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Cytokine assessment and Immunomodulatory Effect of Bee Venom in HBV&HCV Infected Patients

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Abstract

Background: Hepatitis B &Hepatitis C viral infections are common health problems worldwide. New strategies for treatment are now evolving. The therapeutic application of bee venom has been used in traditional medicine to treat many diseases. **Aim:** The aim of this study was to investigate the effect of bee-sting (venom) therapy on progression of chronic viral hepatitis B & C and on the levels of proinflammatory cytokines IL-1β , IL -2 and IL -6 and the anti inflammatory IL -10 in HBV&HCV infected patients. **Methods:** 67 Egyptian patients with chronic hepatitis were enrolled, 20 of them have HBV and 47 have HCV. Bee stings were administered using live bees at apipunctur point. CBC, liver enzymes, Hepatitis B &C RT-PCR, IL-1β, IL -2, IL -6 and IL -10 were estimated before & after bee stings therapy. **Results:** there was a significant decrease in ALT; AST ($P \leq 0.05$) after bee venom injection in both types of hepatitis. viral load was decreased during the course of treatment, it became negative after 9 months therapy in all cases of HBV infection and in 34.04% of HCV infection. IL-1β, IL -2, IL -6 and IL -10 levels were aalso significantly decreased after 9 months therapy in both types of hepatitis patients. **Conclusions**: bee venom stings decreased the viral load and IL-1β, IL -2, IL -6 and IL -10 after 9 month's therapy in both types of hepatitis.

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Introduction

Hepatitis B virus (HBV) infection causes chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC) [1]. Severe hepatitis can develop due to high level of viral replication and expression of protein antigen on cell surfaces, which leads to cytotoxic T lymphocyte (CTL)-mediated immune response, which causes death to liver cells [2]. So inhibition of HBV replication may inhibit immune responses and hence liver cell damage [3].

On the other hand, About 170 million people in the world infected with hepatitis-C virus (HCV) [4]. The prevalence is higher in Africa and Asia. In Egypt, there is about 12 million individuals have Anti-HCV antibody (14.7%) and about 8 million individuals chronically infected with hepatitis C (9.8%)[5]. It is considered the second most common blood-borne disease in the world, [6]. HCV infection should be considered as a systemic infection with multi-organ involvement [7].

Bee venom (BV) has been used in traditional medicine to treat some immune-related diseases, as rheumatoid arthritis [8]. Bee venom pharmacopuncture (BVP) is a combination between acupuncture stimulation and BV extracted from the poison sac of a live honey bee [9].

The BVP is applied to trigger points and regions of pain and acupuncture points. A small quantity of BV can cause anaphylactic shock or critical injury in some persons [10]. BVP was reported to have anti-inflammatory, analgesic, antipyretic and anticonvulsant effect. BVP has been used to treat autoimmune diseases, cancer, painful diseases, and musculoskeletal diseases, arthritis, neuralgia, frozen shoulder [10].

BV contains many biologically active peptides, including melittin(MLT), apamin, adolapin, mast cell degranulating peptide and enzymes (phospholipase A2 (PLA2), and hyaluronidase), as well as non-peptide components, such as histamine, dopamine and norepinephrine[11]. Melittin which is the major peptide component of BV has anti-inflammatory and anti-arthritis effects, and an inhibitory effect on nuclear factor kappa (NF-kB) [12].

The development of the infection with the hepatotropic virus depends on the defense of the organism which was found under the control of many cytokines and chemokines. The mechanisms that are causing viral persistence and hepatic pathology are not completely elucidated[13].

IL-1 has a role in neuroinflammation., increased levels of TNF and IL-1 was demonstrated during inflammation [14].IL-2 has essential roles in key functions of the immune system, tolerance and immunity, primarily via its direct effects on T cells [15].IL-6 is a multifunctional cytokine that acts on numerous target cells, being involved in the immune answer, inflammation and in hematopoiesis. IL-10, is an antiinflammatory endogenous mediator through the inhibition of the production of proinflammatory cytokines. It has an immunosupressor effect through the inhibition of the function of the macrophage of cell presenting antigen.

