Journal of Advances in Medicine and Medical Research



22(3): 1-12, 2017; Article no.JAMMR.33412 Previously known as British Journal of Medicine and Medical Research ISSN: 2231-0614, NLM ID: 101570965

# Treatment of Refractory Chronic Lateral Epicondylitis by Ultrasound Guided Injection of Autologus Stem Cells versus Autologus Whole Blood

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# Authors' contributions

This work was carried out in collaboration between all authors. Author OAN designed the study, wrote the first draft of the manuscript, performed U/S examinations and assists in U/S guided injection. Authors AMO and IHH performed the statistical analysis, wrote the protocol, managed the analyses of the study and perform U/S guided injection. Author MAET prepared the bone marrow mesenchymal stem cells. Author HIK performed U/S examinations and assists in U/S guided injection and managed the literature searches. All authors read and approved the final manuscript.

# Article Information

DOI: 10.9734/JAMMR/2017/33412 <u>Editor(s):</u> (1) Fatima Mubarak, Department of Radiology, Aga Khan University, Karachi, Pakistan. (2) Paulo Sérgio da Silva Santos, Department of Surgery, Stomatology, Pathology and Radiology, Bauru School of Dentistry, University of São Paulo, Brazil. (3) E. Umit Bagriacik, Department of Immunology, Gazi University, Turkey. (1) David A. Hart, University of Calgary, Canada. (2) Meghnad Joshi, D.Y.Patil University, Maharashtra, India. (3) Terry Ellapen, University of Kwa Zulu Natal, South Africa. (4) Ayhan Goktepe, Selcuk University, Konya Complete Peer review History: http://www.sciencedomain.org/review-history/19527

> Received 13<sup>th</sup> April 2017 Accepted 4<sup>th</sup> June 2017 Published 14<sup>th</sup> June 2017

Original Research Article

# ABSTRACT

Background: Lateral epicondylitis, or tennis elbow, is a very common cause of elbow pain among the general population. It is a common presentation in orthopedic clinics.
Patients and Methods: Thirty patients with chronic lateral epicondylitis were included in this prospective study. The patients were divided into two treatments groups. The first group contains

seventeen cases treated by local injection of autologous whole blood (group I) whereas the second group contains thirteen cases treated by local injection of autologous stem cells (group II). **Results:** In the first group, after a mean follow up of 21.2 months, the average VAS improved from 8.2 to 3.2, the average DASH score improved from 74 to 50 and the average Nirchl score improved from 5.9 to 2.7. In the second group, after a mean follow up of 18.7 months, the average VAS improved from 8.7 to 1.7, the average DASH score improved from 76 to 46 and the average Nirchl score improved from 5.8 to 1.7

**Conclusion:** Both stem cells and whole blood injections are safe and helpful for treating chronic lateral epicondylitis. Stem cell injection proved to be safer and more effective for treating tendinopathy. Ultrasonography plays an important role in diagnosing the condition, guiding the injection site as well as assessment of the response to treatment.

Keywords: Lateral epicondylitis; ultrasound guided injection; stem cells.

# 1. INTRODUCTION

The terms lateral epicondylitis and tendinitis are misleading. The pathophysiology of this process is degenerative in nature. The term angioblastic tendinosis may be a more suitable term to describe the lesion. Repeated microtrauma is the usual offending cause. The body responds in an effort to repair the damaged tissue by regulation of local angiogenesis together with fibroblast proliferation. The findings of Kraushaar and Nirschl [1] supported that hypothesis. They evaluated surgical specimens collected from 9 patients after failed conservative management for lateral epicondylitis. Histological examination suggested inflammatory response, general absence of polymorphonuclear leukocytes, lymphocytes, and macrophages. There were areas of poorly organized collagen fibers and matrix with microvasculature, picture denotes healing and regeneration. However, obtaining biopsy is not applicable for early stage of epicondylitis; so it remains obscure if it starts as an inflammatory process.

The ideal treatment for tennis elbow has still not been determined. Non operative measures consisting of activity restriction, splints and orthotics, non steroidal anti-inflammatory drugs and physiotherapy are usually the first lines of management [2].

