Original Article

Comparative study of levamisole-selenium supplementation effect on CD4 increase in HlV / AIDS patients

Feizollah Mansouri(MD) [1]
Alireza Janbakhsh(MD) [*1]
Siavash Vaziri (MD) [1]
Babak Sayad(MD)1
Mandana Afsharian(MD) [1]
Farzaneh Hosseinpor (MD) [1]
Behzad Mahdavian (MD) [1]

1- Department of Infectious Diseases, Kermanshah University of Medical Sciences Kermanshah, Iran.

*** Correspondence:**
Alireza Janbakhsh, Associate Professor of Infectious Diseases, Kermanshah University of Medical Sciences, Kermanshah, Iran

E-mail: a_janbakhsh@yahoo.com
Tel: 0098 831 4276315
Fax: 0098 831 4276315

Received: 30 May 2011
Revised: 10 June 2011
Accepted: 17 June 2011

Abstract

Background: *Given to the abundant incidence of malnutrition in HIV$^+$ patients and its effect on progress of AIDS disease, several studies have recommended supplementation therapy (such as Selenium, Levamisole, Zinc).*

Methods: *This clinical trial was prefunded on patient's with HIV + in Behavior Diseases Consulting Center, Kermanshah, Iran 2006-2007. One hundred-seventy eight out of all patients with CD4 1ess than 350 cell/mm^3 who did not receive antiretroviral drugs were in this study. They were divided into four groups: the first group received 200 micg selenium per day, the second group received levamisole 50 mg every other day, and third group received both two drugs. The fourth group was the control group. All four groups were studied for six months. Patients' baseline CD4 and other data were recorded in a form. CD4 was rechecked after six months and collected values were compared with basic values. CD4 changes were compared among all groups, either.*

Results: *One hundred-seventy eight patients initiated treatment and 108 cooperated in the 6-month follow up assessment. Niuety-two (85%) were males and 15% were female. CD4 decreased in control group and Levamisole group during the study which was significant, but 13 units increase was seen in Selenium-Levamisole group. CD4 count decreased 36 units in Selenium group. Comparing CD4 count change among 4 study groups showed that only CD4 change between Selenium-Levamisole group and control group was significant.*

Conclusion: *Regarding to collected results, Selenium-Levamisole supplementation can be used as a supplementation therapy besides antiretroviral therapies.*

Key words: *HIV, CD4, Levamisole, Selenium, Kermanshah.*

Caspian J Intern Med 2011; 2 (2): 218-221.

Diagnosing malnutrition and nutritional management principles are considered as an important aspect of primary health care in patients with HIV/AIDS. Generally, weight loss more than 5% may lead to disease progress, dysfunction and increasing of mortality. Despite the advances in anti retroviral treatment in HIV patients, different types of malnutrition have a high incidence among these patients (1). Consuming supplementation therapy during all HIV steps can prevent the effects of malnutrition on patient's immune system. Selenium is an essential trace mineral which its deficiency is observed during different stages of HIV infection and its lower serum concentration predicts mortality for infected adults and children and has been linked to enhanced viral virulence, diminished natural killer cell and increased replication of HIV virus (2). In vitro inoculation of HIV infected monocytes with Selenium suppresses HIV-1. replication (3). Despite normal nutrition, taking Selenium supplementation 200µ/day improves immune functioning (1). A study has shown that Selenium consumption with this dose, does not have any serious side effects (2).

Levamisole can increase chemotactic effect of macrophage and T lymphocyte function. Nowadays, regarding to immunomodulatory and antiviral activity, Levamisole is used in treating of HIV patients. Recommended dose in HIV patients was 50mg every other days or 2.5mg/kg/w but intake duration is not mentioned exactly. It is recommended to take it before patient's entrance to AIDS stage (4).

In a study, 50 HIV-infected patients received 50mg Levamisole every other day for six months, opportunistic infection occurrence rate was 5% VS. 34% in control group and progression to AIDS was 14% VS. 60% in control group (5). A double blind, randomized trial prefunded on HIV infected patients who received 200µg/day Selenium for 9 months. No related adverse event was observed. 150 unit increase in CD4 count and decrease in viral load was seen. The results of this study support the use of Selenium as a simple, inexpensive and safe adjunct therapy in HIV spectrum disease (2). This present study aims to assess Levamisole and Selenium on CD4 count and decrease of mortality and opportunistic infections in HIV infected patients. Levamisole and Selenium have few side effects and different studies have supported their effect on improving the function of cell-mediate immunity but no study is available to show the simultaneous intake effect of these two drugs. Because there was not any interaction between the two drugs that have been reported, therefore, concomitant prescription of them may increase length and quality of life and decrease rate of opportunistic infections in HIV infected patients and probably inhibit progression of infection to AIDS.

