

RESEARCH ARTICLE

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Efficacy of Oral Zinc Sulfate Supplementation on Clearance of Cervical Human Papillomavirus (HPV); A Randomized Controlled Clinical Trial

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Abstract

Aim: Human Papillomavirus is one of the most crucial infectious disease in gynecology disease. To assess the efficacy of supplemental zinc treatment in clearance of HPV infection. **Methods:** Eighty zinc-sufficient women between 21-55 years, with positive HPV DNA testing, and abnormal cervical cytology in Pap test (ASCUS or LISL) were randomly divided to case (n=40) and control group (n=40). Case group received oral tablets of zinc sulfate twice a day for 3 months while control group received no placebo. During follow-up patients underwent repeat HPV DNA test and PAP test and were evaluated for clearance/persistence of HPV infection and regression/progression in the lesion grading. **Results:** As far as demographics, serum zinc levels and the relevant risk factors for persistence of HPV were concerned, there was no significant difference between two groups, except for the frequency distribution of HR-HPV which was significantly higher in case group. Zinc treatment for 3 months reduced the risk of persistence of HPV infection and progression from baseline cytology (OR = 0.130) (CI 95% 0.04-0.381; p <0.001) and 0.301 (95% CI 0.777-0.116; p = 0.012), respectively. Age, initial cytology, HPV type, and contraceptive method were not related to persistence of HPV. Serum zinc levels increased in the case group as a result of oral zinc consumption for 3-month period, though without any statistical significance (p = 0.407). **Conclusion:** The results of the following study suggested that oral intake of zinc sulfate supplement for 3 months increases the rates of HPV clearance and resolution of pre-existing cervical lesion.

Keywords: Zinc Sulfate- Supplementation- Human Papillomavirus- Uterine Cervical Neoplasm- Trace Elements

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Introduction

Persistent infection with human papillomavirus (HPV) is the leading cause of virtually all types of cervical neoplasms which comprises the second most prevalent neoplasm of women between 15 and 44 years (Pirog et al., 2000; Arbyn et al., 2020). Although the massive scale-up of vaccination and screening efforts led to significant reduction in the disease burden in developed countries, cervical neoplasms seems to remain as a major health concern in developing communities for a long time (Arbyn et al., 2020). While more than 100 serotypes of HPVs have been isolated, severe types of HPVs (HR-HPV; 16, 18, 31, 33 and 45) were found to be associated with 99% and 20% of carcinomas of genital tract and oropharynx respectively (Muñoz et al., 2003). The majority of patients develop transient HPV infection which is characterized by clearance of virus by host immune system within 12-24 months, however in rare cases, chronic infection with certain HR-HPVs (particularly 16 and 18) leading to intraepithelial dysplasia and subsequently full-blown neoplasm (Münger et al., 2004; Shanmugasundaram and

You, 2017). Determinants of viral infection persistence have been focus of numerous studies aiming to unravel potential contributors in clearance of HR-HPV and progression of present lesion to higher- grade of CIN (Liu et al., 1995).

The potential relationship between imbalanced trace elements and various malignancies, cervical cancer in particular, has been recently investigated (Cunzhi et al., 2003; MeGhana et al., 2019). Among several antioxidants and minerals, studies on the regulatory role of serum zinc level in immune response induction, tumor microenvironment, oxidative stress modulation and redox hemostasis has been investigated in recent decades. Use of different zinc formulations against recurrent herpes labialis (Femiano et al., 2005), low-risk HPVs (LR-HPV) in warts (Simonart and de Maertelaer, 2012), respiratory papillomatosis (Gallagher and Derkay, 2009), frank parasitic infection in cutaneous leishmaniosis (Sharquie et al., 2001) and an immune-mediated complication of leprosy (erythema nodosum leprosum) (Mahajan et al., 1994) has yielded promising results which is attributable to immunomodulatory characteristics of zinc.

