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COMPARISON BETWEEN THE EFFECT OF TITANIUM DIOXIDE NANOPARTICLES AND IVERMECTIN ON HEAD LICE

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Abstract

Head lice cause social problems for patients as embarrassment, inflammation, skin irritation and secondary bacterial infection. Treating head lice is difficult because of development of resistance to drug. In this study, our aim was to evaluate the effect of titanium dioxide, Ivermectin and Ivermectin-loaded on Titanium dioxide nanoparticles on head lice in vitro. This study was conducted on 50 patients infected with head lice from Beni Suef Governorate. These patients were of all age groups and both sexes.

Patients were 13 males and 37 females, with ages ranged from 5 to72years (26.84±19.3). They were 34 rural residents, and 16 urban ones, 37 were at a low socioeconomic level and 13 at a moderate socioeconomic one. Number of family members ranged from (3 to 11) with an average of (6.42±1.9).

The results showed that mortality rate for topical Ivermectin (0.2% & 0.5%) was 86% & 94%, respectively, against adult head lice, while 88% and 94%, respectively, against nymphs.

Regarding the effect of Titanium dioxide, the percentage mortality effects of Titanium dioxide were 34, 58, & 100% at (2, 6, & 10 mg/L), respectively, against adult head lice, while Titanium dioxide mortality rate was 40, 68 & 96% at (2, 6 &10 mg/L), respectively, against nymphs.

Key words: Patients, Head lice, Ivermectin, Titanium dioxide

Introduction

Lice are parasitic insects that can be found on people's heads (*Pediculus h. capitis*), and bo-dies (*P. h. capitis*), including the pubic area (*Phthirus pubis*), were they survive on human blood, but differ from each other (Nana *et al,* 2017). The commonest symptom of a lice infestation is itching on scalp, neck and ears, as allergic reaction to louse bites. When a person has a lice infestation for the first time, itching may not occur for four to six weeks after infestation. Also, lice may be visible but are difficult to spot because they're small, avoid light and move quickly. Lice eggs (nits) stick to hair shafts. Incubating nits may be difficult to see because they're very tiny, as easiest to spot around the ears and the hairline of the neck. Empty nits may be easier to spot because they're lighter in color and further from the scalp. However, the presence of nits doesn't necessarily indicate an active infestation. Scratching can lead to small, red bumps that may sometimes get infected with bacteria (Pickering *et al,* 2012). Among the 3 human lice, body louse is a vector of infectious diseases, which lives and multiplies in clothes and human infestation is associated with cold weather and a lack of hygiene. It transmits 3 pathogenic bacteria: 1- Epidemic typhus fever caused by *Rickettsia prowazekii*, 2- Epidemic relapsing fever caused by *Borrelia recurrentis*, & 3- Trench fever caused by *Bartonella quintana*, or bacillary angiomatosis, chronic bacteremia, and lymphadenopathy (Morsy *et al,* 2001), as well as asthmatic bronchitis (Abou-Ghamra *et al,* 1992)

Lice parasitized man for millions of years and likely dispersed worldwide with human migrations out of Africa, as good markers to study human evolution (Boutellis *et al,* 2014). Lice infestations occur almost exclusively in vulnerable groups: school children, homeless people, refugees, and slum dwellers (prevalence 0.7% to 61% (Falagas *et al,* 2008). Head lice can be detected by looking closely by hair & scalp for nits, nymphs, or adults (Feldmeier, 2010). Louse comb was

preferred than visual inspection alone for sc reening head lice (Jahnke *et al,* 2009).

Different head lice treatments are available on the market, which can be divided into two broad categories, chemical and physical. Physical methods include combing with nit combs. These drugs as malathion, permethrin, benzyl alcohol, Spinosad**,** Lindane and Crotamiton. Other drug as Ivermectin is a semisynthetic derivative of one of the avermectins, a group of macrocyclic lactones produced by streptomyces avermitils. Ivermectin was approved by the FDA in 2012 for treatment of head lice in persons 6 months of age and older. It is not ovicidal, but prevented nymphs emerging.

The nanoparticles were used to treat head lice as titanium dioxide, with photocatalytic TiO2 antimicrobial effect reaction (Fujishima and Honda, 1972). Effectiveness of photocatalytic oxidation by UV irradiation was evaluated against many gram-positive bacteria (*Lactobacillus acidophilus*), yeast (*Saccharomyces cerevisiae*), gram-negative bacteria (*Escherichia coli*) & green algae (*Chlorella vulgaris*). Since then, many studied on photocatalytic disinfection were intensively carried out on a wide range of microorganisms such as viruses, fungi and many bacteria species (Verdier *et al,* 2014).

This study aimed to assess the effect of TiO_2 nanoparticles, Ivermectin® and ivermectin-loaded TiO_2 on head lice in vitro.

