

# Role of bee Venom Acupuncture in improving pain and life quality in Egyptian Chronic Low Back Pain patients

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## ABSTRACT

Chronic non-specific low back pain is considered to be the commonest medical symptom for which patients seek complementary and alternative medical treatment, including bee venom acupuncture. This study was done to detect the effect of bee venom acupuncture (BVA) for controlling of chronic low back pain (CLBP). We compared the effects of BVA on 40 patients with CLBP, pre-and post-treatment. The age of patient ranged from 38 to 65 with history of back pain more than 6 months. The curative effect was measured by scoring of visual analog scale (VAS), Oswestry Disability Index (ODI), serum levels TNF $\alpha$ , IL1 $\beta$ , IL-6, and NF- $\kappa$ B as well as ESR before and after BVA treatment. The obtained results revealed that the application of BVA ameliorated the disturbances induced by CLBP, as it showed a significant improvement in VAS (65%) accompanied with a significant improvement in ODI (75.6%) in all patients. Moreover, BVA treatment resulted in a significant ( $p < 0.05$ ) amelioration in serum level of TNF $\alpha$  (-14%), IL1 $\beta$  (-52%), IL-6 (-53%) and NF $\kappa$ B (-32.6%) and ESR (-39.8%). From the mentioned findings, it could be concluded that BVA performed an improvement in CLBP patients, regarding pain intensity, disability and quality of life supported with improvement in serum levels of TNF $\alpha$ , IL1 $\beta$ , IL-6 and NF- $\kappa$ B and ESR.

## INTRODUCTION

Chronic non-specific low back pain (CLBP) is a common medical problem characterized by being multifactorial where musculoskeletal pain and psychosocial factors interact with each other (Vereckei *et al.*, 2013). CLBP can be defined as back pain that extend for more than 7–12 weeks (Dillon *et al.*, 2004). Many studies have shown the high frequency of back complaints and 70–85% of people have back pain at some time in life (Andersson, 1999). Patients with CLBP have increasingly been using complementary and alternative medicine (CAM) to improve their symptom, despite of variable accessibility of

conventional treatments (Hughes *et al.*, 2011). The use of CAM therapeutic modalities including, herbal medicine, acupuncture, herbal acupuncture, cupping and chiropractic manipulation has been increased (Grazio and Balen, 2011). Pharmaco-puncture therapy is a form of therapy derived from the conjunction of herbal medicine theory and meridian system (Lee, 1999).

Apitherapy is the medical use of honey bee products (honey, pollen, bee bread, propolis, royal jelly, apilarnil and bee venom). Bee venom therapy is the part of apitherapy which utilizes bee venom in the treatment of health problems (Hegazi *et al.*, 2015). However, bee venom is a complex mix of a variety of proteins and peptides, some of which have strong immunogenic (Hegazi, 2009) and neurotoxic effects (Ali, 2012). Park *et al.* (2010) stated that bee venom therapy is used for treatment of many different autoimmune disorders including rheumatoid arthritis, lupus, scleroderma and MS (Hegazi *et al.*, 2015).

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It is also used for a group of other diseases, including menstrual cramp, depression, varicose veins and skin conditions (Prado *et al.*, 2010). BVA is one of the most frequently performed pharmacopuncture to improve cervical pain (Kim *et al.*, 2013). Also, BVA is utilized for the treatment of acute ankle sprain, osteoarthritis, shoulder pain, post-stroke, low back pain and lumbar disc herniation (Lee *et al.*, 2008). BVA involves injecting of purified and diluted bee venom into acupoints (Baek *et al.*, 2006 and Hegazi, 2012). BVA exhibits many pharmacological actions including anti-cancer, anti-arthritic anti-inflammatory and analgesic effects (Lee *et al.*, 2013). Most claims of apitherapy have not been proved to the scientific standards of evidence-based medicine and are anecdotal in nature (Hegazi, 2012). Thus, the main objective of this study was to evaluate the therapeutic effect of BVA as a complementary modality for controlling of CLBP.

