

Simple random allocation was performed for either Group A or Group B and was done by an

independent personnel who was also blinded to the drug assigned to each lettered code. The examining physician was not aware also of the coded assignments. The test drugs were also dispensed by an independent personnel. After randomization, a sealed envelope containing the group assignment was opened in front of the parents/ children and the test drugs were given. Parents were given identical small white containers so there will be no clue on the nature of the intervention drug.

Examination of head lice

Visual inspection

This method involved a brief examination of the hair by parting the hair in spots to determine whether live lice were present. Dry-combing was done in conjunction with this to determine active infestation with live lice.

Dry Combing

This involved using a metal-toothed head lice comb to run through from the scalp to the hair tips without using water or conditioner. The hair was de-tangled with a wide-gap comb before dry combing.

At baseline, dry combing was continuously done for 5 minutes until the adult lice and nymphs drop on a white cloth that had been prepared to catch the lice. Using a magnifying glass, a preliminary count was done to document burden of infestation. The rating utilized was based on the study by Jhanke et.al. [23]

If the hair was curly or frizzy and the lice comb cannot be used, the scalp was inspected by hand using a magnifying glass with a squared grid to count the adult lice, nits and eggs per square inch. A total of 5 square inches were examined before a final rating was established. A total examination time of 3 to 5 minutes per square inch was observed.

Figure 1. Arbitrary Rating for Severity of Head Lice Infestation.

Severity of Infestation	**Findings**
Grade 1 (Mild)	1-2 adult lice and or 1-2 nymphs , with or without eggs
Grade 2 (Moderate)	3 – 4 adult lice and or 2-4 nymphs , with or without eggs
Grade 3 (Heavy)	≥ 5 adult lice and or ≥ 5 nymphs , with or without eggs

*Jhanke et.al, Accuracy of Diagnosis of Pediculosis Capitis Visual Inspection vs Wet Combing, Arch Dermatol. 2009; 145(3):309-313

Wet Combing

Citronella shampoo was applied liberally on the hair. Using a metal toothed lice comb, every part of the hair was combed 6 times, from the scalp to hair tips. During combing, the comb was wiped onto a white tissue which was examined for lice. After combing, the citronella shampoo was rinsed off or removed using a towel, depending on the preference of the subject. Wet-combing is used to determine the final infestation status of a subject at the end of an efficacy trial. It is an effective detection technique because it uses oil to trap the lice, thus making it highly unlikely not to detect all lice. This decreases the likelihood of a subject being incorrectly categorized as louse free.

Combing and visual inspection was conducted at baseline, and on the succeeding 2nd, 7th, and 14th day of treatment at the health center while the principal investigator was present. Parents were given instructions on how to carry out the procedures and not to apply any other agent (oils, gels, and pomade or hair lotion) that will mask the effect of the two agents. Excessive combing was also discouraged to prevent injury to the scalp.

Citronella Shampoo

The test formulation contains a standard formulation of Lyecare Citronella shampoo manufactured by Swiss Pharma Research Labs. Inc, which was purchased from a local pharmacy. It is available in 10ml sachet (cost P18.00 pesos per sachet) which was repacked in small white container for easy dispensing to look identical to the permethrin shampoo. The Lyecare shampoo contains the following ingredients: Citronella oil, polyquatemum 7, aluminum lauryl sulfate and co- diethanolqmine (surfactants), methylchloro-isothiazoline, Methylisothiazo-linone, citric acid, diazolidinyl urea, Methyl-paraben and Propyl-paraben (preservatives), Disodium EDTA (stabilizer), Ammonium Chloride (thickening agent), Propylene glycol (moisturizer), Woodruff green (fragrance) and purified water

The test shampoo was applied once a day for two weeks. After combing, the parents were instructed to apply 10mL to 15 mL of the solution on the hair, depending on its length (more is required for lengthy hair) and to wash it off afterwards. After the first rinse, a second coat (10mL to15mL) was applied and was left on for 10 minutes prior to washing. No other oil, gel or hair lotion was applied during the trial.

Permethrin Lotion.

After combing, standard 5% permethrin lotion which is also commercially available in 30ml sachet (cost P94.60pesos per sachet) shall be given to the control arm after randomization. Thirty (30) mL of permethrin hair lotion was applied on the scalp and massaged for 10 minutes. The lotion should stay on the hair for a minimum of 45 minutes and then rinsed off. The hair was toweled dry and combed using a fine toothed lice comb before grading the severity. The permethrin lotion was given once a week on Day 1 and Day 8, for two consecutive weeks.

Co-interventions

All research subjects in the permethrin group received a hypoallergenic base shampoo (30) ml for free that they can use during the intervening days.

In case of severe itching, oral antipruritic agents like cetirizine di-hydrochloride were given.

