Research Article

Value of Mesotherapy for Treatment of Chronic Low Back Pain: A Randomized Trial

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Abstract
Background: Chronic low back pain is a common painful medical problem which has significant socioeconomic impact. Conventional pharmacological therapy usually associated with adverse effects. Mesotherapy is a minimally invasive technique done by subcutaneous injections of drugs, plant extracts, homeopathic agents, or other bioactive substance[١٢]. **Objectives:** To evaluate the value of mesotherapy, either by traditional drugs or by bee venom, as a therapeutic modality for management of chronic low back pain and compare it versus conventional systemic administration of nonsteroidal anti-inflammatory drugs and corticosteroids for patients with chronic low back pain. **Methods:** A randomized controlled clinical trial with three parallel arms carried out at the Department of Rheumatology and Rehabilitation -Faculty of Medicine, Fayoum University in Egypt. The study was assessed and approved by the Faculty of Medicine Fayoum University Ethics Committee and has therefore been performed in accordance with the ethical standards laid down in the ١٩٦٤ Declaration of Helsinki. One hundred and twenty (١٢٠) patients (both sexes) aged ١٩– ٦٥ years and suffering from back pain since more than ٣ months and reported a current pain intensity >٦٠ on a ١٠٠mm visual analogic scale. Patients are randomly allocated to be divided to three main groups: Group I: ٤٠ patients received drug therapy according to the following protocol: ketoprofen ١٥٠ mg /day orally for ١٢ days + methylprednisolone (MP) intramuscularly ٤٠ mg/day for the first ٤ days, then ٢٠mg/day for ٣ days, then ٢٠ mg/day at alternate days + esomeprazole ٢٠ mg/die for ١٢ days. Group II: ٤٠ patients received: ٢٪ lidocaine (١ mL) + ketoprofen ١٠٠ mg (٢ mL) + MP ٤٠ mg (١ mL) at day ١ and ٤, then ٢٪ lidocaine (١ mL) + ketoprofen ١٠٠ mg (٢mL) + MP ٢٠ mg (٠.٥ mL) day ٧, ١٠, and ١٣, five repeated injections. Group III: ٤٠ patients received (٠.٥ mL) diluted purified bee venom + ٢٪ lidocaine (٠.٥ mL) twice weekly for three weeks. Pain intensity and functional disability were assessed at baseline (T٠), at the end of treatment (T١), and ٦ months thereafter (T٢) by using visual analogic scale (VAS) and Roland-Morris disability questionnaire (RMDQ). **Results**: In the three groups, VAS and RMDQ values were significantly reduced at the end of drug treatment and after ٦ months, in comparison with baseline. there was no significant difference in mean basal VAS and RMDQ scores between three groups, at the end of treatment (T١) but mean VAS and RMDQ scores level in group II showed significant decrease than G I and G III (p value <٠.٠٥). At T٣, the mean VAS and RMDQ scores showed further decrease in GII in comparison with GI and GIII. **Conclusions**: Mesotherapy by using conventional drugs; NSAIDs and corticosteroids or by bee venom is an effective and well-tolerated method for managing low back pain in the short-term, and may be a valid alternative to conventional therapy in the treatment of low back pain with corticosteroids and NSAIDs.
KeyWords: Chronic low back pain, mesotherapy, treatment

Introduction
A significant proportion of the population are affected by Low back pain (LBP) which is a common condition, with an estimated prevalence of ٧٠٪–٨٥٪ [١&١١]. In the developed countries, Low back pain affects a high proportion of adult population and has a major impact on health care system and society[٣١]. The socioeconomic impact of LBP is related to its greater comorbidities and more frequent prescriptions of pharmacotherapies which used to reduce pain, inflammation, and functional disability[٢٣]

The extensive use of nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol (acetaminophen), corticosteroids, and various opioids as, Conventional pharmacological therapy is associated with these painful conditions. However, the major drawback of pharmacological therapy with analgesics and anti-inflammatory drugs is the frequent association with adverse effects[٤٨]; in particular, NSAID-related toxicity is connected to the inhibition of constitutive prostaglandins (PGs), with consequent impairment of gastric mucosal defense and renal homeostasis[٥٣].On the other hand, the availability of selective cyclooxygenase-٢ (COX-٢) inhibitors (Coxibs), despite providing a reduction in the gastrointestinal toxicity, resulted in a high risk of developing serious cardiovascular and renal side effects[١٣&٣٥].