Methods

In this clinical trial which was conducted on HIV/AIDS patients in a convenient sampling method in Behavior Diseases Consulting Center, Kermanshah, Iran 2006-2007, 140 cases were included. Inclusion criteria were: HIV infected patients who were over 20 years old and did not receive antiretroviral drugs, with CD4 count <350. They had no other opportunistic infection or malignancy except for HIV. After the approval of the Ethics Committee and signing of the informed consent, the participants were divided into 4 groups as follows:

1) Levamisole (50mg pills every other day, poursina Inc) treated group;
2) Selenium (200µg capsule, 21 century Inc) treated group;
3) Levarnisole -Selenium treated group;
4) Control group who received no drug.

All were assessed for 6 months.

Collected data were recorded in their medical file and the results of monthly and end of therapy check up were recorded as well. Safety of drugs was explained to subjects before drug intake.

Regarding the 95% confidence interval and 80% power test, 35 participants were considered as sample size for each group (Total 140 patients).

Monthly examination included precise drug intake, drugs' side effects, opportunistic infection and data recorded in patient's file. If drug side effects were seen, the treatment would be stopped and after correcting the complications, the treatment was started again.

Treatment was continued after occurring opportunistic infections. After 6 months, CD4 count was compared with baseline CD4 and opportunistic infection occurrence and patients' mortality were assessed.

Sysmex instrument and Flowcytometry method were used for measuring CBC & CD4 count in Behavior Diseases Consulting Center and Chi square test used for comparing CD4 count in both treating and control groups. ANOVA test used for comparing CD4 count in all studied groups regarding to other variants. Paired t and t-tests used for comparing pre and post treatment CD4 count and comparing changes in studied groups, respectively.

Results

From 178 subjects 108 cases completed the study that included 35, 32, 24 & 17 patients in Control group, Levamisole-Selenium treated group, Levamisole group and Selenium group respectively. 85% (92 people) were males and 15% (16 people) were females. Age mean was 37.7±7.2 which is illustrated in table 1; 87% out of studied participants were IDU. Also incidence of hepatitis C&B among them were 88% and 12% respectively. From these participants, 9 suffered from flatulence and epigastric pain after taking Selenium which only one had to stop the treatment and excluded the study. Comparing CD4 count mean and P values in groups are shown in Table 2.

CD4 count decreased 41 units in control group within 6 months (monthly 7 units) that was statistically significant (p=0.002). Levamisole-Selenium treated group had 13 units increase in CD4 count that was not statistically significant

(p=0.207). Rate of CD4 decrease in Levamisole treated group was 36 units (6 units/month) as same as control group that was significant (p=0.046).

Average CD4 count decrease in Selenium treated group was 9 units (1.5 units/ month) that was not significant (p=0.668). Mean ofCD4 changes during 6 month period has been compared between study groups that results of this comparison is available in table 3. According to these results Levamisole plus Selenium could increase mean CD4 counts significantly (p=0.016), but Selenium and Levamisole could not improve CD4 count significantly during study period (p=0.44 and 0.992 respectively).

20 participants developed opportunistic infection which 9 were in control group, 4 in Levamisole-Selenium treated group and 3 in Levamisole treated group. From these patients, 19 developed tuberculosis and 1 got pneumocystis carini pneumonia (PCP).

Also 5 out of studied participants died which 3 were in control group, 1 in Levamisole- Selenium treated group and 1 in Selenium treated group.

Table 1: Comparison of Multiple Variables in Different Groups with Control Group

Groups		Case			
Variable		Levamisole	Selenium	Levamisole, Selenium	Control
Sex	M	21	15	28	28
	F	3	2	4	7
Age		38	36.29	40.19	36.17
CD4		269.2	232.1	215.8	240.1

Table 2: Comparison of CD4 changes Between Different Groups with Control Group

Groups	CD4 change	CD4 change in Control	Pvalue
Levamisole	-35.8	-41.3	0.992
Selenium	-8.3		0.44
Levamisole, Selenium	+13.2		0.016

Discussion

In this study CD4 count, decreased 41 units in control group which was expectable regarding to last studies (1). Our findings in Levamisole group were as same as control group that suggested the poor effect of Levamisole on preventing CD4 count decrease. A study on HIV infected patients in Amsterdam revealed CD4 count decrease after

Six months treatment by Levamisole and patients' weight loss of 1.1 kg which its results were the same as those of us. Also no changes were seen in these patients' clinical presentation (10). But most studies support that Levamisole is an effective treatment in HIV infected patients. For example, a study in Zambia concluded that taking Levamisole 150mg/week for six months can decrease the disease progression to AIDS as 1.5 fold in control group (11).