Aim of the work:

The aim of this study was to investigate the effect of bee-sting (venom) therapy on progression of

chronic viral hepatitis B & C patients. The patient response was assessed through measuring viral load (RT-PCR for the virus) before and after 3, 6, 9 months treatment sessions and also to estimate IL-1β, IL -2, IL -6 and IL -10 before and after bee stings.

Patients and methods

Subjects:

67 Egyptian patients with chronic hepatitis were enrolled, 20 of them have HBV and 47 have HCV infection.All patients were subjected to detailed history, Clinical examination, and Laboratory investigation in the form of complete blood count and serum transaminases (ALT, AST) and hepatitis B & C RT- PCR(Qiagen, Valencia, CA, USA)., IL-1β, IL -2, IL -6 and IL -10 by ELISA(BioLegend, Inc.) before and after administering schedules of bee stings sessions according to ***Amber Rose, 1994*** protocol; one to two bee stings were administered each session using live bees; gradually we increased the number of bee stings. Trigger points or acupuncture points include two stings on liver site, two sting obverse of the first stings at the body, another two behind to and under knees on the left leg and at the last two stings on the foot in the left leg **[16].**Skin test was performed to prove that the patient isn't allergic to bee venom prior to beginning the sessions.

Statistical Analysis

Data was collected and coded to facilitate data manipulation and double entered into Microsoft Access and data analysis was performed using SPSS software version 18 in windows 7. Student t-Test used to compare measures of two independent groups of quantitative data. Repeated measures ANOVA were used to compare mean level of more than two readings at the same time. The level $P \leq 0.05$ was considered the cut-off value for significance.

Results:

80% of hepatitis B virus patients were males and 20% of them were females, the mean age was (30.6 ±4.6) years old. While 55.3% of hepatitis C virus patients were males and 44.7% of them were females, the mean age was (42.9 ±12.5) years old; Table 1.

There is statistically significant increase in the levels of segmented neutrophils, staff, lymphocytes, and monocytes after 9 months therapy. There is statistically highly significant decreased in the levels of liver enzyme (SGPT, and SGOT) after 9 months treatment among HBV patients, Table 2.

Table 4 illustrates that there is a statistically significant increase in segmented cells and lymphocytes after treatment. There is statistically significance decreased in liver enzyme (SGPT, and SGOT) after 9 months treatment among HCV patients.

Tables 3& 5 illustrate that there is statistically significant decreased in PCR level in both HBV and HCV patients after treatment.

Of a total number of 20 patients suffering from hepatitis B, all patients became negative after 9 months. In hepatitis C cases, 30 patients (63.82%) improved, 16 patients (34.04%) become negative and only one patient (2.13%) wasn't improved at the end of the 9 months therapy (table 6).

Table (1): Demographic characters in hepatitis B and hepatitis C virus (HCV) patients

	Hepatitis B virus patients (n=20)	Hepatitis C virus patients. (n=47)
Sex, Male	16 (80%)	26(55.3%)
Female	4(20%)	21(44.7%)
Age (years) Mean±SD	30.6±4.6	42.9±12.5

Table (2): Comparisons of complete blood count and liver enzymes before and after 9 months treatment among hepatitis B virus (HBV) patients

Variables (n=20)	Before treatment	After treatment	p-value
WBCs ($x10^3$/µL)	4.9±0.16	5.7±0.38	<0.001
RBCs ($x10^6$/µL)	4.3±0.46	4.5±0.29	0.02
PLT ($x10^3$/µL)	240±32.9	240±20.4	0.9
Hb (g/dl)	12.7±1	12.4±0.97	0.7
Leukocytes counts			
Segmented neutrophils	38.6±5.9	50±7.8	0.001
Saff	2±0.67	3.2±0.78	0.01
Lymphocytes	28.9±14.9	42.6±3.7	0.02
Monocytes	4.6±3.6	21.9±14.9	0.01
Eosinophil	1.02±1.5	3.6±3.4	0.07
Basophil	0.12±0.20	0.08±0.2	0.7
Liver Enzymes			
SGPT(IU/L)	90.6±17.2	32.6±5.9	0.000
SGOT(IU/L)	85±23.9	29±5.2	0.000

Table (3): Comparisons of PCR level follow up among hepatitis B virus (HBV) patients

Variables (n=20)	p-value	
	Mean IU/mL±**SD**	
Before treatment	1694043.3±2560880.1	**0.02***
After 3 months	15666.7±24270.7	
After 6 months	3000.5±2345.65	
After 9 months	0	

Table 7 illustrates that there is statistically significant difference with p-value < 0.05 between different Hepatitis groups and its controls as regards to different IL types with low mean among cases who received treatment

Discussion

Hepatitis B virus (HBV) is moderately endemic in Egypt in which 4% of the population has evidence of chronic HBV infection [14].Egypt has the highest prevalence of HCV in the world [17].