Chronic therapy with systemic corticosteroids may afford a variety of serious untoward reactions, leading to hypertension, diabetes, glaucoma, gastric ulcer, osteoporosis, and psychiatric disorders[٤٢&٤٥]. Finally, opioids, used either alone or in combination with paracetamol and/or NSAIDs, may cause a variety of side effects which are dose-limiting and reduce quality of life, bowel dysfunction being one of the most common and persisting problems[٤]. Thus, new therapeutic options endowed with comparable efficacy and better safety are warranted[١٢].

Among the various attempts to reduce drug toxicity, the use of local therapy (neural block, intraarticular, or periarticular injections of corticosteroids) has gained popularity among physicians *and* [٤٩&٢١] despite some controversies concerning its efficacy as a therapeutic remedy[٦]. During the last decades, researchers and patients have become increasingly interested in complementary and alternative medicine (CAM) as a possible mean to ensure efficacy, while improving therapeutic safety[٤٤,٣٩,٢٦]. Back pain, in particular, is the most common medical problem for which patients seek complementary and alternative medical treatment, including bee venom therapy. However, the effectiveness and safety of such treatments have not been fully established by randomized clinical trials[٢٦&٤٣]. However, despite the large favour by the general population and several published clinical studies, only few physical treatments are supported by strong scientific evidence [٩,٥,١٧], likewise, controlled clinical studies evaluating the effectiveness of the most popular CAM therapies used for low back pain are still scarce[١٧], very few mechanistic studies are available[٥١&[٥٢]the quality of research is generally poor, and general conclusions are difficult to reach[٩]. Mesotherapy was introduced ٥٠ years ago by Michel Pistor, a French physician who utilized this technique as a novel analgesic therapy for a variety of rheumatologic disorders[٣٨].

Mesotherapy is a minimally invasive technique that consists of subcutaneous injections of drugs and, occasionally, plant extracts, homeopathic agents, or other bioactive substances; for this reason, it has been often considered a CAM, rather than a conventional medical therapy[١٤&١٢].

Since its introduction, the use of mesotherapy has been expanded, and therapeutic indications have increased; although most applications are found in osteoarticular pathologies[٤٠&٧]. Over the recent years, this technique has become popular in cosmetic medicine for the treatment of cellulite and fat deposition[٧&٢]. Despite of variable accessibility to conventional treatments, patients with low back pain (LBP) have increasingly been using complementary and alternative medicine to alleviate their symptoms[٢٥]. The tendency towards the use of complementary and alternative medicine in CLBP may reflect the deficits and unfulfilled patient expectations in conventional medical treatment[٤١&٢٢]. But evidence of effectiveness of therapeutic modalities of complementary and alternative medicine has not been fully established[٤٣].

Bee venom has many pharmacological actions, including analgesic, anti-inflammatory, anti-arthritic, and anti-cancer effects by activation of the central inhibitory and excitatory systems, modulation of the immune system and through other mechanisms[٤٦]. The analgesic effects

of Bee venom have been reported in animal experiments[٣&٨] and in the clinic[٢٩&٣٠]. Researchers have found that Bee venom could be a therapeutic option for reliving LBP[٢٧]. There has been relatively little evidence in clinical trials on Bee venom to treat CLBP, especially rigorous randomized controlled clinical trials on the efficacy of Bee venom. However, a rigorous randomized controlled trial is more and more needed to develop clinical indications and the optimal practical guidelines of Bee venom injection[٤٣]. We designed this study to evaluate the effectiveness of mesotherapy, either by traditional drugs or by bee venom, as a therapeutic modality for management of chronic low back pain and compare it versus conventional systemic administration of nonsteroidal anti-inflammatory drugs and corticosteroids for patients with chronic low back pain.

Various LBP treatments, such as pharmacotherapy, physical therapy, manual therapy, psychological therapy, educational therapy, and invasive therapy were recommended by Current Clinical Practice Guidelines (CPGs)[٣١]. ٧٠٪ to ٨٠٪ of the population in many developed countries has used some form of alternative or complementary medicine (e.g., acupuncture).Traditional medicine (TM) is defined as indigenous medicine used to maintain health and to prevent, diagnose, and treat physical and mental illnesses and is distinct from allopathic medicine based on theories, beliefs, and experiences[٥٤].