There are other treatment modalities such as prolotherapy, topical nitroglycerin, iontophoresis, phonophoresis, therapeutic ultrasound, extra corporeal shock wave therapy and low-level laser therapy. However, they have less evidence of effectiveness in treatment of tendinopathies [3]

Currently, some materials are commonly used for local injection for lateral epicondylalgia, such as botulinum toxin, platelet-rich plasma and autologous blood injection [4]. The principle of using autologous blood injection for tendinopathy is to promote healing through the action of growth factors. It aims at providing cellular and humoral mediators to promote healing in areas of degeneration [5] [6] [7].

Recently, mesenchymal stem cell therapy has been used as a novel regenerative approach for treating tendinopathy [8].

# 2. PATIENTS AND METHODS

Between March 2012 and May 2015, thirty cases with unilateral chronic lateral epicondylitis were included in this study. All patients were treated first with modalities such as NSAIDs, splints, physical therapy, local steroid injection but without improvement.

# 2.1 Inclusion Criteria

Chronic unilateral lateral epicondylitis with duration of symptoms more than 6 months and pain severity with minimum VAS score of five.

# 2.2 Exclusion Criteria

Bilateral affection, pregnancy, bleeding tendency, coagulopathies, local infection at the site of the procedure, history of local injection of any medications in the past 6 months, associated neurological lesions such as carpal tunnel syndrome, cervical radiculopathy or peripheral nerve injury. Also cases with collagen diseases and bony malformations or old fractures at the affected elbow were excluded.

# 2.3 Patient Evaluation (Fig. 1) (Table 1)

Pre-treatment plain radiography of the affected elbow was taken to detect any bony lesion or calcification before intervention. Ultrasound examination was done for all cases before the start of treatment to assess the degree of tendon pathology, presence of defect and measuring the thickness of the affected tendon. In addition, ultrasound was used during injection for better localization of the site of injection and used for follow up after treatment.

### 2.4 Patient Groups

The patients were divided into two groups, first group to receive a single local injection of their own blood (Group I), second group to receive a single local injection of stem cells derived from their own bone marrow (Group II).

The process of treatment was simply explained to the patients. Then a written consent was obtained from all patients included in the study. Patients who accepted to receive stem cell injection signed two separate consents one concerned with harvesting bone marrow from iliac crest and one for local injection of stem cells.

# 2.4.1 Group I (autologus blood injection)

This group contains seventeen cases, the age ranged between 26 and 55 years old with an average of 39.7 years old, they were 11 males and 6 females, 14 cases have tendinopathy in the dominant hand and 3 cases in the nondominant hand, the pre-treatment duration of symptoms was 21.8 months (range 7-36 months), the average VAS was 8.2 (range 6-9), the average Nirchl score was 5.9 (range 5-7), the average DASH score was 74 (range 67-86), using ultrasound the average thickness of the extensor tendon was 5.18 mm (range 4-6.2 mm).

Table 1. Pre-treatment data

	Group I	Group II
Average age (years)	39.7 +/- 7.5	40.2 +/- 8.0
Sex (M/F)	11/6	8/5
Hand dominance(dominant/non dominant)	14/3	10/3
Average duration of symptoms (months)	21.8 +/- 8.5	19.4 +/- 7.5
Average VAS	8.2 +/- 1.7	8.7 +/- 1.6
Average Nirchl score	5.6 +/- 1.6	5.8 +/- 1.7
Average DASH	74 +/- 8.8	76 +/- 8.5
The average thickness of the tendon(mm)	5.18 +/- 0.9	5.19 +/- 0.8



#### Fig. 1. Pre-treatment data

Group I (average age 39.7 +/- 7.5 years, average duration of symptoms 21.8 +/- 8.5 months, average VAS 8.2+/-1.7 cm, average Nirchl score 5.6 +/- 1.6, average DASH 74 +/- 8.8, average tendon thickness 5.18 +/- 0.9 mm) Group II (average age 40.2 +/- 8.0 years, average duration of symptoms 19.4 +/- 7.5 months, average VAS 8.7 +/- 1.6 cm, average Nirchl score 5.8 +/- 1.7, average DASH 76 +/- 8.5, average tendon thickness 5.19 +/- 0.8 mm)

# 2.4.2 Group II (stem cell injection) c

This group contains thirteen cases, treated by local injection of stem cells, the age ranged between 28 and 53 years old with an average of 40.2 years old, they were 8 males and 5 females, 10 cases have tendinopathy in the dominant hand and 3 cases in the non-dominant hand, the pre-treatment duration of symptoms was 19.4 months (range 6-32 months), the average VAS was 8.7 (range 7-9), the average Nirschl score was 5.8 (range 4-7), the average DASH score was 76 (range 66-87), using ultrasound, the average thickness of the extensor tendon was 5.19 mm (range 4.1-6.3 mm).

