Novel Therapeutic Modality Employing Apitherapy for Controlling of Multiple Sclerosis

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Abstract

Objective: Study the effect of bee sting therapy (Apitherapy) in the treatment of Multiple Sclerosis.

Methods: Fifty patients with MS, their ages ranged between 26-71 years, were subjected to complete clinical and neurological history and examination to confirm the diagnosis. All cases were under their regular treatment they were divided into two main groups, Group I received honey, pollen, royal jelly and Propolis and were treated with acupuncture 3 times weekly, for 12 months, in addition to their medical treatment, while group II remains on their ordinary medical treatment only. Acupuncture was done by bee stings for regulating the immune system.

Results: Results revealed that 4 patients showed some improvement regarding their defects in gait, bowel control, constipation and urination, while 12 cases, showed some mild improvement in their movement in bed, and better improvement in bed sores, sensation, and better motor power, only two cases of them were able to stand for a few minutes with support. Interleukin (IL) 1β, tumor necrosis factor alpha (TNFα), and IL-6 were detected. The level of TNF-α was significantly elevated in patients in Group II, while IL-1β was reduced in Group II than Group I and no significant differences were found for IL-6 between the 2 groups. The mean values of IgE level in both groups of M.S. Patients were low, but with no statistical significance, while by the end of the study there were an elevation in the levels of IgE for both groups, which was statistically significant.

Conclusion: Although Apitherapy is not a curable therapy in MS, but it can be used to minimize the clinical symptoms of MS, and can be included among programs of MS therapy.

Keywords: Multiple sclerosis; Apitherapy; Bee venom; Cytokine; Food supplements

Introduction

Multiple sclerosis (MS) is a chronic and putatively immune mediated inflammatory disease of the central nervous system [1]. MS altered immune function in patients. It exhibits many of the hallmarks of an inflammatory autoimmune disorder including breakdown of the blood-brain barrier, the recruitment of lymphocytes, microglia, and macrophages to lesion sites, as well as the presence of multiple lesions [2]. It is characterized by the damage of fatty myelin sheaths around the axons of the brain and spinal cord, leading to demyelination and scarring as well as a broad spectrum of signs and symptoms [3].

Apitherapy is the medical use of honey bee products. This includes the use of honey, pollen, bee bread, propolis, royal jelly, and apilarnil and bee venom. Most claims of apitherapy have not been proved to the scientific standards of evidence-based medicine and are anecdotal in nature. Bee venom therapy is an alternative form of healing. Bee venom therapy is the part of apitherapy which utilizes bee venom in the treatment of health conditions. However, bee venom is a complex mix of a variety of peptides and proteins, some of which have strong neurotoxic and immunogenic effects [4]. It has been used since ancient times to treat arthritis, rheumatism, back pain, skin diseases and in this modern age as an alternative therapy to treat autoimmune diseases, Lyme disease and chronic fatigue syndrome [5-7]. Some reports have shown beneficial effects of bee venom in post herpetic neuralgia [8], fibromyalgia and multiple sclerosis [9]. Interleukin (IL) 1β, tumor necrosis factor alpha (TNFα), and IL-6 are cytokines which mediate cellular responses during immune activation and inflammation. In Multiple Sclerosis (MS) they might be responsible for T-cell activation (IL-1β), for demyelination (TNFα), and for immunoglobulin (Ig) synthesis (IL-6) within the central nervous system [10]. There is no standardized practice for the administration of bee venom. The aim of this investigation was to evaluate the effect of bee venom therapy (Bee Sting) and other bee products on the immunological status of cases with MS.

Materials and Methods

The aim of this study was to determine the immunological status of MS patients. Patients had to be free of immunomodulatory treatment during the study period and for at least the preceding 12 months. This study was carried out on fifty MS patients diagnosed and confirmed by clinical examination and radiological studies [11-13,7]. Twelve males and thirty eight females, their ages ranged between 26-71 years, with a mean of 38.7 ± 4.8. 2, were selected from patients attending the outpatient clinic of Adult Neurology in National Research Centre, Dokki, Egypt,” over a period of three years from September 2008 till April 2011. All cases were subjected to complete clinical and neurological history and examination to confirm the diagnosis. They
were signed consent according to medical ethic committee (14146). There were 32 cases with quadriparesis (8 males and 24 females) and 18 cases with paraparesis (4 males and 14 females). All cases were under their regular treatment either by corticosteroids, or interferon. These cases were divided into two main groups, each group consists of 25 cases (6 males and 19 females), Group I received honey, pollen, royal jelly and Propolis and were treated with bee stings (from honeybee (Apis mellifera L.) workers of pure Carniolan race) 3 times experiment respectively. In contrast, no significant differences were found for IL-6 between the group I and group II.