Although studies on the use of TM are increasing[١٨&٢٠], differences in medical circumstances, culture, or poor evidence in support of TM seem to complicate the inclusion of TM in CPGs. CPGs are systematically developed to assist practitioners and patients in making decisions about appropriate healthcare in specific clinical circumstances[١٩].

Methodology and Study Design in details:

Study Design and setting:

The study was randomized controlled parallel multiple three arm clinical trial with ratio (١:١:١) conducted on ١٢٠ patients, carried out at the Department of Rheumatology and Rehabilitation -faculty of medicine of Fayoum University.

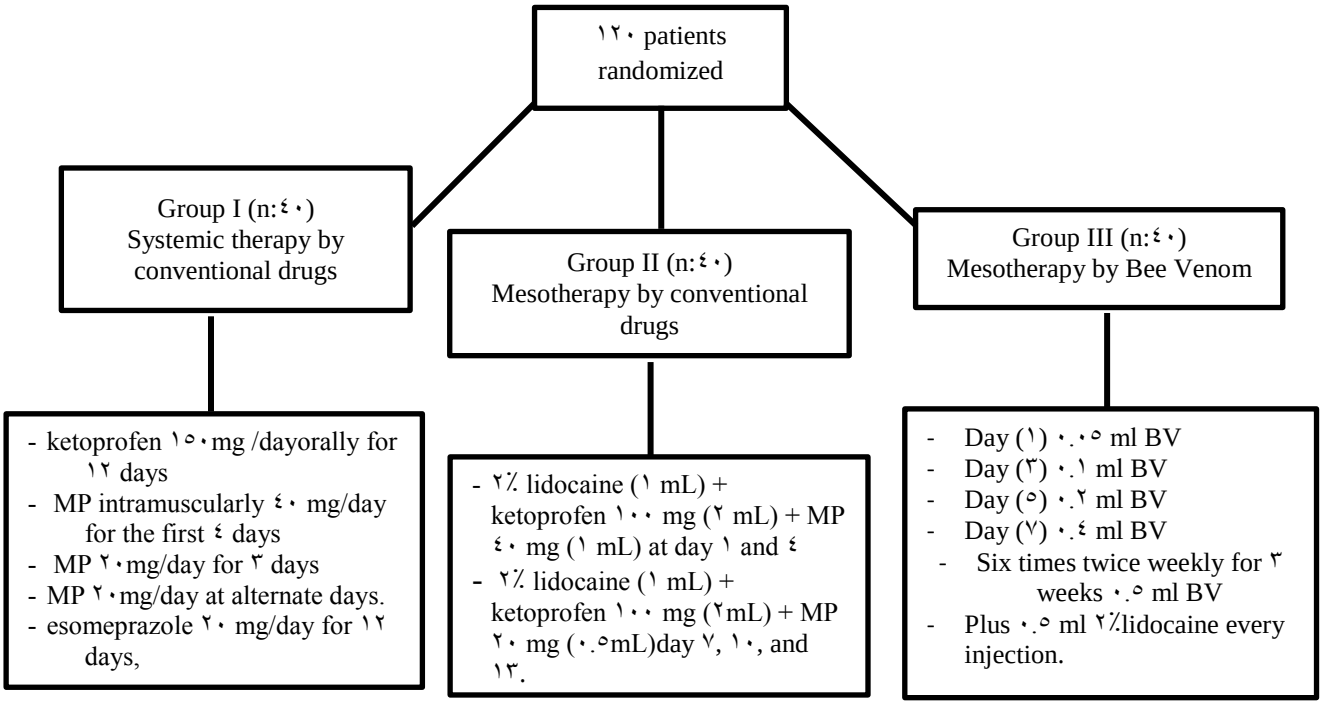
The study was assessed and approved by the Faculty of Medicine Fayoum University Ethics Committee and has therefore been performed in accordance with the ethical standards laid down in the ١٩٦٤ Declaration of Helsinki, and according to the guidelines for experimental investigation with human subjects required by the local University. Informed written consent was obtained from each patient.