## 2.5 Method of Treatment

### 2.5.1 Group I

The patient is placed in an appropriate and comfortable position that allows for sterilization and access to the site of injection. Sterilization and draping of the elbow region followed by injection of two ml of lidocaine 1% 5 minutes before local whole blood injection. A variable amount of blood is withdrawn from the patient by venesection and about 2-3 ml of whole blood is injected in the extensor carpi radialis brevis with tendon ultrasound guidance and under complete aseptic technique.

#### 2.5.2 Group II

In this group, two steps are performed, first step is preparation of stem cells and second step is injection of the stem cells.

2.5.2.1 Step A: Autologous BMMSC preparation

Patients planned to have stem cell injection are usually sent to lab three to four weeks before the estimated date of the procedure.

#### 2.5.2.1.1 Culture and expansion of BMMSCs

Bone marrow is aspirated from iliac crest under local anaesthesia and under aseptic technique. Harvested bone marrow is received into a heparinized syringe. Bone marrow aspirate is processed within one hour. Then the aspirate is mixed with a one-fifth volume of 6% (w/v) dextran (molecular weight 100 000) (Sigma-Aldrich) and left standing at room temperature for 30 minutes. The remaining cells are washed twice with DMEM and cultured into 75 cm2 tissue culture flasks (Nunc) with an initial culture medium consisting of DMEM supplemented with 50 µg/mL L-Ascorbic acid 2phosphate sesquimagnesium salt hydrate, and 1% antibiotic-antimycotic (100 units 120 /mL penicillin, 0.1 mg/mL streptomycin, amphotericin B 0.25 µg/mL) and 10% fetal bovine serum (FBS) (Sigma-Aldrich). Initial medium change is done after 5 days when adherent cells are recognized. Subsequently, culture media without antibiotics are used and changed 2 to 3 times a week. Three to four weeks after harvesting, the cell sheets are now ready.

#### 2.5.2.1.2 BMMSCs sorting

It was achieved using Multiparameter Flow Cytometer.

Flow Cytometer is an extremely powerful, highthroughput, diagnostic technique which can measure the physical and/or chemical characteristics of single cells as they pass individually through a laser beam. Exposure to the laser beam causes light scattering in two planes, forward angle light scattering and right angle light scattering, which provide information about the size and refractive properties of the cell. More specific cell characteristics can then be determined through the use of fluorescent probes and multiparametric analysis can be performed. Flow cytometers also have the added ability to sort cells within a heterogeneous mixture (also known as a cell or flow sorter) based on the light scattering and fluorescence characteristics of the cells. Such flow cytometers are referred to as fluorescence activated cell sorting (FACS) devices. We used FACS technology to purify MSCs from heterogeneous cell populations based on the identification of cell surface markers expressed by MSCs. We identify and isolate MSC subsets from bone marrow based on the following CD markers CD105+, CD90+ and CD73+ while CD34-, CD11b-, CD HLA-DR- and CD 45-

#### 2.5.2.2 Step B: Injection

Injection technique is done using the same principles as in the first group with the same precautions.

# 2.5.2.2.1 Post injection care

For pain relief only, oral paracetamol and ice therapy were used. Elbow support is advised and the patients are usually instructed to avoid highimpact activities for few weeks, and to follow a program of stretching exercises.

#### 2.6 Evaluation of Response to Treatment

All patients were subjected to questionnaire, physical examination and evaluation using the VAS, Nirschl Pain Scale and DASH score. Pain severity was evaluated before injection and reevaluation was done at 4, 6 and 8 weeks, after the injection.