## PATIENTS AND METHODS

Forty female patients with chronic back pain were recruited from the attendants at the Complementary Medicine Clinic of the Medical Service Unit, National Research Centre, Egypt, during the period between March-August 2016. Before starting BVA treatment and as a screening process for eligibility, hypersensitivity test was performed on each patient by bee sting at GV14 acupoints. A local swelling greater than 10 mm in diameter or redness greater than 20 mm in diameter was considered a positive reaction; those patients were excluded from the study.

### Inclusion Criteria

The criteria those were mostly included in this study were age of patients that ranged from 38-65 years; painful restriction of lumbar spine mobility that was more than 6 months; no treatment for 2 weeks prior the study; radiological examination was carried out of plain X-ray lumbo-sacral spine both anteroposterior (AP), lateral views to diagnose and detect degenerative changes; and MRI to rule out surgical causes of back pain. Patients must be  $\geq 3$  points on a 10-cm VAS scale at the time of screening.

### Exclusion Criteria

Diabetes mellitus, neurological deficits, rheumatoid arthritis, ankylosing spondylitis, organ failure, cancer, and previous history of surgery in the back or dislocation or fracture, chief musculoskeletal pain other than back pain were excluded in this investigation. Conditions for which administration of BVA might not be safe including clotting disorders, administration of an anticoagulant agent, pregnancy and seizure disorders, a documented hypersensitive reaction to previous BVA treatments; bee stings or insect bites, a positive reaction observed during a hypersensitivity test, a severe psychiatric or psychological disorders, current use of corticosteroids, narcotics, muscle relaxants or herbal medicines to treat back pain or any medication considered inappropriate by the investigator. The selected CLBP patients were subjected to BVA treatment in the form of bees' stinging at standard acupoints (GB30, BL25, BL26, BL40, BL37,

BL57, GB34, GV3, ST36 and LIV3) according to Traditional Chinese. All procedures, including the bee venom acupuncture increment protocol administered into predefined acupoints, are designed by a process of consensus with experts and previous researchers according to the standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) (MacPherson *et al.*, 2010) and Medical Ethics Committee, National Research Centre, Egypt, where each patient received 2 sessions weekly for 6 weeks.

### Allowance of Concurrent Treatment of Patients

During the study period, all other interventions, drugs and treatments for back pain were prohibited including surgical procedures, injections, acupuncture, physical therapy or the use of muscle relaxants, narcotics and analgesics. Regular medications not intended to affect back-pain related dysfunction were allowed. Any change in concurrent treatment was recorded at every visit. Medical history and socio demographic characteristics, including age, gender, marital status, residence and, occupation as well as education level were recorded from the screening visit. Any unpredicted, adverse events also were recorded at each visit. For all patients experiencing LBP lasting for at least the previous six months, the pain intensity of LBP was assessed using VAS 10cm a fast and straightforward method for evaluating the subjective degree of pain intensity (Carlsson, 1983). Participants were asked to report the degree of pain intensity using the 10 cm VAS (0, absence of pain; 10, the worst pain imaginable). Also, back pain related dysfunction was assessed using the Oswestry Disability Index questionnaire (ODI) that contains 10 questions about daily activities, including inventories of pain intensity, personal care, lifting, walking, sitting, standing, sleeping, social life, travelling and sexual life (was excluded). Each question was rated on a scale from zero to 5 points; the lower the score, the less disabled (Roland and Morris, 1983). The pain VAS and ODI were assessed at baseline and after 6 weeks of the end of the study.

### Safety

All adverse events and vital signs were observed and reported. Liver & renal functions of each participant were assessed before the treatment and one week after the end of treatment.

### Withdrawal and Dropout

Participation in the study will end at any stage if the patient refuses to continue, withdraws consent, violates inclusion or exclusion criteria or the trial protocol, or completes less than four treatment sessions as determined by the attending researchers. The trial will be stopped if the principle investigator believes that there are unacceptable risks of serious adverse events.