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At cellular scale, cervical neoplastic cells tend to have lower intracellular zinc levels and are fully capable of compensating for intracellular depletion of zinc via accelerated uptake of zinc from environment upon addition to cell culture medium (Bae et al., 2017). A certain preparation of zinc citrate has been found to induce apoptosis in cervical neoplastic cells via both p-53 dependent and independent pathways. Additionally, zinc citrate has been demonstrated to considerable decrease expression of E6-E7 peptide in HPV-infected cells (Bae et al., 2017). While zinc deficiency intuitively induces host defense mechanisms, when compared to patients with lower grade CIN, individuals with higher grade CIN are found to have lower serum zinc levels though unnecessary becoming zinc deficient. Similarly higher serum zinc levels have been found to be protective against cervical dysplasia progression in HPV positive patients (Grail and Norval, 1986; Liu et al., 1995; Xie et al., 2018). It is probably due to the rapid zinc intake in growing malignant cells, as zinc is an essential element for maintenance of cell membrane integrity (Naidu et al., 2007). An increase in serum trace elements (selenium and zinc) has been also reported among patients with cervical cancer after undergoing chemotherapy (Subramanyam et al., 2013). Aforementioned evidences set the rationale to seek for clinical trials where supplementary zinc salts are administered to subjects without zinc insufficiencies, while taking caution not to cause toxicities. Present study has been designed to determine efficacy of supplemental zinc sulfate in shortening the duration for clearance of HR-HPVs.

Materials and Methods

The study protocol was approved by Ethical board under code: IR.UMSU.REC.1397.366. The present randomized clinical trial study was in accordance with CONSORT guidelines (IRCT code IRCT20210407050882N1). Sample size was calculated based on the prevalence estimates by Keem et al (52%) (Allameh et al., 2012). Assuming the previously reported odds ratio (OR) of 0.07 (95% CI 0.03-0.16) from a pilot study (Kim et al., 2011), where patients treated with intravaginal zinc citrate solution were less likely to develop persistent HR-HPV infection, a total of 80 subjects would detect a significant effect with 80% power ($\alpha=0.05$).

From October to December 2018, HPV infected women aged between 21- 55 with abnormal Pap test presenting to gynecologic oncology clinic of Motahari hospital in Urmia, Iran, the study participants were selected randomly. Inclusion criteria were having a positive HPV DNA test (PCR) and a Pap smear cytology report of either ASCUS or LSIL. Patients with abnormal serum zinc levels, ongoing pregnancy, breast feeding, immunocompromised state diagnosis and prior history of cone biopsy were excluded from the study. Informed written consent was obtained from each of the participants. Demographic details were recorded and the history of tobacco and OPC consumption were evaluated. Finally eligible subjects were randomly assigned to intervention (n=40) versus control (n=40) groups. Intervention group

was instructed to take oral zinc sulfate tablets (220 mg, every 12 hrs.) for three months while control group received no treatment and were asked to revisit the clinic in 3 months. Both groups were checked for their serum zinc levels at start and the end of study, which is before the start of zinc supplement and 30 days after the last dose of zinc for the intervention group. None of the patients were lost to follow-up. Persistence of HR-HPV infection was evaluated at the conclusion of follow-up with all of patients undergoing HR-HPV DNA testing as well as HPV genotyping if applicable.

Statistical analysis

Proportions of nominal variables between two groups of treatment and control were compared using Chi-square test or Fisher's exact test, when indicated. Like-wise numerical values were compared with application of independent t-test or its nonparametric equivalent, as appropriate. Data obtained before and after treatment were analyzed with paired t-test or paired samples. Logistic regression analysis was conducted to predict odds of HPV clearance in association with zinc treatment and other variables. Statistical analysis was carried out using IBM SPSS Statistics for Windows (Version 16.0. Armonk, NY: IBM Corp) and findings with p-values less than 0.05 were regarded to be statistically significant.

Results

Demographics and clinical characteristics of 80 patients are summarized in Table. 1 under two divided groups of intervention and control. Mean age and contraceptive method did not differ significantly between two groups (in respect of order: independent t-test; p-value=0.436 and chi-square; p-value=0.105).

Intervention group had a higher gravidity when contrasted with control group (independent t-test; p-value=0.038) which translates into a skewed distribution of gravida among two groups. Same pattern was present in terms of distribution of HR-HPV versus LR-HPV between two groups of patients. Ninety- five percent of individuals (n=2) in the intervention group were infected with HR-HPVs and in only 5% of them (n=2) HPV infections were confined to LR-HPVs. Conversely in the control group, 27.5% (n=11) were solely infected with LR-HPV subtypes and HR-HPV DNAs were detected in 72.5% (n=29). Kolmogorov Smirnov test revealed that the frequency distributions of HR-HPV and LR-HPV were not normal between two intervention and control groups (p-value<0.001).