1. Visual Analog Scale for Pain (VAS score) (range, 0 [no pain] to 10 [agonizing pain]).

#### 2. Nirschl pain scale [9]

- Phase 1. Stiffness or mild soreness after activity. Usually disappears within 24 hours.
- Phase 2. Stiffness or mild soreness before activity that is relieved by warm-up. Symptoms are not present during activity, but return afterward, lasting up to 48 hours.
- Phase 3. Stiffness or mild soreness before specific sport or occupational activity. Pain is partially relieved by warm-up. It is minimally present during activity, but does not cause the athlete to alter activity.
- Phase 4. More intense than phase 3 and interferes with athletic activity. There is mild pain with activities of daily living, but does not lead to major change in them.
- Phase 5. Marked pain which occurs before, during, and after activity, causing alteration of activity. Pain occurs with activities of daily living, but does not cause a major change in them.
- Phase 6. Same pain of phase five that persists even with complete rest. Pain disrupts simple activities of daily living and prohibits doing household activities.
- Phase 7. Sever pain to the degree that it disrupts sleep. It is aching in nature

and intensifies with activity. It is the worst degree with marked disability.

- 3. Disabilities of the arm, shoulder, and hand (DASH) score: It is a 30-point functional score designed to assess function in people with musculoskeletal disorders of the upper limb. Each item is scored from 1–5, and the total score is converted to a 1–100 scale.
- 4. Ultrasound evaluation: A blind observer, a musculoskeletal radiologist, did ultrasound evaluation and evaluation stressed on the pathology present, measuring the thickness of the affected tendon, the hypoechoic changes, the fibrillary pattern, and vascularity of the tendon. All pretreatment changes are recorded.

# 3. RESULTS (Fig. 2) (Table 2)

3.1 Pre-Treatment Ultrasonography, U/S Guided Injection and Post-treatment Ultrasonography: (Fig 3, Fig 4 and Fig 5)

All patients were available for follow up in both groups.

In group I (whole blood group), the period of post-treatment follow up ranged between 6 months and 38 months with an average of 21.2 months, the VAS ranged between 1 and 4 with an average of 3.2, the Nirschl Pain Scale ranged between 1 and 4 with an average of 2.7 and the DASH score ranged between 46 and 57 with an average of 50. The average thickness of the affected tendon was 4.77 mm (range 3.66-5.3). Also, there was reduction of the size of the hypo echoic area and partial restoration of the fibrillar pattern in most of cases. The patients start to feel some pain relief by the week 4 after intervention with the average VAS of 3.7.

#### Table 2. Post-treatment data

	Group I	Group II
Average follow up (months)	21.2 +/- 8.0	18.7 +/- 7.5
Average VAS	3.2 +/- 0.9	1.5 +/- 0.8
Average Nirschl score	2.7 +/- 0.7	1.7 +/- 0.8
Average DASH	50 +/- 7.2	46 +/- 6.8
The average thickness of the tendon (mm)	4.77 +/- 0.8	4.55 +/- 0.8



# Fig. 2. Post-treatment data

Group I (average follow up period 21.2 +/- 8 months, average VAS 3.2 +/- 0.9 cm, average Nirschl score 2.7 +/-0.7, average DASH 50 +/- 7.2, average tendon thickness 4.77 +/- 0.8 mm) Group II (average follow up period 18.7+/- 7.5 months, average VAS 1.5 +/- 0.8 cm, average Nirschl score 1.7 +/-0.8, average DASH 46 +/- 6.8, average tendon thickness 4.55 +/- 0.8 mm)



Fig. 3. Pre-treatment ultrasonography showing thickened hypoechoic tendon with loss of normal fibrillary pattern. This is a case of Group II

In group II (stem cell group), the period of posttreatment follow up ranged between 6 months and 28 months with an average of 18.7 months, the VAS ranged between 1 and 2 with an average of 1.5, the Nirschl Pain Scale ranged between 1 and 2 with an average of 1.7 and the DASH score ranged between 40 and 54 with average of 46. The average thickness of the affected tendon was 4.55 mm (range 3.80-5.1), there was marked reduction of the size of the

hypo echoic changes, decreased vascularity and more restoration of the fibrillary pattern to near normal pattern, but no case achieved normal tendon architecture. In this group, patients start to feel pain relief at 6 weeks after treatment the average VAS was 3.1 and patients of this group continued to have improvement in both pain and elbow function until late follow up.