Patient recruitment

Patients with a sample size of one hundred and twenty (١٢٠) patients (both sexes) aged ١٩– ٦٥ years and suffering from chronic low back pain, were included into the study. Patients were recruited for the study from March ٢٠١٤ and December ٢٠١٤ (about ١٠ months) and check for eligibility by the clinical investigator. Patients are enrolled into the study, provided that they have been suffering from back pain since more than ٣ months and reported current pain intensity > ٦٥ on a ١٠٠ mm visual analogic scale (VAS). **Exclusion criteria** are represented by diabetes, anticoagulant therapy, or pregnancy. Patients are also excluded if they had evidence of cardiovascular, renal, hepatic, gastrointestinal, or psychiatric diseases. Informed written consent was obtained from each patient. Patients can leave the study at any time for any reason.

- Study Design: Patients who met the eligibility criteria are randomly allocated to be divided to three main groups Figure (١):

Figure ١: Study design and drug treatment.



(٤٠ patients) receive drug therapy according to the following protocol: ketoprofen ١٥٠mg/day orally for ١٢ days; MP intramuscularly ٤٠ mg/day for the first ٤ days, then ٢٠mg /day for ٣ days, then ٢٠ mg/day at alternate days. Patients of this group received esomeprazole ٢٠ mg/die for ١٢ days, as gastroprotective therapy.

Group II:

٤٠ patients receive drug therapy according to the following protocol:

٢٪ lidocaine (١ mL) + ketoprofen ١٠٠ mg (٢ mL) + MP ٤٠ mg (١ mL) at day ١ and ٤, then ٢٪ lidocaine (١ mL) + ketoprofen ١٠٠ mg (٢mL) + MP ٢٠ mg (٠.٥ mL) day ٧, ١٠, and ١٣. Five repeated injections (٤ mL, for each injection, for the first and second and ٣.٥ml, for each injection, for the last three) were administered

Group III:

٤٠ patients receive bee venom by the following protocol:

٢٪ lidocaine (٠.٥ mL) + (٠.٥ mL) diluted purified bee venom which we get from the Holding company for Biological Products and Vaccines (VACSERA) [٥١, Wezaret ElZeraa St., Agouza, Giza, Egypt. Tel:٧٦١١١١١ Fax:٧٤٨٣١٨٧ – ٧٦٠٩١٧٧ E-mail:oeo @vacsera.com Web Site: www. vecsera.com] and the patients receive the venom according to VACSERA dosage schedule recommendation after sensitivity test and preparatory gradually increased doses in the first week and then ٠.٥ ml twice weekly for three weeks (table ١).

Table ١: The dosage schedule recommended by VACSERA:

Rush treatment	Day (١)	Day(٣)	Day(٥)	Day(٧)	Day(٩)
	٠.٠٥ ml	٠.١ ml	٠.٢ ml	٠.٣ ml	٠.٥ ml
Maintenance Treatment	٠.٥ ml ٢-٣ times weekly				

Both of group II and group III patients administered a perpendicular, subcutaneous injection at a depth of about ٠.٥ cm after sterile skin preparation with the patient lying in the prone position and at inter and paravertebral level and along the running of sciatic nerve (about ten sites), through specific needles (٣٠ G × ٤ mm), which were inserted deeply for the whole length (Figure ٢). Lidocaine was used to minimize pain at site of injection.

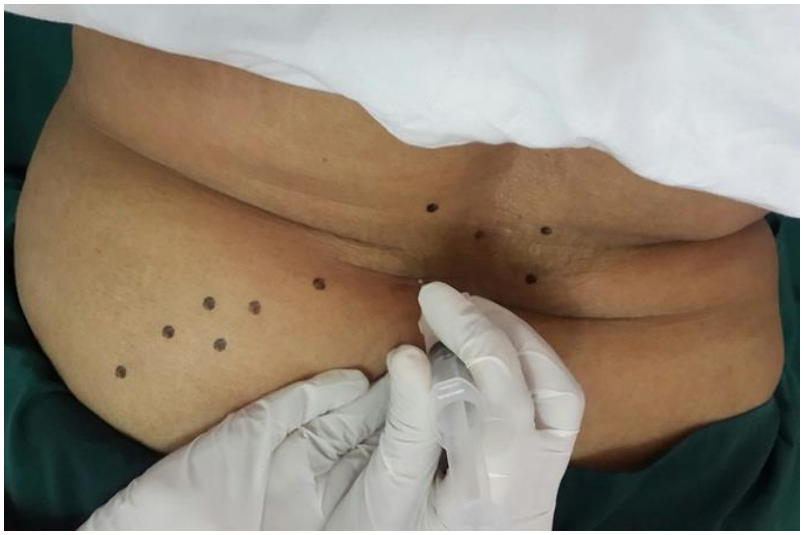


Figure ٣: Injection points of a single mesotherapy treatment. Drug injections were administered along the running of sciatic nerve, through specific needles (٣٠ G × ٤ mm) (see Methods, for details).