Results are shown as the mean ± standard error in pictograms per milliliter (Table 2). All patients with MS had significantly higher cytokine concentrations. The level of TNF-α was significantly elevated at the end of the study there were an elevation in the levels of IgE for both groups, which was statistically significant among cases of group (I). As shown in Table 1 there was a gradual assessment of signs and symptoms every 2 months as shown in Table 1 as well as in the scores of symptoms recorded during the same period among patients for both groups.

Results revealed that 4 patients out of 9 (44.4% of quadriparesis cases), showed significant improvement regarding their defects in gait, bowel control, constipation and urination, while 12 cases out of 16 cases (75% of quadriparesis cases), showed mild improvement in their movement in bed, and better improvement in bed sores, sensation, and better motor power, only two cases of them (12.5%) were able to stand for a few minutes with support among patients of group I. As well as rigidity and muscle spasms.

In this study, the mean values of IgE in both groups of M.S. Patients (Table 2) were low, but with no statistical significance, while by the end of the study there were an elevation in the levels of IgE for both groups, which was statistically significant among cases of group (I). The aims of the present study were to evaluate the pro-inflammatory tumor necrosis factor (TNF-α) and interleukin (IL)-1β, and IL-6. Results are shown as the mean ± standard error in pictograms per milliliter (Table 2). All patients with MS had significantly higher cytokine concentrations. The level of TNF-α was significantly elevated in Group II patients (6.1 ± 1.3 pg/mL) vs control Group I subjects (4.3 ± 0.1 pg/mL) at the end of experiment (12 months), as was the level of IL-1β (123.0 ± 2.2 vs 224.1 ± 1.4 pg/mL; P ≤ .0001) at the end of experiment respectively. In contrast, no significant differences were found for IL-6 between the group I and group II.

Discussion

MS affects the ability of nerve cells in the brain and spinal cord to communicate with each other effectively [19]. Theories include genetics or infections as causes for MS. Different environmental risk factors have also been found [20]. Life expectancy of people with MS is 5 to 10 years lower than that of the unaffected population [3]. Several subtypes, or patterns of progression, have been described. Subtypes use the past course of the disease in an attempt to predict the future course. They are important not only for prognosis, but also for therapeutic decisions [21]. Although there is no known cure for multiple sclerosis, several therapies have proven to be helpful.
Bee sting therapy is increasingly used to treat patients with MS in the belief that it can stabilize or ameliorate the disease. However, there are no clinical studies to justify its use [22]. Found that there were no improvement of disability, fatigue, and quality of life. Bee sting therapy was well tolerated, and there were no serious adverse events. They concluded that the treatment with bee venom in patients with relapsing multiple sclerosis did not reduce disease activity, disability, or fatigue and did not improve quality of life.

Table 1: Scores of signs recorded every two months (1-12), for patients of both groups.
related to the marked edema induced by the venom. According to myelin is being attacked by the immune system in a person with MS administered either by live bees or by injection. This treatment can considered effective. The median lethal dose (LD50) for honeybee of acupuncture in combination with the effects of the venom, while exerts not only pharmacological actions from the bioactive compounds isolated from bee venom but also a mechanical function on blood cells, influences immuno-active blood cells and hormone transaminases, creatinine, urea nitrogen, uric acid, sodium and potassium levels, antiarhythmic, heart stimulating therapeutic effects, antiinflammatory, immunoactivating, immunosupressive, analgesic, radioprotective, anticarcinogenic, accelerates heartbeat, increases blood circulation, lowers blood pressure, improves haemoglobin synthesis, anticoagulant, lowers cholesterol levels, membrane effects on blood cells, influences immuno-active blood cells and hormone levels, antiarhythmic, heart stimulating therapeutic effects, improvement in hypertension and artherosclerosis [38-40].