### Laboratory Analysis

Before and after treatment with BVA, blood samples (5ml) were withdrawn from each patient. A part (2ml) from each whole blood sample was used in determination of erythrocyte sedimentation rate (ESR), while the other part (3ml) was left to coagulate then centrifuged at 300rpm, the sera were separated into

aliquots and stored at -70 till the determination of the TNF $\alpha$ , IL1 $\beta$ , IL6 and NF $\kappa$ B using ELISA (enzyme linked immunosorbent assay) technique as soon as possible. Serum TNF $\alpha$ , IL1 $\beta$  and IL6 levels were determined using human ELISA reagent kits purchased from Assaypro, Charles, MO 63301-4046, USA, while serum NF $\kappa$ B level was estimated using human ELISA reagent kits purchased from Glory Science Co., Ltd, 2400 Veterans Blvd.Suite 16-101, Del Rio,TX78840,USA.

**Statistical Analysis**

As the same group patients was assigned to one specific treatment condition, the data were analyzed using One-Way ANOVA followed by Tukey’s test using statistical analysis system (SAS) program software; copyright (c) 1998 by SAS Institute Inc., Cary, NC, USA. Unpaired t-test was used for comparison and determining the significance level. Differences were considered statistically significant when the probability of type I error was less than 0.05.

**RESULTS**

Investigations suggested diabetes mellitus in 10 patients among the chosen 50 patients with CLBP; consequently, they were excluded out of this study, therefore only 40 CLBP female patients aged between 38–65 years were included in the trial. All of them completed the study period.

The baseline demographic characteristics of the patients of our study recorded an age range between 38-65years with average of 50 years; the disease duration was from 1 to 5 years with mean of 2.56 years; the weights of those patients ranged between 61-122kg with an average of 80.0kg; their heights were between 146-168cm with average of 155.5cm and the body mass index (BMI) of them ranged between 25-52 with average value 32.99 (Table 1).

In comparing with the values of VAS and ODI of the patients before bee stinging, the obtained data of both VAS and all items of ODI, after exposing the CLBP patients to BVA, showed a significant improvement at p <0.0001level; while lifting recorded a significant reduction at p<0.05 level (Table 2).

In addition, BVA treatment resulted in a significant improvement in the immunological status that achieved from the reduction in serum inflammatory cytokines; as there was a significant (p<0.05) decrease in serum TNF $\alpha$  (-14%), IL1 $\beta$  (52%), IL6 (-53%) and NF $\kappa$ B (-32.6%) matched with a significant (p<0.05) reduction in ESR (-39.4 %) in compare to the corresponding values before treatment (Figures 1 and 2).

**Table 1:** Demographic characteristics of patients with CLBP included in study.

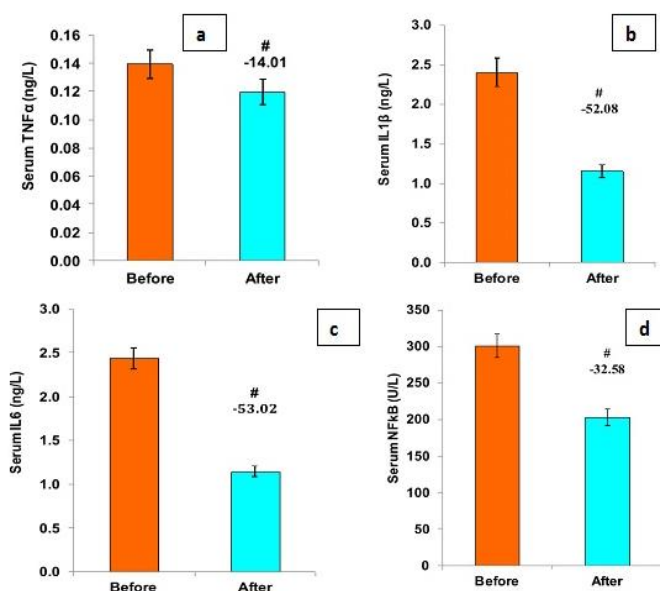
Parameters	Range	Mean $\pm$ SD.
Age / years	38-65	50.9 $\pm$ 6.22
Disease duration/ years	1-5	2.65 $\pm$ 1.31
Weight /Kg	61 – 122	80.83 $\pm$ 14.81
Hight /cm	146 – 168	155.45 $\pm$ 4.8
BMI (body mass index)	25.5 - 52	32.99 $\pm$ 6.03