The disclosed difference in frequency proportions of each cervical pathology among intervention group (35 ASCUS; 5 LISL) versus control group (32 ASCUS; 8 LISL) did not bear any statistical significance (chi square; p-value=0.546). However, after 3 months the frequencies of cytology changes was no longer statistically negligible (chi-square; p-value=0.038) (Table 1).

According to the results of repeat pap tests in 3 months, cytology regression rate in the treatment group (n=21) was remarkably higher than that of control group (n=10) (chi-square; p-value=0.021). In the zinc-treated group 20 cases

Table 1. Baseline and Follow- up Characteristics of Patients in Treatment and Control Group

		Total (n=80)	Intervention group (n=40)	Control group (n=40)	P-value
Age, Mean (SD)		38.6	39.4 (8.7)	37.92 (8.05)	0.436
Gravida, Mean (SD)		2.35	2.65 (1.05)	2.05 (1.44)	0.038
Contraception,	Natural	30(37.5%)	11(27.5%)	19(47.5%)	0.105
Frequency (% of column)	OCP	26(32.5%)	14(35%)	12(30%)	0.105
	IUD	13(16.2%)	10(25%)	3(7.5%)	0.105
	DMPA	11(13.8%)	5(12.5%)	6(15%)	0.105
LR-HPV, Frequency (% of column)		13(16.2%)	2 (5%)	11 (27.5%)	0
HR-HPV, Frequency (% of column)		67(83.8%)	38 (95%)	29 (72.5%)	0
Cervical cytology (Pap test); Baseline	ASCUS	67(83.8%)	35(87.5)	32(80%)	0.546
	LISL	13(16.3%)	5(12.5%)	8(20%)	0.546
Cervical cytology (Pap test); Follow-up	NL	31(38.7%)	21(52.5%)	10(25%)	0.038
	ASCUS	37(46.3%)	15(37.5%)	22(55%)	0.038
	LISL	12(15%)	4(15%)	8(20%)	0.038
Serum Zinc	Baseline	86.6	86.7(9.2)	86.5 (8.9)	0.91
Mean (SD)	Follow-up	87.95	89.2(8)	86.7(8.5)	0.187
	Variation	1.35	2.5(13.5)	0.2(10.6)	0.407
HPV cleared in F/U		29(36.2%)	23(57.5%)	6(15%)	0
HPV persisted in F/U		51(63.8%)	17(42.5%)	34(85%)	0

Table 2. Rate of Cytology Regression in Treatment Group is Significantly Higher than Control Group

Baseline Cytology		Cytology in Follow- up Pap test				Frequency of regressed pathology	P-value
		NL	ASCUS	LISL	HISL		
Intervention Group (n=40)	ASCUS	35	20	15	0	21/40 52.50%	0
	LISL	5	1	0	4	0	0
Control Group (n=40)	ASCUS	32	10	22	0	1/4	0
	LISL	8	0	0	8	25%	0

of ASCUS and one case of LISL were reported as normal cytology at the follow-up. Whereas among the controls only 10 initial pathology of ASCUS had resolved back to normal (Table 2). A regression in baseline cytology in repeat Pap test was more frequently encountered among zinc-treated patients than the controls (OR= 3.316; 95%CI 1.286-8.550; p-value= 0.012).

After 3 month follow-up, evaluation of zinc-treated subjects for HPV infection status and cervical pathology demonstrated clearance of HR-HPV infection in 23 patients (57.5%) versus persistence of HR-HPV infection in 17 patients (42.5%). On the other hand, control group suggested spontaneous clearance of HPV in only 15% (n=6) while 85% (n=34) remained unresolved. This observed difference in the rates of HPV clearance was statistically appreciable among the groups (McNemar test; p-value<0.001). Neither age nor contraceptive methods were statistically related to the clearance of HPV in the zinc-treated group (independent t-test; p-value=0.87 and Fisher's exact test; p-value=0.59).