Monitoring of Outcomes

Apart from the initial baseline assessment at the clinic, the subjects were asked to come to the clinic for the subsequent lice counting. Succeeding severity grading was done on the 2nd, 7th, and 14th day. The principal investigator declared the final outcome of each patient. Even if there was no nits adult lice, or egg seen on the patient as early as the 2nd day of treatment, the patient was still requested to come to the clinic for verification of findings. All adverse reactions were reported and recorded.

Endpoints

Cured – is the state when the child is declared free of adult lice, nits or eggs in any of the assessment days.

Failure of treatment – when on the 14th day, the combing still reveals either eggs, nymphs, or adult lice.

Re-infestation – when a previously declared cured patient still reveals nymphs, adult lice on the 7th day of observation.

Monitoring compliance to therapy

Subjects were given financial assistance to cover transportation expenses during clinic visits. The principal investigator required each subject to present the container of the Citronella shampoo or the Permerthrin lotion during the visit. Telephone calls were also made to check whether there was daily compliance to the treatment and to remind the subjects of their scheduled follow-up dates.

Provision for drop-outs and protocol violators

All subjects who dropped out were followed up in order to investigate the true reason for dropping out. Drop outs were those who, for any reason, decided to voluntarily withdraw from the study, and those who stopped the treatment because of adverse events.

STATISTICAL ANALYSIS OF DATA

MEDCALC biostatistical software was used to analyze data. Descriptive statistics included mean and standard deviation for continuous data while percentages were used to summarize categories. Chi-Square test was used for testing baseline homogeneity of categories and independent T-test for continuous numerical data. Comparison of cure rates between the two groups was expressed as proportions and compared using Chi-Square test. All p-values <.05 was considered statistically significant.

ETHICAL CONSIDERATIONS

This clinical trial conformed to the Declaration of Helsinki concerning the utilization of human subjects for clinical studies. All procedures, drugs, and tests were in accordance to the Code of Ethics of Good Research in Medical Practice of the World Health Organization (WHO). This clinical research was granted approval by the MPI-MCM Pediatric Department's technical and ethical review board.

RESULTS

A total of 86 patients met the inclusion criteria and were randomized to receive either citronella (n=43) or permethrin lotion (n=43.) Two from each group voluntarily dropped out. A total of 82 subjects were included in the final analysis.

Table 1. Baseline Profile of Children, Medical Center Muntinlupa, 2010.

Characteristics	Citronella *n, (%)*	Perme-thrin *n, (%)*	P-Value
Age			
4 – 5	4 (13)	5 (12)	.79
6 – 7	12 (29)	5 (12)	
8 – 9	6 (15)	9 (22)	
10 -11	8 (20)	11 (27)	
12 – 13	8 (20)	6 (15)	
14 – 15	3 (3)	2 (12)	
Sex			
Male	9 (22)	8 (19)	.68
Female	32 (78)	33 (81)	
Weight (mean ± SD)	23.7 ± 9.5	24.3 ± 8.1	.79
Height (mean ± SD)	124.01 ± 18.7	117.5 ± 32.1	.28
Education			
Pre-School	1 (2)	1 (2)	.65
Kindergarten	0	1 (2)	
Elementary	31 (76)	31 (76)	
High School	3 (7)	3 (7)	
None	6 (15)	5 (13)	
Number of Children			
1 – 3	21 (51)	15 (37)	.24
4 – 6	13 (32)	19 (46)	
7 – 9	2 (5)	4 (9)	
10 – 13	5 (12)	3 (8)	
Family members with head lice			
1 – 3	30 (74)	25 (61)	.27
4 – 6	5 (12)	11 (27)	
7 – 9	2 (5)	3 (7)	
10 – 13	4 (10)	2 (5)	
Frequency of Bathing (No. per Week)			
1	3 (7)	5 (12)	.51
2	8 (20)	4 (10)	
≥ 3	30 (73)	32 (19)	
Shampoo Use (No. per Week)			
1	3 (7)	1 (2)	.66
2	6 (15)	5 (12)	
≥ 3	32 (78)	34 (83)	
None	0	1 (3)	

**No significant difference- by Chi-Square Test, Independent T-test, p values>.05*

There was no statistically significant difference in both groups in terms of the age (p=.79), sex

(p=.68), mean weight (p=.79), mean height (p=.28), educational level (p=.65), number of children (p=.24), number of family members (p=.27), number of family members with head lice (p=.27), frequency of bathing (p=.51), and frequency of shampoo use (p=.66) (Table-1)

Severity of head lice infestation

Baseline severity ratings of head lice infestation were not significantly different between the two groups. A slightly higher percentage of children with heavy infestation were randomized to permethrin (67% versus 53%) while moderate infestation was seen more in the citronella group (33% versus 19%).

Table2. Baseline Severity of Head Lice Infestation, Medical Center Muntinlupa, 2010.