Fig. 4. U/S guided tendon injection of BMMSCs



Fig. 5. Post-treatment ultrasonography of the same case after 12 weeks showing reduced tendon thickness with partial restoration of the normal tendon echogenicity and of normal fibrillary pattern

# **3.2 Complications of Treatment**

In Group I, one patient developed severe pain after injection which could not be relieved by the usual ordinary measures and was given narcotics for a few days to relieve pain. In another patient, pain was not severe but the range of motion markedly decreased after intervention (range of flexion 95 degrees and extension 160 degrees) even after intensive course of physiotherapy. Finally, he was treated by percutaneous tenotomy of the extensor carpi radialis brevis to increase the range of motion.

In Group II, there were not any reported complications either from harvesting bone marrow or from local injection.

# 3.3 Statistical Analysis

Analysis of data was done using SPSS-16 (SPSS Inc Chicago, Illinois, USA).

# 3.3.1 Demographic data

Demographic data and results were collected and presented as mean (SD), median and count as appropriate. Means were analyzed using unpaired Student's t test for differing variances, medians by Mann–Whitney U tests, and counts or proportions by Fisher–Freeman–Halton generalized extraction tests.

The changes in the post-treatment results were evaluated using Wilcoxon matched pairs test.

## 3.3.2 In the pre-treatment data

There was no significant difference concerning patients'age, sex, pre-operative VAS (p=0.07865), Nirschl score (p=0.06986) or DASH score (p=0.06764).

## 3.3.3 Regarding post-treatment data

In group I the mean change in the post treatment VAS was 5, the mean change in the post-treatment Nirschl score was 3.2, the mean change in the post-treatment DASH score was 24 and the mean change in the thickness of the tendon by ultrasound was 0.41 mm.

In group II, the mean change in the posttreatment VAS was 7, the mean change in the post-treatment Nirschl score was 4.1, the mean change in the post treatment DASH score was 30 and the mean change in the thickness of the tendon by ultrasound was 0.64 mm.

When comparing the results of both groups, there was significant difference in favor of the stem cell group concerning the post-treatment VAS (p value = 0.0001) and DASH score (p value = 0.001).

# 4. DISCUSSION

Most of the non-operative measures for treating lateral epicondylitis have concentrated on suppressing an inflammatory process that does not actually exist since the main pathology of the lesion is tendinosis [10].

The hypothesis beyond the use of autologous blood injection for recalcitrant or refractory tennis elbow is based on the histopathological observation that, tennis elbow is not an inflammatory condition, but a fibroblastic and vascular response called angiofibroblastic degeneration more commonly known as tendinosis. The affected tissues show invasion of micro vessels, fibroblasts and lymphatics [1] [10].

Injection of autologous blood has been reported to be effective in early as well as late results for treatment of lateral epicondylitis. Chemical modifiers of cellular activity carried in the blood and are known to be mitomorphogenic. Injection of autologous blood might provide the necessary cellular and humeral mediators to induce a healing cascade.

Ultrasound guidance improves the outcome and can be helpful for monitoring changes of the common extensor origin. Ultrasound guided injection allows better localization of the lesion and improves outcomes [5] [10] [11] [12] [13].

Using ultrasound guided injection of whole blood, Connell et al. [5] treated 35 patients with refractory lateral epicondylitis. They reported improvement in the VAS and Nirchl score as well as in the sonographic appearance of the affected elbows.

Edwards and Calandruccio [10] injected autologous blood under the extensor carpi radialis brevis for twenty-eight patients with lateral epicondylitis. Ninteen patients improved after single injection, seven patients need second injection while two patients need third injection. In a similar study, Gani et al. [14] treated twentysix patients with refractory tennis elbow with autologous blood injection. After a mean follow up of 8 months, the mean pain score improved from 3.3 to 1.2. The mean Nirschl score improved from 5.5 to 2.1. Only nine patients needed more than one injection.

In Group I of our study where we inject AWB, we agree with Connell et al. [5], Edwards and Calandruccio [10] and Gani et al. [14] as we found improvement of VAS score from 82 to 32 mm and Nirschl score from 5.6 to 2.7 and tendon thickness from 5.18 mm to 4.77 mm.

All patients in our study underwnt single injection.

In contrary to our study, Wolf et al. [15] compared saline, corticosteroid, and autologous blood injections for lateral epicondylitis. Patients were planned to receive either saline with lidocaine, corticosteroid with lidocaine or autologous blood and lidocaine. There were no significant differences in the VAS or DASH scores among the three groups at 2 and 6 month follow-up.