Subjects and Materials

This study was conducted on 50 patients infested with head lice who do not receive any treatment for at least one month from Beni-Suef Governorate. These patients were from all age groups and from both gender. They were selected from attendance of Beni-Suef University Hospitals. They were 13 males and 37 females (26% vs. 74%), with ages ranged from (5 to 72years) averaged (26.84±19.3). Patients (34) were rural residents and (16) urban ones (68% vs. 32%). The socioeconomic level was scored into middle, low and very low according to the family income. The samples were collected from April to October, 2019. Every patient was subjected to a medical questionnaire sheet.

Collection of head lice: Adults and nymphs were collected from all patients, with the approval of children's parents by raking a metal louse comb through the scalp sections. Lice were obtained by an earlier published procedure (Picollo *et al,* 2014). They were pooled by carefully removing them from the metal teeth of the comb into clean plastic boxes. Once collected, head lice were transported to our laboratory**.** The patients had not been treated with any pediculocide solution for at least the preceding month, using only the louse comb.

Titanium (Ti) isopropoxide, sodium carboxymethyl cellulose (Na CMC), sodium dodecyl sulfate was acquired from Sigma-Aldrich (St. Louis, MO, USA). Ivemectin was kindly provided by Amoun Company, Egypt. All other ingredients used were of analytical grade.

Synthesis of titanium dioxide (TiO_2) nanoparticles: A 7.4ml of titanium tetra isopropoxide was added, drop by drop, to 30ml of 1 M HNO_3 aqueous solution, and then agitated for 2 h to give a transparent solution, in which 2.0g TiO_2 were contained. The pH of the colloidal solution was adjusted to pH 3, with the addition of 1 M NaOH solution after dilution of the colloid with 100 ml water, resulting in a turbid TiO_2 colloid. The suspension was agitated at room temperature, centrifuged and then washed with distilled water. The isolated TiO_2 was dried for 1hr at 100°C in air. The resulted powder was calcinated 450°C for 3hr (Manivannan *et al,* 2008).

TiO_2 nanoparticles power were dissolved using double-distilled water according to the desired concentrations (2, 6, & 10mg/L).

Ivermectin suspensions: Ivermectin was used in two different concentrations; 0.2 & 0.5% w/v as follows: Ivermectin suspension (0.2% w/v) was prepared by dispersing in purified water containing 0.5% (w/v) of Na CMC, and (0.5% w/v) was prepared by disp-

ersing in purified water containing 0.5% (w/v) of Na CMC.

Conjugation of ivermectin to TiO_2 nanoparticles: Ivermectin-loaded TiO_2 nanoparticles were prepared by adding TiO_2 nanoparticles (10mg/ml) to ivermectin in dichloromethane (Concentration= 0.2 or 0.5% 0.5% w/v) in mass ratio of 1:1.5, and stirred for various times at room temperature.

Particle size analysis and Polydispersity index (PDI): Particle size and PDI were determined by dynamic light scattering (Zetasizer Nano ZS, Malvern instruments, Malvern, UK) at an angle of 90° in 10mm diameter cells at 25°C. Before size measurement, 1 milliliter from each formulation was diluted with 10ml distilled water to a suitable scattering intensity (Aboud *et al,* 2018).

In vitro application: Fifty of each of adults and nymphs were used in each concentration, side by side with controls in distilled water. Each louse was carefully transferred into a glass dish, and 0.02ml of tested samples was topically applied using a micrometer syringe (Morsy et al, 2000), and then louse was transferred into a filter paper lined Petri-dish put in a dark chamber at 26±0.5°C & 70±1% humidity for 24hrs under close observation using hand lens. Died ones were verified by motility cessation and/or appendages waggling on fine needle touch (Oladimeji *et al,* 2000).

Ethical considerations: Protocol was approved by Faculty of Medicine Ethical and Research Committee. An informed consent was taken from patients prior to study.

Statistical analysis: Data was coded, entered and analyzed using Microsoft Office Exc el 2010 & Statistical Package for Social Sciences (SPSS). Quantitative variables were described using M±SD using frequency and percentage. Chi-square tested the significance level where $P < 0.05$ was significant.

Results

TiO_2 nanoparticles and ivermectin-loaded TiO_2 nanoparticles gave successfully results with divulged formation of low polydispersity indices (PDI) small sized. TiO_2 nanoparticles were 15.89±2.31nm, & 26.97±3.45 nm for ivermectin-loaded TiO_2 nanoparticles. PDI values were 0.129 for TiO_2 nanoparticles & 0.215 for ivermectin-loaded TiO_2 nanoparticles. The patients (37) were of low socioeconomic level and (13) mode- rate socioeconomic one (74% vs. 26%), and family members were 3 to 11 (6.42±1.9).

Details were given in tables (1 & 2) and figures (1, & 2).