While comparing two groups, no statistically difference was reported in terms of mean serum zinc level before intervention (independent t-test; p-value=0.91), after intervention (p-value=0.187) and serum zinc

variations during the three-month period (p-value=0.407). Association between correlated independent variables and persistence of HPV (as dependent variable) was analyzed using logistic regression analysis one at a time; zinc treatment was found to markedly decrease the risk of persistent HPV infection (OR= 0.130; CI 95% 0.04-0.381; p-value<0.001). Moreover, initial cytology of ASCUS reduced the risk of HPV persistency (OR=0.103; 95%CI 0.013-0.836; p-value=0.012) (Table 3).

Discussion

Protective role of dietary essential elements against

Table 3. Applying Logistic Regression Yielded that Zinc Treated Patients are 0.13 Times Less Likely to have Persistent HPV Infection after 3 Months

Independent Variable	OR	95% CI	p-value
OCP	0.868	0.330-20.833	0.775
Cytology			
ASCUS	0.103	0.013-0.836	0.012
LSIL	9.73	1.196-79.142	0.012
Zinc Supplementation	0.13	0.04-0.381	<0.001

carcinogenesis, particularly in pathogenesis of cervical neoplasm, are becoming somewhat approved in several studies which emphasize on the antioxidant activity and immunomodulatory characteristics of these trace minerals (Borges et al., 2018; MeGhana et al., 2019; Obhielo et al., 2019; Sreeja et al., 2019; Barchitta et al., 2020). Moreover, zinc is proved to exert distinctive antiviral activity against a handful of viruses (Read et al., 2019) including but not limited to RSV (Suara and Crowe, 2004), HSV (Arens and Travis, 2000), HIV-1 (Haraguchi et al., 1999) and HPV (Gibbs, 2003). However, in the absence of frank zinc deficiency, sever enough to hinder the ability of immune cells to fight against infection, the benefits of zinc supplementation are yet to be elucidated. According to a systematic review conducted by Simonart et al., (2012) due to the fundamental heterogeneity in study designs, only a limited evidence is so far available to support significance of the highly debated effect of zinc in treatment of cutaneous and anogenital warts (Kanelleas and Nicolaidou, 2015).

Barchitta et al., (2020) conducted a cross-sectional study on 251 Italian women with normal cervical cytology and concluded that participants with higher zinc and dietary antioxidant intake have lower odds of infection with HR-HPVs (OR = 0.46; 95% CI = 0.27–0.80; p-value = 0.006).

In a cross-sectional study of Okunade et al. on 50 case of cervical SCC, serum zinc and selenium was found to be substantially lower in women with invasive cervical cancer rather than 100 cancer-free controls (Okunade et al., 2018). An uncontrolled study of 28 patients with HR-HPV has suggested that serum levels of inflammatory cytokines (IL-1, IL-12) decrease in response to 3 months oral zinc sulfate treatment (Fadhil et al., 2017). There is a case-report of successful treatment approaches of cervical adenocarcinoma in a pregnant patient with vaginal infusion of zinc citrate, who was willing to continue pregnancy (Choi et al., 2006).

In a comparison of 144 patient with CIN against 53 control, made by Atoe and Peter, serum zinc and antioxidant levels were revealed to be markedly lower among the cases with higher grades of CIN (Atoe and Peter, 2019). Meta-analysis of data from 12 articles has demonstrated an appreciable association between level of serum zinc and risk of developing cervical cancer among Asian women (Xie et al., 2018).

Following the radiosurgical treatment approaches in HPV infected patients, administration of a zinc sulfate and usnic acid preparation, as an adjuvant therapy, has been found to considerably decrease the risk of recurrence in 75 patient compared to 50 controls (Scirpa et al., 1999).