Thanasas et al. [16] compared platelet rich plasma (PRP) versus whole blood for twentyeight patients with resistant tennis elbow. They found no statistically significant difference between groups regarding Liverpool elbow score.

The result of Thanasas et al. [16] study pushed us to use AWB in our study as it is more simple and cheap.

However, Zao et al. [17] treated 40 patients in two groups. Each contained 20 cases: PRP group and AWB group. On the 4th week after injection, the VAS and Mayo score of AWB group were lower than those of PRP group. On the 8th week, the VAS of AWB group was higher than that of PRP group; but the Mayo score of AWB group were lower than those of PRP group.

Bone marrow stromal or mesenchymal stem cells (MSCs) can differentiate into various cell types including bone, cartilage, and fibrous connective tissue including tendon [18]. The resultant cells are non-immunogenic which ensures that there is no major histocompatibility [19]. Therefore, allogeneic transplantation of MSCs does not require immunosuppression of the receiving host. Moreover, MSCs themselves are immunosuppressive and help to suppress the proliferation of lymphocytes [20].

Stem cells (SCs) have the feature of self-renewal capability [21] which means the ability of rapid and continuous autodivision to create new SCs and progenitors more differentiated than the mother cells. Another feature is the high plasticity i.e. the ability to transform into cells from various different tissues.

Plasticity can be explained by transdifferentiation (direct or indirect) and fusion. Trans-differentiation is the acquisition of the identity of a different phenotype through the expression of the gene pattern of other tissue. When incorporates to a cell of another tissue, a SC can express a gene from that cell and acquire a phenotypic element of another tissue [22].

Smith et al. [23] found that injecting MSCs into a strain injury of pony's superficial digital tendon improved the lamination but ultrasonography did not show marked increase in the substance or cross section of the tendon.

Godwin et al. [24] found similar results after injecting 141 racehorses 16 with tendon injuries.

In another study by Watts et al. [25], who randomized the injection of fetal-derived embryonic stem cells (ESCs) to eight horses. Although there was no difference in collagen, DNA, or total proteoglycan between groups, the treatment group showed significantly improved tissue architecture, tendon size, tendon lesion size, and tendon linear pattern.

Moreover, stem cells can improve the density of collagen fibrils, as reported by Hankemeier et al. [26]. They have been shown to have a regenerative effect on tendon-bone healing.

Nourissat et al. [27] induced damage in rat tendoachillis in the area of bone-tendon junction followed by local injection of either chondrocytes or MSCs after surgical repair. A control group has surgical repair without injection. At follow up, cell therapy was proved to be efficient procedure for reconstructing the degenerative entheses. MSC treatment produced better organ regeneration than chondrocyte treatment. The morphological and biochemical properties were similar to those of a native enthesis.

Lim et al. [28] reported similar results in rabbits after anterior cruciate ligament repair. There are not available enough reports about the use of stem cell therapy for humans as those reported in animals. Lee et al. [8] injected adipose-derived mesenchymal stem cells for tennis elbow under ultrasound guidance for twelve cases. After a follow up period of 52 weeks, the VAS scores progressively decreased from 66.8 ± 14.5 mm to 14.8 ± 13.1 mm. It agrees with Group II of our study where we inject BMMSCs, the VAS score improved from average 87 mm to average 15 mm. Also in Lee et al. [8] study, the modified Mayo clinic performance index for the elbow score improved from  $64.0 \pm 13.5$  to  $90.6 \pm 5.8$ . This agrees with Group II of our study where DASH score impreoved from average 76 to average 74. Regarding structural improvement, in Lee et al. [8] study, ultrasound shows that tendon defects significantly decreased. This agrees with Group II of our study where ultrasound shows that tendon shows reduction of its thickness from 5.19 mm to 4.77 mm with partial restoration of the normal tendon echogenicity and normal fibrillary pattern. Regarding safety, Lee et al. [8] and Group II of our study did not show any complications.

In our study, When comparing the results of both groups: Regarding efficacy, there was significant difference in favor of the stem cell group concerning the post-treatment VAS (p value = 0.0001) and DASH score (p value = 0.001). So MSCs injection proved to be more effective than AWB injection. Regarding safety, two patients of the first group had complications one in the form of severe pain and the other in the form of reduction of range of movement while all cases of the second group have not any complications.