Table 1: Percentage of died Lice by drugs:

Pediculicide		Nymph		Adult		
		No.	%	No.	%	
Ivermectin	0.2%	44	88.00	43	86.00	0.500
	0.5%	47	94.00	47	94.00	0.661
	2 mg/L	20	40.00	17	34.00	0.339
Titanium dioxide TiO_2	6 mg/L	34	68.00	29	58.00	0.204
	10 mg/L	48	96.00	50	100.00	0.247
TiO_2 10mg/L-Ivermectin	0.2%	46	92.00	47	94.00	0.500
	0.5%	48	96.00	50	100.00	0.247

Drug on head lice showed that the best result was by TiO_2 (10mg/L) and ivermectin (0.5%)-loaded TiO_2 nano-particulate (10mg /L) with 100% died adults and 96% died nymphs. Lowest efficacy was with TiO_2 (2 mg/L). All control lice survived during the study period. By increasing the drug concentration, the lice (adults and nymphs) died percentage increased, with significant moderate positive correlation between TiO_2 concentrations & died lice % ($r= 0.526$, $P = 0.001$). Correlation between ivermectin doses and TiO_2 10mg/L-ivermectin was non-significant.

Table 2: Drug concentrations and died lice %:

Drug concentration	R	p-value
Ivermectine	0.119	0.092
TiO_2	0.526	0.001*
TiO_2 10 mg/L ivermectine	0.121	0.089

*P-value ≤0.05 significant

Discussion

The control of pediculosis is a very ancient concern and different ways have been used to combat it. Removal of lice by hands or with a lice comb and shaving scalp were some of the oldest methods of human lice control (Pajot *et al,* 2000). Despite the introduction of other resources as chemicals and insecticides, the numbers of lice infestation cases and resistance have increased (Sangare *et al,* 2016). Chemical methods of treatment include topical treatments (herbal treatments and chemical ones as pyrethrins, permethrin, carbaryl, lindane, and malathion as well as oral ones as Ivermectin and cotrimoxazole. Topical treatments are by far the most common initial method of treatment of head lice infestation (Salavastru *et al,* 2017).

As regarding the effect of Ivermectin, other studies agreed with the present one, Pariser *et al.* (2012) who studied the effect of single application of 0.5% Ivermectin lotion for the elimination of infestations without nit combing in patients 6 months age or older, mortality adult head lice by topical ivermectin on day 2 (94.9%). Deeks *et al.* (2013) studied pharmacology, pharmacokinetics, efficacy, & adverse action of a single topical ivermectin 0.5% lotion for head lice found that patients were lice-free after 2 weeks.

Meinking *et al.* (2013) studied the effectiveness of ivermectin lotion concentrations (0.15, 0.25, & 0.5%) compared with vehicle placebo in eliminating head lice infestation. Evaluations were completed at two and six hours post-application, on days 2, 8 (±1), and 15 (+2). All ivermectin concentrations resulted in significant ($P \leq 0.003$) eradication of head lice through day 15, with the highest level of eradication (73.7%) in subjects who received the 0.5% concentration. All three ivermectin treatment strengths and vehicle were well tolerated. Also, Ahmed *et al.* (2014) compared the efficacy and safety of topical versus oral ivermectin in treatment of pediculosis *capitis*, found that a week after treatment, the eradication rates and improvement of pruritus were significantly higher among patients who received topical than oral ivermectin. When a second treatment, topical or oral was given to the non-responders, the infested cure rates and pruritus were 100% & 97% among those treated with topical and oral ivermectin, respectively without significant difference between both groups.

The present result of TiO_2 on head lice agreed with Rajakumar *et al.* (2014) who assessed the peddiculidial efficacies of synthesized TiO_2 nanoparticles against adult *P. h. capitis*, and showed 31, 42, 63, 82, & 100 mortality% at 2, 4, 6, 8, & 10mg/L respectively. This study may provide the first report on the pediculocidal activity of synthesized TiO_2 nanoparticles. This is an ideal eco-friendly, novel, low-cost, and simple approach to satisfy the requirement of large-scale industrial production bearing the advantage for the control of head lice**.**

The other study was carried out to establish the pediculocidal activity of synthesized TiO_2 nanoparticles against the head louse. The maximum activity was observed in the synthesized TiO_2 nanoparticles against lice, ($LC50= 24.32$ mg/L,$r^2= 0.924$). The findings revealed that the synthesized TiO_2 nanoparticles possess excellent anti-lice activity. Synthesis of TiO_2 nanoparticles was used as an ideal agent for head lice control (Rajiv Gandhi *et al,* 2016).

The FDA approved titanium dioxide pigment safety as a color additive in food, drug, and cosmetic applications (Lu *et al,* 2015). But, Kawasaki (2017) in Japan reported that chronic titanium dioxide exposure caused a slight but significant pulmonary inflammation in experimental animals, and among potential mechanisms. Aranha *et al.* (2020) in USA added that TiO2 nanoparticles found in an array of consumer and industrial products, and that human exposure to them caused interaction with biological membranes

Conclusion

Head lice treatment is must for infested persons. All household members and close contacts must be checked; those persons with evidence of an active infestation must be tre-

ated. Some experts believe prophylactic treatment is prudent for persons who shared the same bed with actively-infested ones. All infested persons (household members, and any close contacts) and their bedmates must be treated at the same time.

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Explanation of figures

Fig. 1: Particle size distribution curves of (a) TiO_2 nanoparticles and (b) ivermectin-loaded TiO_2 nanoparticles.

Fig. 2: Correlation between medications concentrations and died lice%.