The data of all patients are expressed as mean  $\pm$  standard deviation

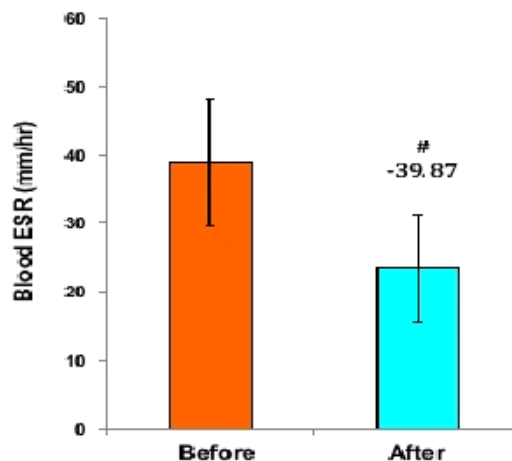
**Table 2:** Mean of VAS and all items of ODI of patients with CLBP pre- and post treated with BVA.

	Before	After	% improve	p value	
VAS	8.35 $\pm$ 1.31	2.9 $\pm$ 1.77	65.27	<0.0001	sig
PI	2.80 $\pm$ 0.95	0.45 $\pm$ 0.51	83.93	<0.0001	sig
PC	2.0 $\pm$ 0.56	0.35 $\pm$ 0.48	82.50	<0.0001	sig
Lifting	1.85 $\pm$ 1.08	1.15 $\pm$ 0.88	37.84	<0.05	sig
Walking	2.40 $\pm$ 0.75	0.75 $\pm$ 0.78	68.75	<0.0001	sig
Sitting	2.65 $\pm$ 0.81	0.30 $\pm$ 0.47	88.68	<0.0001	sig
Standing	3.35 $\pm$ 0.18	2.94 $\pm$ 0.17	12.24	<0.0001	sig
Sleeping	3.05 $\pm$ 1.27	0.75 $\pm$ 0.96	75.41	<0.0001	sig
Social	2.35 $\pm$ 0.87	0.45 $\pm$ 0.61	80.85	<0.0001	sig
Travelling	2.95 $\pm$ 1.23	0.55 $\pm$ 0.60	81.36	<0.0001	sig
Total	23.4 $\pm$ 5.4	5.70 $\pm$ 3.89	75.64	<0.0001	sig

Data are expressed as mean  $\pm$  standard deviation.



**Fig. 1:** Shows the effect of BVA treatment on serum level of TNF $\alpha$  (a), IL1 $\beta$  (b), IL6 (c), and NF $\kappa$ B (d) of CLBP patients.