No doubt, these findings are affected by the relatively low nomber of cases in our study. Further studies on larger sclae of patients will be helpful to verify our findings.

To our knowledge, our study is the first comparing the use of stem cells versus whole blood for treating tennis elbow. Moreover, the source of stem cells in our study was derived from bone marrow not from adipose tissue.

Ultrasonography proved to be helpful in tennis elbow. It is used for accurate detection of the lesion within the extensor carpi radialis brevis for the purpose of diagnosis as well as treatment of lateral epicondylitis of elbow. The abnormal lesion detected by ultrasonography corresponds to the point of maximum tenderness when compressed by the probe in the symptomatic patients [29]. In our study, diagnosis / pre-treatment assessment, injection technique and follow up / post-treatment assessment all were based on ultra sonographic guidance. Sonography was used to confirm the diagnosis and the accurate localization of the injection site was also based on ultrasonography. Furthermore, ultrasonographic evaluation of results was a cornerstone in this work.

The current study augments our experience and lengthens our learning curve in treatment of lateral epicondylitis.

# **5. CONCLUSION**

Both whole blood and stem cells can be used for refractory cases of chronic lateral epicondylitis. The method of using whole blood is, easy, simple and cheap but is not free of risk and complications. Stem cell treatment though a new field but it seems to be safer and more effective than whole blood for treating resistant tendinopathies.

Sonography of the common extensor origin can be used to confirm lateral epicondylitis and provide information about severity of the disease in patients with lateral elbow pain. It also guides injection site as well as used to assess the response after treatment.

In future, treatment of all types of tendinopathies may be totally achievable by the use of biological methods.

## CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

# ETHICAL APPROVAL

All authors hereby declare that the study has been examined and approved by the appropriate ethics committee of Madina national hospital and have therefore been performed in accordance with the ethical standards of ministry of health in Saudi Arabia.

# **COMPETING INTERESTS**

Authors have declared that no competing interests exist.

## REFERENCES

- Kraushaar BS, Nirschl RP. Tendinosis of the elbow (tennis elbow): Clinical features and findings of histological, immunohistochemical, and electron microscopy studies. J Bone Joint Surg Am. 1999;81(2):259-279.
- Pattanittum P, Turner T, Green S, Buchbinder R. Non-steroidal anti inflammatory drugs (NSAIDs) for treating lateral elbow pain in adults. Cochrane Database Syst Rev. 2013;5:CD003686.
- Childress MA, Beutler A. Management of chronic tendon injuries. Am Fam Physician. 2013;87:486–90.
- Dong W, Goost H, Lin XB, Burger C, Paul C, Wang ZL, Kong FL, Welle K, Jiang ZC, and Kabir K. Injection therapies for lateral epicondylalgia: A systematic review and Bayesian network meta-analysis. Br J Sports Med. 2016;50(15):900-8. Epub 2015 Sep 21.

DOI: 10.1136/bjsports-2014-094387

- Connell DA, Ali KE, Ahmad M, Lambert S, Corbett S, Curtis M. Ultrasound-guided autologous blood injection for tennis elbow. Skeletal Radiol. 2006;35(6):371– 377.
- Suresh SPS, Ali KE, Jones H, Connell DA. Medial epicondylitis: Is ultrasound-guided autologous blood injection an effective treatment? Br J Sports Med. 2006;40:935– 939.
- Lee TG, Ahmad TS. Intralesional autologous blood injection compared to corticosteroid injection for treatment of chronic plantar fasciitis. A prospective, randomized, controlled trial. Foot Ankle Int. 2007;28:984–990.
- Lee SY, Kim W, Lim C, Chung SG. Treatment of lateral epicondylitis by using allogenic adipose-derived mesenchymal stem cells: A pilot study. Stem Cells. 2015;33(10):2995-3005, DOI: 10.1002/STEM.2110
- 9. Nirchel RP. Elbow tendinosis/ tennis elbow. Clin Sports Med. 1992;11(4):851-870.
- Edwards SG, Calandruccio JH. Autologous blood injections for refractory lateral epicondylitis. J Hand Surg Am. 2003;28(2): 272–278.
- 11. Wadsworth TG. Lateral epicondylitis (tennis elbow). Lancet. 1972;1:959–960.
- 12. Baumgard SH, Schwartz DR. Percutaneous release of the epicondylar

muscles for humeral epicondylitis. Am J Sports Med. 1982;10:233–236.