There is a worldwide necessity for development of new antiviral agents, to offer alternatives for the control, prevention, and management of the spread of diseases caused by RNA and DNA viruses.. In humans Bee venom has been used as an anti-inflammatory agent to relieve pain in rheumatoid arthritis [18], tendonitis, multiple sclerosis, wounds and gout [19].

Table (4): Comparisons of complete blood count and liver enzymes before and after 9 months treatment among hepatitis C virus (HCV) patients

Variables (n=47)	Before treatment	After 9 months treatment	p-value
	Mean ± SD	Mean ± SD	
WBCs ($x10^3$/µL)	5.6±1.6	5.9±1.3	0.2
RBCs ($x10^6$/µL)	4.2±0.88	4.8±0.73	<0.001
PLT ($x10^3$/µL)	198.9±68.9	265.1±86.8	<0.001
Hb(g/dl)	12.2±1.4	12.9±1.3	<0.001
Segmented	36.3±7.8	45.4±7.1	<0.001
Staff	3.3±0.92	1.8±0.58	<0.001
Lymphocytes	37.6±7.4	45.3±12.1	<0.001
Monocytes	11±11.2	17.6±16.7	0.03
Eosinophil	2.8±2.4	1.7±2.1	0.01
Basophil	0.20±0.43	0.07±0.31	0.09
Liver Enzymes			
SGPT (IU/L)	58.1±44.2	36.9±5.9	0.001
SGOT (IU/L)	57.9±28.2	38.6±20.3	<0.001

Table (5): Comparisons of HCV RNA by PCR levels follow up among hepatitis C virus (HCV) patients

Variables (n=47)	PCR level	p-value
	Mean, IU/mL ±SD	
Before treatment	1549134.2±404683.1	0.001**
After 3 months	319302.2±111333.6	
After 6 months	171782.5±91383.1	
After 9 months	128757.2±97622.2	

Table (6): Comparisons between HBV & HCV patients response to treatment

	Improved	Negative	No Improvement
HBV patients	---	20(100%)	---
HCV patients	30 (63.82%)	16 (34.04%)	one (2.13%)

Table (7): Comparisons of Interleukins levels between different hepatitis patients, and controls before and after 9 months treatment

Variables	HBV before	HBV after	p-value	HCV before	HCV after	p-value
	Mean± SD	Mean± SD		Mean± SD	Mean ± SD	
IL-1β (pg/ml)	19.6±6.02	9.51±6.04	<0.0001	21.8±8.5	14.2±6.2	0.002
IL- 2 (pg/ml)	41.1±0.1	28.7±0.05	0.001	38.8±0.1	27.9±0.92	<0.001
IL- 6 (pg/ml)	20.3±5.05	15.1±4.1	0.001	18.4±2.2	16.3±4.27	0.0035
IL- 10 (pg/ml)	20.9±4.05	16.4±8.1	0. 03	20.5±4.2	17.7±4.49	0.002

We aimed to study the effect of bee venom via scheduled bee stings on the progression of chronic viral hepatitis B & C patients and on the levels of IL-1β, IL -2, IL -6 and IL -10 in HBV&HCV infected patients. We found a significant increase in segmented, lymphocytes, and monocytes cells after stings in patients with HBV.

Also there is a statistically significant increase in segmented cells and lymphocytes in patients with HCV after stings .These results may be due to stimulation of immune system by bee venom injection, [20].

On the other hand, liver enzymes levels were significantly decreased after bee venom injection in both types of hepatitis. the decrease in these enzymes can be considered as indicator for the anti-inflammatory effect of bee venom. These results go in accordance with that of **El-Abd et al.,** [21] who showed that treatment of hepatitis C patients with bee venom resulted in a significant decrease in ALT and AST levels starting from the 3rd month, and along the test period of bee venom injection.