**Fig. 2:** Shows the effect of BVA treatment on level of ESR of CLBP patients.

## DISCUSSION

In order to choose the CAM therapy to a part for treatment in a various conditions, it is important to consider the relevant problem such as: curability of the illness by conventional treatment, degree of adverse effect, toxicities, invasiveness of conventional treatment, also safety, availability and quality of desired CAM treatment (Adam *et al.*, 2002). The results from our study may be a good evidence for the effectiveness and safety of BVA on CLBP as an adjunctive to conventional therapy. In addition, it can be provided as clinical evidence regarding whether BVA can be beneficial in improvement of disease related functional status and daily life activity for the patients. Safety intervention is important for estimating its risk-benefit framework. In this study, VAS and all items of ODI Q were significantly improved post intervention with BVA; these improvements could be attributed to the antioxidative potential of BVA injection that significantly reduced the level of reactive oxygen species (ROS) and activity of proteolytic enzyme leading to inhibition of free radical responsible for damage of synovial fluid proteins (Kim *et al.*, 2002). Our finding is in agreement with that of (Shin, 2011) who reported that VAS was significantly reduced in BV-treated patients group and controlled the early pain compared to acupuncture treated group. Lee *et al.*, (2011) suggested that BVA has been reported to have anti-inflammatory and analgesic effects; thus, BVA is applied to treat painful diseases and musculoskeletal diseases such as lumbar spinal stenosis, herniation of an intervertebral disc, arthritis, neuralgia, myofascial pain syndrome and frozen shoulder; this study positively supported our results for using BVA to alleviate pain in chronically complaining patients and improving their quality of life. The analgesic anti-inflammatory effect of BVA has been proven in several animal arthritic models (Jae-Dong *et al.*, 2005). BVA injection at acupoint BI 23 significantly reduced the level of reactive oxygen species (ROS) and proteolytic enzyme activity as these free radical leads to damage of synovial fluid proteins in a rat inducing arthritis by a mixture of type II collagen (Kim *et al.*, 2002). Bee venom at acupoint GB 34 was found to decrease the numbers of white blood cells, infiltration of fibroblasts and leukocytes into synovial joints, IL-1B, IL-2R, CD56, CD54 and CD 106 in synovial membrane when compared with controls in lipopolysaccharide- induced arthritis in rat model (Do *et al.*, 2001). Stimulation of ST36 acupoint by BVA can decrease chronic constrictive injury of sciatic nerve-induced neuropathic pain by activation of  $\alpha$ -adrenoceptors, but not through opioid receptors (Roh *et al.*, 2004). Also, Tsai *et al.*, (2015) suggested that BV injection at a certain acupoints (LI4, SI3, KI3, ST36, BL23, BL40, CB30, GB34, LR3, unilateral GV1) can enhance treatment of canine neurological dysfunction by intervertebral disk disease.

From the previous studies, the difference in the mechanism between acupuncture and bee venom acupuncture therapy can be monitored, as acupuncture is one of the commonest treatment modalities to treat several chronic inflammatory diseases like osteoarthritis, rheumatoid arthritis,

(Ezzo *et al.*, 2001 and Berman *et al.*, 2002), neuropathic postoperative pain and low back pain (Han *et al.*, 2010 and Joaquim *et al.*, 2010) also it can trigger the release of endogenous endorphins, dynorphins, enkephalin (Kim *et al.*, 2009) as well as it can stimulate the noradrenergic inhibitory systems (Zhang *et al.*, 2004, Koo *et al.*, 2008 and Kim *et al.*, 2011); while BVA has been reported to attenuate neuropathic pain system through activation of  $\alpha$ -adrenergic receptors, but not opioid receptors (Kang *et al.*, 2012). However, Chen and Lariviere (2010) considered that BV having nociceptive and anti-nociceptive effects together this is called a "double-edged sword". Also, other descending inhibitory systems like GABA, serotonergic and/or cholinergic systems might be involved (Kim *et al.* 2005, Kim *et al.*, 2005 and Park *et al.*, 2009). BV injections can cause the adrenal gland cortex and pituitary gland to increase the concentration of cortisol (Knepel and Gerhards, 1987 and Vick and Shipman, 1972). Several studies suggested that the effects of BVA depend on the site of injection as the acupuncture points are more effective than non-acupoints. So, anti-nociceptive action of BV is only produced when BV is injected into a specific acupoint (Lee *et al.*, 2001, Seo *et al.*, 2003, Kim *et al.*, 2003). Also, BVA exerts its action not only pharmacological but also mechanical function from acupuncture stimulation; it believed that BVA has been proposed as another approach for treatment rather than needle acupuncture (Lee *et al.*, 2005), so we designed our study as the bee sting must be at a specific acupoints related to LBP according to traditional Chinese Medicine (TCM). The results of many studies give a good idea for applying this therapy as a clinical treatment for many conditions in human being (Lee *et al.*, 2006). Kim and Song (2005) and An and Song (2007) those carried out on two groups of cervical pain patients, one group received electro-acupuncture and the other group received bee venom therapy; they suggested that the bee venom showed better results. Another more recently study (Gang *et al.*, 2012) was done to compare bee venom pharmacopuncture therapy and acupuncture therapy in patients with cervical herniated intervertebral disc there was more improvement in VAS of bee venom group than acupuncture group. These two mentioned studies supported our findings. Kwon *et al.* (2001) designed an experiment to detect whether BVA is a clinically safe and effective method for decreasing pain in knee osteoarthritis patients compared to traditional needle acupuncture. They found that BVA group showed a better response for pain relieving than needle acupuncture group. We concluded from the results of these several randomized controlled trials studies that bee venom acupuncture is more effective in treatment of arthritis than acupuncture.