- 13. Anitua E, Andía I, Sanchez M. Autologous preparations rich in growth factors promote proliferation and induce VEGF and HGF production by human tendon cells in culture. J Orthop Res. 2005;23:281–286.
- 14. Gani M, Butt S, Dhar M, Farooq M, Mir K, Halwai M. Autologous blood injection in the treatment of refractory tennis elbow. The Internet Journal of Orthopedic Surgery. 2006(5):1.
- Wolf JM, Ozer K, Scott F, Gordon MJ, Williams AE. Comparison of autologous blood, corticosteroid, and saline injection in the treatment of lateral epicondylitis: A prospective, randomized, controlled multicenter study. J Hand Surg Am. 2011; 36(8):1269-72. DOI: 10.1016/j.jhsa.2011.05.014 367 Epub 2011 Jun 25.
- Thanasas С, Papadimitriou G. 16. Charalambidis C, Paraskevopoulos I, Papanikolaou A. Platelet-rich plasma versus autologous whole blood for the treatment of chronic lateral elbow epicondylitis: A randomized controlled clinical trial. Am J Sports Med. 2011;39(10):2130-4. DOI: 1177/0363546511417113 Epub 2011 Aug 2.
- Zhao LL, Tong PJ, Xiao LW, Zhu QL, Xu B, Yan MH, Zhongguo Gu Shang. Casecontrol study on local injection of autoallergic platelet rich plasma or whole blood for the treatment of tennis elbow. 2014;27(11):908-11.
- Zaidi N, Nixon AJ. Stem cell therapy in bone repair and regeneration. Ann N Y Acad Sci. 2007;1117:62-72.
- Javazon EH, Beggs KJ, Flake AW. Mesenchymal stem cells: Paradoxes of passaging. Exp Hematol. 2004;32:414-425.
- Klyushnenkova E, Mosca JD, Zernetkina V. T cell responses to allogeneic human mesenchymal stem cells: Imrnunogenicity, tolerance, and suppression. J Blamed Sci. 2005;12:47-57.
- Zhong W. Timing cell-fate determination during asymmetric cell divisions. Curr Opin Neurobiol. 2008;18(5):472-478.
- 22. Fortier LA. Stem cells: Classifications, controversies, and clinical applications. Vet Surg. 2005;34(5):415-423.
- 23. Smith RK, Korda M, Blunn GW, Goodship AE. Isolation and implantation of

autologous equine mesenchymal stem cells from bone marrow into the superficial digital flexor tendon as a potential novel treatment. Equine Vet J. 2003;35:99-102.

- 24. Godwin EE, Young NJ, Dudhia J, Beamish IC, Smith RK. Implantation of bone marrow-derived mesenchymal stem cells demonstrates improved outcome in horses with overstrain injury of the superficial digital flexor tendon. Equine Vet J. 2012;44:25-32.
- 25. Watts AE, Yeager AE, Kopyov OV, Nixon AJ. Fetal derived embryonic like stem cells improve healing in a large animal flexor tendonitis model. Stem Cell Res Ther. 2011;2:4.
- 26. Hankemeier S, van Griensven M, Ezechieli M. Tissue engineering of tendons and ligaments by human bone marrow stromal cells in a liquid fibrin matrix in immunodeficient rats: Results of a

histologic study. Arch Orthop Trauma Surg. 2007;127:815-821.

- 27. Nourissat G, Diop A, Maurel N. Mesenchymal stem cell therapy regenerates the native bone-tendon junction after surgical repair in a degenerative rat model. PLoS One. 2010;5:e12248.
- Lim JK, Hui J, Li L, Thambyah A, Goh J, Lee EH. Enhancement of tendon graft osteointegration using mesenehymal stem cells in a rabbit model of anterior cruciate ligament reconstruction. Arthroscopy. 2004;20(9):899-910.
- Noh KH, Moon YL, Jacir AM, Kim KH, Gorthi V. Sonographic probe induced tenderness for lateral epicondylitis: An accurate technique to confirm the location of the lesion. Knee Surg Sports Traumatol Arthrosc. 2010;18(6):836-9. DOI: 10.1007/s00167-009-1037-0 Epub 2010 Jan 29.

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