Outcome Measures

Self-rated pain intensity was assessed by using the VAS scale (٠ = no pain, ١٠٠ intolerable pain), a horizontal, unmarked ١٠٠ mm scale widely validated to assess pain [٣٦].

Functional disability in the daily life activity was measured by the Roland-Morris disability questionnaire (RMDQ) (varying score from ٠ to ٢٤). Both parameters were evaluated at baseline (T٠), at the end of the drug treatment (١٢ days, T١), and at ٦ months thereafter (follow up, T٢) independently to the pharmacological treatment.

Statistical Analysis:

Data was analyzed using the statistical package SPSS version ١٦. Descriptive statistics were used to describe variables; number, percent, for qualitative variables. Mean, SD, range for Quantitative variables. Paired t test was utilized to analyze the variations among values obtained at baseline (T٠), end of treatment (T١), follow up (T٢). Comparison between groups was done using the χ^2 test for qualitative variables as sex, Comparison of quantitative variable was done using ANOVA test followed by post hoc tests for more than two groups. P value <٠.٠٥ was considered statistically significant

Result

Table ٢: Baseline characteristics of patients

	G I	G II	G III	P – value
Gender **Males. no** **Females. No**	 ٢١ ١٩	 ٢١ ١٩	 ٢٠ ٢٠	٠.٩٦
Age, mean ±SD	٣٧.٥٨±٧.٩٣	٣٧.١٨±٩.٧	٣٧.٨٥±٩.٤	٠.٩٤٥
VAS, mean ±SD	٨٣.٨٨±٨.٧	٨٤..٠±٨.٨٥	٨٣.٢٥±٩.٣	٠.٩٢٣
RMDQ, mean ±SD	١٩.٠٨±٢.٠٦	١٩.١٥±٢.١	١٨.١٨±٢.٣	٠.١٠٨

This table showed that the three groups were balanced with respect to demographic and baseline characteristics; there was no significant difference between study groups regarding age and sex distribution, also there was no difference regarding basal VAS and RMDQ scores.

Table ٣: Comparisons of VAS scores between groups

VAS	Group I	Group II	Group III	P – value		
	Mean±SD	Mean±SD	Mean±SD	GI GII	GI GIII	GII GIII
T٠	٨٣.٨٨±٨.٧	٨٤±٨.٨	٨٣.٢٥±٩.٣	٠.٩٥	٠.٧٥	٠.٧١
T١	٩.٠±٨.١	٤.٧٥±٥.٥	١٢.٥±١٠.٣	٠.٠١٧	٠.١١٢	٠.٠٠١
T٢	٨±٩.٦	٠.٢٥±١.٥٨	٢٠.٣±١٧.٥	٠.٠٠	٠.٠٠١	٠.٠٠

This table showed that there was no significant difference in mean basal VAS scores between three groups (T٠). After treatment: T١ , although reducing mean VAS level in three groups, but mean VAS score level in group II showed marked decrease than G I(p value= ٠.٠١٧) and G III (p value= ٠.٠٠١). After follow up, the mean VAS scores showed further decrease in GI and GII, and slight increase in GIII. There were significant differences between three groups.