We also found a significant decrease viral load along the test period in HBV cases, the viral load decreased after 3 to 6 months and become negative after 9 months. Serum HCV load was also significantly decreased along the test period.Our results go in accordance with **El-Abd et al.,** [21] who denoted that 37% of HCV infected patients became negative and 53 % markedly decreased, while 10 % show no decrease after12 month of bee venom injection. but they did not include HBV patients in their study.

Our results also agree with a case report study presented by **El-Bassiony and Bdr** [22]; a 47 year old male patient suffered from chronic hepatitis C virus infection received Bee Venom Therapy (BVT) courses for three months. At the end of BVT course quantitative PCR for HCV was done and the result was negative. Repeated quantitative PCR for HCV-RNA were negative for several successive years later.

Our results don't agree with the results of **Kochlios et al,** who denoted that there was no patient reached the negative PCR results or below the detectable level after interferon, bee stings or conventional liver support drugs and bee stings together [23].

Our results could be explained by the results of Uddin et al., who revealed that BV and mellitin (MLT) derived from BV exhibited potent antiviral activity against various enveloped and non-enveloped viruses in vitro and Influenza virus in the in vivo mouse model. Moreover, its antiviral mechanism has been confirmed to involve direct interaction with the viral surface. Apart from BV virucidal activity, BV can stimulate type I IFN, which subsequently could stimulate the antiviral state in the host cell and also inhibit the viral replication. Consequently BV or MLT may exhibit a prophylactic or therapeutic role for infectious viral diseases [24].

No studies exist, so far, on the role of bee stings on the progression of cytokines in these patients. In our study levels of proinflammatory cytokines; IL-1B, IL-2 and IL-6 and the anti-inflammatory cytokine IL-10 were found to be lower after bee stings. Antonelli et al, 2010 revealed that Serum levels of IL-1beta were high in patients with HCV [25].Furthermore, Antonelli et al, 2009 demonstrate elevated serum levels of IL-1beta, IL-6 in patients with HCV [26].On the other hand Bozkaya et al denoted that active liver injury in chronic hepatitis C is associated with increased circulating Th1 cytokine IL-2 but not with Th2 cytokine IL-10 and that levels of these cytokines do not expect the response to IFN treatment, as they found no constant and regular change in levels of these cytokines under IFN treatment [27]. Bruno et

al showed no significant difference in IL-10 values between controls and patients with chronic C hepatitis but they found that subjects with more severe necroinflammation had increases levels of IL-10 than others and they argue for a potential pathophysiological role for IL-10 in hepatitis [28].

We found decreased levels of IL-10 after bee venom treatment. correspondingly, a reduction of circulating IL-10 levels has been also described by some authors, in patients treated with interferon or interferon plus ribavirin, especially in responder subjects[29].

On the other hand Das et al (30) showed that IL-10 levels were correlated with spontaneous exacerbations of liver disease, and IL-10 levels were increased with hepatitis B viral load increase and the peak of liver damage. In another study by Özgüler et al, IL-10 levels were increased with increased viral load [31].

It was reported that IL-1β, IL-6 and IL10 levels increased in patients with liver cirrhosis than patients with chronic hepatitis B. This might be an important marker in progression of chronic hepatitis B into liver cirrhosis [32]. In a study conducted on patients with occult HBV infection, IL-10 levels of 352 patients were determined, and it was found that the levels were higher than controls [33].

The long-term effects of bee stings therapy are not yet known, but our results show that in untreated subjects,there was increased cytokines level, the controversy about il-10 yet still unclear. Whether the increase of IL-10 in some studies is only an outcome of persistent inflammation or whether it may play a role in favoring the persistence of virus infection and chronic disease. It can reasonably argue that the increased levels of IL-10 in patients with CHC reflect the degree of necroinflammation [28].

In conclusion, we found that Bee venom therapy decreased viral load in both HBV&HCV patients and also decresed IL-1β, IL -2, IL -6 and IL -10, further studies are needed to explain the role of each component of bee venom in changing the viral load in patients.

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