In a study carried out by Seo *et al.* (2013) on 54 CLBP, patients were randomized into 2 parallel arms, one group received diluted BV acupuncture and other group received normal saline; they found that there was a significant improvement in VAS and ODI in BV acupuncture group than saline or sham group. Same as our results that also showed BVA is effective in reducing VAS and ODI. It was stated that specific immunotherapy with bee venom can cause a nearly complete protection against allergic reactions from stings in most of patients (Severino *et al.* 2008). According

to Janik *et al.*, (2007) who found that bee venom was administered in the form of injection of a venom extract or a direct bee sting the same as design twice a week. It is claimed that bee venom therapy works with the patient's own body to decrease level of inflammation, as the stings produce inflammation; the body mounts an anti-inflammatory response (Park *et al.*, 2010 and Prado *et al.*, 2010)

The major component of BV was found to suppress inflammation by decreasing phospholipase (PLA) enzymatic activity is melittin (Saini *et al.*, 1997) that is why the cytokines levels (TNF $\alpha$ , IL1 $\beta$ , IL6 and NF $\kappa$ B) were reduced after stinging the patients with BV. NF- $\kappa$ B is one of the most important regulators of expression of pro inflammatory genes such as COX<sub>2</sub>, and TNF $\alpha$  (Jeon *et al.*, 2000 and Surh *et al.*, 2001). BV or melittin has a potent anti-inflammatory effect through inhibition of the DNA binding activity of NF- $\kappa$ B by inhibition of I $\kappa$ B phosphorylation, leading to decrease of P50 translocation, resulting in reduction of inflammatory gene expression (Hye *et al.*, 2004) this can explain the reducing potential of BVA on serum level of NF- $\kappa$ B which in its turn down regulating TNF $\alpha$ . That is an important mechanism of the anti-arthritis effect of BV In this study, the serum levels of TNF $\alpha$ , NF- $\kappa$ B, IL-1 $\beta$  and IL-6, after 6 weeks of BVA, recorded a significant improvement compare to their values before BVA therapy. This result is in agreement with the results of Martins *et al.*, (2011) who suggested that ten of the thirteen cytokines were significantly different between control and patients subjects. In this study, there was a statistically significant improvement in patients regarding their health, general conditions as well as their immunity in particular modulation of the immune system, and this is in agreement to that explained by (Son *et al.*, 2007, Park *et al.*, 2010).

Concerning the correlation between non-specific low back pain and raised titers of inflammatory cytokines and other non-specific immunological responses, IL-23 was significantly increased in chronic low back pain patients as proved by Luchting *et al.* (2014). Moreover, Cheng *et al.* (2015) reported that exercise intervention, the most effective back pain treatment, enhances expression of Sirtuin 1 and up-regulates the expression of peroxisome proliferator-activated receptor-gamma, PPAR- $\gamma$  coactivator-1 and FoxOs family proteins and also increases the activity of catalase and superoxide dismutase compared to untreated patients.

## CONCLUSION

There is concerned about the extra cost of BVA; it considers as the cheapest mode for therapy from an economic point of view. In order to widespread the clinical therapeutic field of BVA around the world, rigorous trials of well-organized design are urgently required to detect its role in treatment of arthritis. Understanding of advantage and risks of BVA is also required. However, the quality of the studies and the number of subjects has been limited; BVA is considered to be a highly promising tool for treatment of chronic arthritis.

From the results, it could be concluded that bee venom therapy could be a potential new therapeutic agent in the treatment of low back pain patients, with minimal tolerable side effects. Interleukin-1 $\beta$ , IL6, NF $\kappa$ B and TNF $\alpha$  gave an idea about mechanism of action and chemical changes occurring with BVA. This work is considered a possible starting point for further larger studies with wider scales of applications to confirm our findings.

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