Table ٤: Comparison of RMDQ scores between study groups

RDMQ	Group I	Group II	Group III	P – value		
	Mean±SD	Mean±SD	Mean±SD	GI GII	GI GIII	GII GIII
T٠	١٩.٠٨±٢.١٦	١٩.١٥±٤.١٨	١٨.١٨±٢.٩٤	٠.٨٨	٠.٠٨	٠.٠٦
T١	١.٨٧±١.٤	١.٠±٠.٩٦	١.٣±١.٦	٠.٠٠٦	٠.٠٦	٠.٧٦
T٢	٦.٤±٢.٧	٠٠.٦٧±٠.٩٧	٣.٠±١.٥	٠.٠٠٠	٠.٠٠	٠.٠٠٠

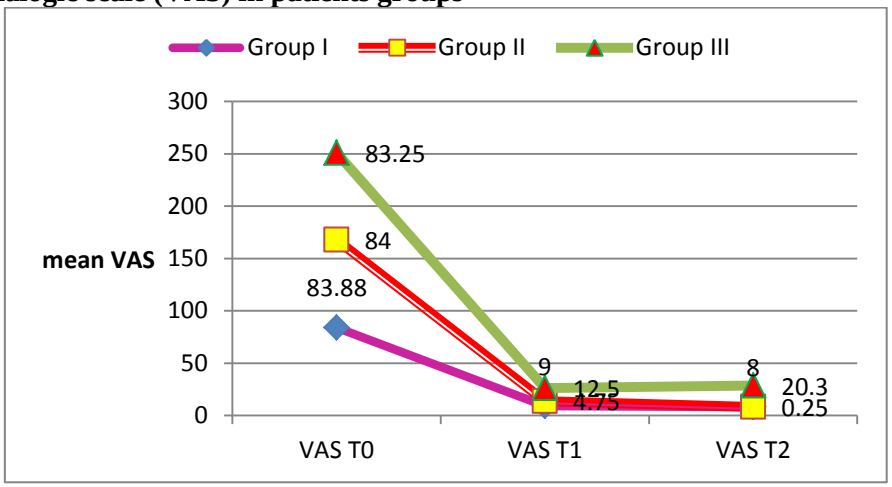
Table ٤ showed that there was no significant difference in mean basal RMDQ scores between three groups (T٠). After treatment T١, the mean RMDQ scores showed decrease level in three groups with significant difference between GI and GII. After follow at T٢; mean RMDQ scores showed further decrease in GII, slight increase in GI and GIII. There were significant differences between three groups.

Table ٥: Comparison of improvement scores between groups

	Group I	Group II	Group III	P – value		
	Mean±SD	Mean±SD	Mean±SD	GI GII	GI GIII	GII GIII
Improvement T١	٩٠.٨٧±٦.٦٧	٩٤.١٤±٥.٥٤	٩٣.٢٣±٨.٠	٠.٠٣٤	٠.١٢٤	٠.٥٥٢
Improvement T٢	٧٠.٥±١١.٤	٩٥.٤٥±٦.٦٢	٨٣.٣±٦.٨	٠.٠٠	٠.٠٠	٠.٠٠٠

By comparing improvement scores at T١; the mean score is significantly higher in G II (٩٤.١٤±٥.٥٤) than G I p value= ٠.٠٣٤. After follow up; mean improvement score shows further increase in GII and decrease in G I and GIII, With significant difference between three groups.

Figure ٢ showed Effect of intervention arms on the reduction of pain, as measured by visual analogic scale (VAS) in patients groups

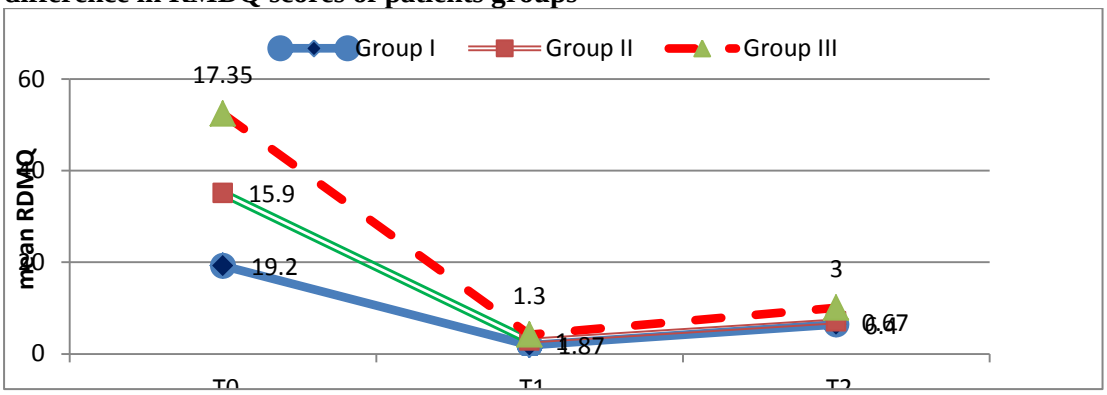


In group I: by comparing T٠ and T١ the mean VAS was significantly reduced from ٨٣.٨٨±٨.٧ to ٩±٨.١ p value = ٠.٠٠٠. After follow up T٢ = ٨±٩.٦٦: still VAS scores significant different from baseline