Characteristics	Citronella	Permethrin	P-Value
Grade I (Mild)	6 (14)	6 (14)	
Grade II (Moderate)	14 (33)	8 (19)	
Grade III (Heavy)	23 (53)	29 (67)	.31

**No significant difference, p>.05, Chi-Square test*

Monitoring of head lice infestation on the 2nd, 7th, and 14th day of treatment

The cure rates between citronella and permethrin lotion were compared on the 2nd (65.1% versus 72.1%, p=.76), 7th (65.1% versus 79.1 %, p=.30), and 14th (81.4% versus 90.7%, p=.33) day of treatment.

No head lice re-infestation was noted.

Table 3. Follow-up of Patients at Day 2 of Treatment Using Citronella versus Permethrin, Medical Center Muntinlupa, 2010

Group	Negative	Positive	Drop out	P-Value
Citronella	28 (65.1)	13 (30.2)	2 (4.7)	.76
Permethrin	31 (72.1)	10 (23.3)	2 (4.7)	

**No significant difference, p>.05, Chi-Square test*

Table 4. Follow-up of Patients at Day 7 of Treatment Using Citronella versus Permethrin, Medical Center Muntinlupa, 2010

Group	Negative	Positive	Drop-out	P-Value
Citronella	28 (65.1)	13 (30.2)	0	.30
Permeth-rin	34 (79.1)	7 (16.3)	0	

**No significant difference, p>.05, Chi-Square test*

Table 5. Follow-up of Patients at Day 14 of Treatment Using Citronella versus Permethrin, Medical Center Muntinlupa, 2010

Group	Negative	Positive	Drop-out	P-Value
Citronella	35 (81.4)	6 (14)	0	.33
Permethrin	39 (90.7)	2 (4.7)	0	

**No significant difference, p>.05, Chi-Square test*

Magnitude of effect size

Citronella, with a statistical post-hoc power of only 18.44%, did not prove to be more effective than permethrin in the eradication of head lice on 14th day of treatment (RR= 2.8, 95% CI 0.64-14.0).

Adverse reactions

Mild itchiness of the scalp and dandruff were noted on the majority of children (67%) who used permethrin. No such complications were noted among citronella users. Citronella was also more tolerable and acceptable in terms of odor and had no irritation on the scalp.

DISCUSSION

This study examined the efficacy of citronella shampoo in treating head lice infestation when compared to permethrin lotion. Initial results showed comparable efficacy in eradicating head lice, even as early as on the second day of

treatment, using adult lice, nymph and egg counts as parameters.

Two percent citronella formulation was utilized in this study since previous studies had shown that higher doses produced scalp irritation.[13] More recently, authors have suggested using a much lower concentration to lessen the odor and decrease the incidence of contact dermatitis. Other laboratory formulations added more fragrances to decrease this odor as well as the itching and burning sensation associated with citronella.[14]

The observation time for head lice eradication in this study was only two weeks. The study of Mumcouglu extended its observation to two months to document re-infestation brought about by continued exposure to an untreated source of head lice. However, we preferred to observe the outcomes at a shorter time frame since two *in vitro* studies had shown that the intrinsic repellant activity of citronella could last only for two days.[15-16] Other factors that can diminish citronella oil's repellent activity include continuous sunlight exposure, frequency of shampooing, high temperature, humidity, sweat and grooming. Since the Philippines is a tropical country this factors can contribute to Citronella oil's repellant activity if used for a longer duration.

Citronella shampoo was compared to permethrin lotion, the more recognized treatment for head lice in children. More recent studies, however, show rising incidence of high resistance to permethrin , thus the search for newer drugs is ongoing.[19-20] Unfortunately, overuse and misuse of permethrin have produced treatment-resistant lice. Parents who become frustrated by the continued presence of lice after treatment may further contribute to resistance by repeatedly applying over-the-counter treatments, using excess product, or applying product for longer periods.

Despite the benefits we observed with citronella, we still caution the public in the use of this herbal shampoo. Treatment failure with citronella may lead parents to resort to aggressive self-medication with more toxic agents and this repeated use of and improper application of pediculocides may potentially result in overexposure to pesticides resulting to toxicity in children.

CONCLUSION

Citronella shampoo is as effective as standard 5% permethrin lotion in the eradication of head lice in children between 5 and 15 years old. The cure rates were comparable on the 2nd day of treatment (Citronella=65.1% vs Permethrin = 72.1%, p=.76); 7th day (65.1% versus 79.1%, p=.30); and on the 14th day (Citronella = 81.4% versus Permethrin = 90.7%, p=.33). No re-infestation was noted in both groups.

No adverse reaction was noted in the use of Citronella and its fragrance was more acceptable.

RECOMMENDATIONS

Natural remedies for head lice like citronella are worth investigating. Comparisons with other herbal agents or citronella in combination with coconut oil may be investigated since coconut-oil-based shampoos have also been shown to be pediculocidal when compared with standard permethrin.[22] We also recommend observing re-infestation rates with citronella by extending the period of observation to at least one to two months.

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