The location of the sting is important, with the sting acting as a sort of acupuncture in combination with the effects of the venom, while others reported that the location is not important. The number of stings also varies widely from a few to hundreds and they may be administered either by live bees or by injection. This treatment can cause pain, and even result in death if the subject has an allergy to bee venom, which can produce anaphylactic shock [22]. For honeybee venom subcutaneous immunotherapy 100 or 200 μg doses are considered effective. The median lethal dose (LD50) for honeybee venom has been reported in a number of reports as 2.8 mg venom/kg body weight for intravenous and 3.8 mg venom/kg body weight for intraperitoneal delivery in mice. A 2004 randomized crossover study was conducted in the Netherlands among 24 people with either relapsing-remitting MS or secondary-progressive MS. While the treatment was well-tolerated, no beneficial effects were seen on the MRIs or clinically among these patients [21,19]. In our study there was a statistically significant improvement regarding the clinical findings while the results of MRIs done to follow up for our patients showed that there is no more changes in the demyelinating lesions which means that demyelination shows no progression as shown in other previous investigation [7].

BV administration was reported to stimulate the function of immune system and to affect the release of cortisol production which is known as natural anti-inflammatory agent [35]. Melittin which is the major component of BV was found to suppress inflammation by inhibiting Phospholipase (PLA) enzymatic activity [36]. This enzyme was abundantly released in severe inflammatory disorders and actively found to cause tissue and organ degradation which will lead to the loss of their functions [37]. Melittin was also found to block the production of neutrophil superoxide [38]. Bee venom (inflammation, allergy, cytotoxic, haemolysis), antibacterial, antiinflammatory, immunoactivating, immunosupressive, analgesic, radioprotective, anticarcinogenic, accelerates heartbeat, increases blood circulation, lowers blood pressure, improves haemoglobin synthesis, anticoagulant, lowers cholesterol levels, membrane effects on blood cells, influences immuno-active blood cells and hormone levels, antiarhythmic, heart stimulating therapeutic effects, improvement in hypertension and artherosclerosis [38-40].

The mechanism of action of bee venom was clarified as follows: bee venom blocks the building of proinflammatory substances and inhibits the proliferation of rheumatoid synovial cells. Today, bee venom is applied directly via sting or injection. This practice was initiated in 1964 in Russia [41] and has been further developed since then, mostly in the Far East [42].

Apamin accounts for less than 2% of venom dry weight, presents a neurotoxic action and possesses unusual functional as well as structural properties. It is remarkable among peptides in its ability to cross the blood-brain barrier and act on the central nervous system. Apamin is known to block calcium dependent potassium fluxes by binding to a Ca2þ-dependent potassium channel. Apamin is the smallest neurotoxic polypeptide known. It has been isolated from bee venom [46].

Nam et al. [47] who stated that bee venom is a mixture of many substances. In this study we found that there is a statistically significant improvement regarding their immunity and the improvement in their health and general conditions and this is explained by Park et al. and Prado et al. [29,30] bee stings cause hemoconcentration which might be related to the marked edema induced by the venom. Following bee stings there is an increase in various cytokines like interleukin (IL-1β), IL-6, tumor necrosis factor-α, etc. In a mouse model using the subcutaneous route, rapid increases in serum alanine aminotransferase and aspartate aminotransferase transaminases, creatinine, urea nitrogen, uric acid, sodium and

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<th>Groups</th>
<th>Mean at the start of the study</th>
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<td>IgE (IL) 1β (TNF) α, IL-6</td>
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<td>Group (I)</td>
<td>664 ± 32</td>
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Table 2: Mean levels of IgE, Interleukin (IL)-1β, tumor necrosis factor alpha (TNF) α, and IL-6 for both groups at the start of the study and by the end of the study.
chloride electrolytes, and creatine kinase were recorded [48,28,29]. The pain and swelling of the sting are caused by histamine, dopamine, serotonin, and norepinephrine. Several toxins are also present, including apamin, melittin, monamine, and mast-cell degranulating peptide. Lastly, the substances responsible for the allergic response include hyaluronidase and phospholipase-A2, enzymes that work to activate immune cells and produce Immunoglobulin E [47].

Despite a lack of scientific evidence, bee venom therapy has been reported by people with MS to increase stability, as well as reduce fatigue and spasticity. More than 1,300 people with MS have sent testimonials to the American Apitherapy Society in support of the therapy [19,7] this is agreed by our study as patients under bee venom therapy showed marked improvement in status, stability, and spasticity, while our study is disagreed with Castro et al. [4] as they found that there were no definite conclusions regarding efficacy and therefore there was little evidence to support the use of honeybee venom in the treatment of MS.