In group II: The mean VAS was significantly reduced from ٨٤.٠± ٨.٨٥ to ٤.٧٥ ± ٥.٥٤ p value =٠.٠٠٠. After follow up; the mean VAS score showed further decrease in comparison with T١ and T٠. In group III The mean VAS was significantly reduced from ٨٣.٢٥± ٩.٣ to ١٢.٥±١٠.٣ p value =٠.٠٠٠. The mean score showed increase at T٢ but still significantly different from baseline.

By comparing mean scores level after follow up; VAS scores were still significantly different from baseline (p = ٠ .٠٠).

Figure ٣ showed Effect of intervention arms on the reduction disability, as measured by difference in RMDQ scores of patients groups



By comparing mean RMDQ scores measurements at T٠, T١, T٢ in each group; there is significant decrease in mean RMDQ scores at the end of treatment (T١) p value= ٠.٠٠٠ in all groups. At T٢; mean RMDQ scores still significantly lower than at baseline (p value ٠.٠٠).

Discussion

This study aims to evaluate the value of mesotherapy, either by traditional drugs or by bee venom, as a therapeutic modality for management of chronic low back pain and compare it versus conventional systemic administration of nonsteroidal anti-inflammatory drugs and corticosteroids for patients with chronic low back pain. Present results showed that mesotherpaic technique either by bee venom or NSAIDs provides the same therapeutic benefit as that induced by conventional drug administration in reducing pain intensity and disability. Our results showed that Both pain intensity and disability in daily life activity measured by VAS and RMDQ values respectively were significantly reduced at the end of drug

treatment, and this effect was maintained up to ٦ months. These results are in accordance with previous study by Costantino et al.,[١٢] who showed that nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids administered via mesotherapy give same results in reducing VAS & RMDQ scores in patients with acute low back pain. Also previous studies showing that naproxen and diclofenac, administered via mesotherapy, were more effective than after oral administration[٣٣,٢٤,٣٧].

Present results showed that by comparing effectiveness of mesotherapy and conventional systemic therapy, improve-ment scores after ٢w of treatment was significantly higher in group II treated with mesotherapy via conventional drug administration. The interesting finding that by following patients six months later, this group showed further improvement manifested by further decrease in VAS and RMDQ scores and increase in improvement score; this could be explained that; Subcutaneous drug administration results in a very slow drug absorption in comparison with other systemic routes, such as oral and intramuscular; thus it could be hypothesized that anti-inflammatory drugs, administered via mesotherapy, achieve a high drug concentration into the subcutaneous tissue and exert local effects in close proximity to inflammatory cells, sensory fibers, and vascular mediators that orchestrate inflammation and pain[١٢].

The new finding in our research is administration of bee venom that new in topic and our research may be considered the pioneer in adding evidence on its efficacy and safety in patients with chronic non-specific low back pain. Our results reported that BVA administration via mesotherapy is beneficial in reducing both VAS and RMDQ scores. By comparing its effectiveness to conventional drug admistation, after ٢ week treatment at T١, similar findings reported and no difference in both VAS and RMDQ scores. But at ٦ months BVA showed significant better results than GI detected by significant lower VAS and RMDQ scores. This could be explained by slow BVA absorption in comparison with other systemic routes.

Previous randomized clinical trials that compared the efficacy of BVA with acupuncture or normal saline injection on LBP[٥٥&٢٨], they underestimated its effect, that may be due to their poor method-logical quality. But Shin et al. have reported in their trail that BVA is effective for treating chronic low back pain and appears to be a safe therapy.

Conclusions Mesotherapy by using conventional drugs; NSAIDs and corticosteroids or by bee venom is an effective and well-tolerated method for managing low back pain in the short-term, and may be a valid alternative to conventional therapy in the treatment of low back pain with corticosteroids and NSAIDs.

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