The present trial on 80 HPV infected women with abnormal Pap teste (confined to ASCUS or LISL) revealed that oral zinc sulfate is associated with higher rates of HPV clearance and regression of cervical pathology. While our findings confirm the effectiveness of zinc in shortening of time to clearance of HR-HPV, demonstrated in the pilot study of 2011 (Kim et al., 2011), for a real concrete change to take place in grading of CIN, follow-up for longer time periods would be required. In the study conducted

by Kim et al., (2011) much the same target group was addressed (women with documented positive HPV DNA test, ASCUS/LISL in Pap smear and colposcopy). A certain commercial preparation of zinc citrate solution (0.5 mM) was administered topically in the form of vaginal douche with an application frequency of twice a week for 3 months. Although their study was designed in retrospective framework, 76 zinc- treated patients were compared against 118 controls in terms of persistency rate of HPV and cervical cytology regression. They reported higher rates of HPV clearance in the treatment group (64.47%) versus spontaneous clearance in the control group (25.51%) (p-value <0.001). Collectively, they concluded that intravaginal infusion of zinc citrate reduces the risk of persistent HPV with an odds ratio of 0.079 (95% CI 0.039–0.165, p-value<0.001). After 12 weeks, they found a regression in cervical cytology in 51.8% versus 45.3% of treatment group and control group, respectively. In regards with LISL lesions, 44.6% of treated patients had a normalized cytology at the follow-up while only 21.4% of controls underwent such a resolution (p-value= 0.182). On the whole, findings of two studies are in complete agreement.

Prevalence of different subtypes of HR-HPVs in our study were in an acceptable accordance with data available from local population studies. Analysis of 1930 CIN specimens obtained from Yangtze River delta area, found types 16, 52, 58, 18, and 33 to be the most common types responsible for infection (Wang et al., 2018). Over the half of patients in our study were infected with type 16 (55%) and the 2nd most common HR-HPV were type 18 (11.3%) and 31 (11.3%) followed by types 33(6.3%), 56 (5%), 39 (3.8%), 35 (2.5%), 58 (1.25%) and 68 (1.25%). A fraction of cases was simultaneously co-infected with LR-HPVs; type 6(20%), type 11(6.3%), 43(2.5%), 52(6.3%), 53(1.3%), 54(7.5%), 55(1.25%), 66(2.5%), 73(1.25%), 82(2.5%).

Pingarrón et al., (2019) carried out a prospective controlled study, in which HPV infected patients who were treated with a certain commercial zinc-containing formula for six months (n=73) had higher rates of HPV clearance and regression of pre-existing lesions than the controls (n= 45). Similarly, patients with initial normal cytology who were tested positive for HR-HPVs were less likely to develop new intracervical lesion in the treatment group (pre-print). However, due to the fact that zinc is just one of the several ingredients of this multivitamin-mineral formula, the mentioned protective effect cannot be solely attributed to the zinc ion.

Despite these findings, our study has some limitations. As current study was limited in terms of its small sample size and short follow-up period, conduction of larger multi-center studies are required to further elucidate exact preventive and therapeutic effects of zinc in HPV infection with different oncogenic subtypes. The fact that control arm did not receive any placebo and hence concerns inherent to its unblinded nature are additional reasons to pursue well-designed clinical trials on this topic.

In summary, present study suggested that oral zinc sulfate supplementation for three months increases

the odds of clearance of HR-HPV infection as well as regression in cervical cytology.

Abbreviations

Human papilloma virus (HPV); high-risk HPV (HR-HPV); Cervical intraepithelial Neoplasia (CIN); Atypical squamous cells of undetermined significance (ASCUS); Low-grade squamous intraepithelial lesion (LSIL); Polymerase chain reaction (PCR); loop electrosurgical excision procedure (LEEP); Intra-uterine device (IUD); Depot medroxyprogesterone acetate (DMPA); Respiratory syncytial virus (RSV); Herpes simplex virus (HSV).

Author Contribution Statement

HA: Conceptual design, methodology, and supervision. ER: Data collection, data analysis, manuscript draft, ZY: Conceptual design, supervision, and scientific revision, ZJ: Data curation, Data interpretation and write-up. All authors reviewed the manuscript and contributed intellectually. The final manuscript was approved by all authors.

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Funding Declaration

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Ethics approval and consent to participate

This study was approved by the Research Ethics committee of Urmia University of Medical Sciences under the code IR.UMSU.REC.1397.366.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

Study registration

Registration of current trial protocol under the scientific name of "Efficacy of Oral Zinc Sulfate Supplementation on Clearance of Cervical Human Papillomavirus (HPV); a Randomized Controlled Clinical Trial" has been approved in Iranian Registry of Clinical Trials at under registration reference code of IRCT20210407050882N1.

Competing interests

Authors declare no conflict of interests.

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