The present study was conducted to evaluate the pro-inflammatory Tumor Necrosis Factor (TNF-α) and interleukin (IL)-1β, and IL-6. Results are shown as the mean ± standard error in picograms per milliliter (Table2). All patients with MS had significantly higher cytokine concentrations. The level of TNF-α was significantly elevated in Group II patients (6.1 ± 1.3 pg/mL) vs control Group I subjects (4.3 ± 0.1 pg/mL), as was the level of IL-1β (123.0 ± 2.2 vs 224.1 ± 1.4 pg/mL; P ≤ .0001), respectively. In contrast, No significant differences were found for IL-6 between the 2 groups. These findings supported by the previous findings of different authors as Martins et al. [10] who found that 10 of the 13 cytokines or markers were significantly different between patients and age-matched control subjects. The increase in proinflammatory and down-regulatory cytokines in patients with MS is consistent with the progression of the disease because inflammatory and restorative processes seem to occur simultaneously. Following bee stings there is an increase in various cytokines like interleukin (IL)-1β, IL-6, tumor necrosis factor-α, etc. In a mouse model using the subcutaneous route, rapid increases in serum alanine aminotransferase and aspartate aminotransferase transaminases, creatinine, urea nitrogen, uric acid, sodium and chloride electrolytes, and creatine kinase were recorded Park et al. and Prado et al. Cytokines are significantly elevated in patients with MS are consistent with the pathologic features of this disease. Interleukin (IL) 1β, Tumor Necrosis Factor alpha (TNF-α), and IL-6 are cytokines, which are increased during immune activation and inflammation [48,49]. IL-1β is released from macrophages and endothelial cells and is involved in the synthesis and release of acute phase proteins. In patients with MS, IL-1β is mainly expressed by microglial cells and infiltrating macrophages throughout the white matter and, especially, in acute lesions [50] and has been shown to promote oligodendrocyte death in tissue culture [51].

Several review articles have stressed the need for the identification of biomarkers in MS as a valuable tool in the diagnosis and identification of disease stages and subcategories of MS and in monitoring treatment of the disease [52-55]. Hagman et al [55] examined cytokine concentrations in 72 patients with clinically definite MS and 21 healthy control subjects. Of the 5 cytokines included in their study (IL-10, TNF-α, IL-6, IFN-γ, and IL-2) they found that TNF-α was significantly elevated in the MS patients compared with control subjects. Martins et al. observed [10] marked increases in the concentrations of proinflammatory IL-1β and TNF-α, and anti-inflammatory (TH2)-type cytokines in patients compared with control subjects, with 9 of the 13 cytokines or markers showing highly significant differences in these 2 groups. Serum TNFα was significantly higher in depressed and MS patients than in normal controls interferon (IFN)-γ, interleukins (ILs)-1β, 6 and tumor necrosis factor (TNF)-α. Significant increases between patients and control subjects were found for IL-1β (mean, 26.0 ± 14.3 pg/mL; P ≤ .0001), IL-6 (mean, 16.8 ± 7.5 pg/mL; P=0.03) and TNF-α (mean, 4.5 vs 1.6 pg/mL; P=0.01) [56].

Concerning to the levels of IgE which showed significant low levels among cases of both groups (I and II), while by the end of the study marked elevation of IgE levels. The previous study was assessed and they can be explained by Nam et al. [47] who stated that bee venom is a mixture of many substances. In this study, we found that there is a statistically significant improvement regarding their immunity and the improvement in their health and general conditions and this is explained by Park et al. and Prado et al. [29,30] bee stings cause histamine, dopamine, serotonin, and norepinephrine. Several toxins are also present, including albumin, melting, Menomamine, and mast-cell degranulation peptide. Lastly, the substances responsible for the allergic response include hyaluronidase and phospholipase-A2, enzymes that work to activate immune cells and produce Immunoglobulin E [47].

Conclusions

From the results we conclude that bee venom injected intradermally could be a potential new therapeutic agent in the treatment of MS patients, with minimal tolerable side effects. Interleukin-1β, 6 and TNF could be considered as an indicator in the treatment of MS with intradermal injection of bee venom. Larger randomized controlled complementary studies are needed to explore their efficacy. This work is a potential starting point for larger studies with wider scales of applications to confirm our findings.

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