Also a study in India suggested that taking Levamisole in children with malnutrition, can increase mean CD4 count up to 20%[6]. All previous studies support the Selenium effect on CD4 count increasing, for example a study showed that taking Selenium 200µg/day, in HIV infected patients for six months decreases viral load and indicated that serum Selenium concentration increase, improves the antiviral drugs effects. Although Selenium effect in participants who do not take ART has been significant either (2). Another study in Liverpool indicated a direct relation between Selenium serum concentration and CD4 count (8). Some studies suggested that lack of antioxidants (Selenium, Zinc, A, B, C, D, E vitamins) can cause rapid progression of HIV and taking antioxidants improves survival rate in HIV infected patients (9,10).

In Tanzania in HIV infected pregnant women in another 5 year follow-up study showed that low serum level of Selenium can increase the risk of mortality and plasma level of Selenium can not stop progression of CD4 count to <200 cell/mm^3 (12).

We have not found a general study to show Selenium serum level situation in Iranian general population, but Nouraei et al. in a study to evaluate the role of Selenium in incidence of esophageal cancer in Iran presented that in Golestan, Kerman, Mazandaran province, serum Selenium level was medium to high but in Ardebil only 29% of people had serum Selenium level over than 90 mic lit/lit (13) while in another study the probable Selenium deficiency in developing Behchet disease had been shown (14), but we did not find any more studies about HIV infected population in Iran.

In our study in Selenium treated group studies, dropping was more than other groups, in fact 60% of participants were

excluded from the study due to disorganized taking drug and poor cooperation. Regarding to a few studies, samples in this group in doing statistical analysis to provide positive or negative effects of Selenium on CD4 was impossible.

Several studies have supported the effects of Levamisole and Selenium on improving cell immune function but no study has shown the effect of simulation Selenium-Levamisole effect. Significant compared values of CD4 change between Selenium-Levamisole treated group and control group indicated that simulation of these two drugs does not only prevent the CD4 count fall but also increases it. It was better if we could assess the role of these drugs in the decreas of HIV viral load, but it was not possible in our group this time.

Selenium-Levamisole can be used as a compound supplementation therapy besides anti retroviral therapy (ART) to prevent CD4 count decrease but taking Levamisole by itself is not recommended.

References

1. High KP, Morse CG. Nutrition, immunity and infectious disease in: Mandell GL, Bennett JE, Raphael Dolin R. Principles and practice of infectious disease. 6th ed. Philadelphia: Churchill livingstone 2005; pp: 142-45.
2. Hurwitz BE, Klaus JR, Llabre MM, et al. Suppression of human immunodeficiency virus type 1 viral load with selenium supplementation: a randomized controlled trial. Arch Intern Med 2007; 167: 148-54.
3. Hori K, Hatfield D, Maldarelli F, Lee BJ, Clouse KA. Selenium supplementation suppresses tumor necrosis factor alpha-induced human immunodeficiency virus type 1 replication in vitro. AIDS Res Hum Retroviruses 1997; 13: 1325-32.
4. Bourinbaiar AS, Jirathitikal V. Low-cost anti-HIV compounds: potential application for AIDS therapy in developing countries. Curr Pharm Des 2003; 9: 1419-31.
5. Castro Garzón M, Mubita M, Kachinka L. Levamisole treatment in HIV-infected Zambian children. Lancet 1992; 340: 1099-100.
6. Prakash MS, Rao VM, Reddy V. Effect of levamisole on the immune status of malnourished children. J Trop Pediatr 1998; 44: 165-6.
7. Ndagije F, Baribwira C, Coulter JB. Micronutrient and TceH subsets: a comparison between HIV - infected and lU1infected, severly malnourished Rwandan children. Ann Trop Paediatr 2007; 27: 269-75.
8. Chan G, Collins J, Horn T. Antioxidants may still have a role in HIV treatment. GMHC Treat Issues. 1997; 11: 6-12.
9. Tang AM, Graham NM, Saah AJ. Effects of micronutrient intake on survival in human immunodeficiency virus type 1 infection. Am J Epidemiol 1996; 143: 1244-56.
10. Castro Garzon M, Mubita M, Kachinka L. Levamisole treatment in HIV-infected Zambian children. Lancet 1999; 340: 1099-100.
11. Anne H, Eussen R, Graafmans J. The effect of levamisole on HIV-infected patients.Int Conf AIDS 1992 Jul 19-24; Amesterdam, Holand. B163 (abstract no. POB 3456).
12. Kupka R, Msamanga GI, Spiegelman D, et al. Selenium Status Is Associated With Accelerated HIV Disease Progression among HIV-1-Infected Pregnant Women in Tanzania. J Nutr 2004; 134: 2556-60.
13. Nouarie M, Pourshams A, Kamangar F, et al. Ecologic study of serum selenium and upper gastrointestinal cancers in Iran.World J Gastroenterol 2004 Sep 1; 10: 2544-6.
14. Esalatmanesh K, Jamshidi AR, Shahram F, et al. Assessment of correlation of serum selenium level and Behcet disease. FEyz, J Kashan Univ Med Sci 2008; 12: 39-43. {In persion}.