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Dr. Rajesh Sajjan Shetty
Assistant Professor Department of Orthopaedics Shridevi Institute of Medical Sciences & Research Hospital, Sira Road, Tumkur, Karnataka, India

Dr. Sridhar DK
Assistant Professor
Department of Orthopaedics
Sri Siddhartha Medical College
Agalakote, Tumkur, Karnataka, India

Dr. Jaipalsinh R Mahida
Junior Resident
Department of Orthopaedics
Sri Siddhartha Medical College
Agalakote, Tumkur, Karnataka, India.

Correspondence
Dr. Jaipalsinh R Mahida
Junior Resident
Department of Orthopaedics
Sri Siddhartha Medical College
Agalakote, Tumkur, Karnataka, India

A single blinded randomised controlled trial: To evaluate the efficacy of local autologous blood injection versus local corticosteroid injection for treatment of lateral epicondylitis

Dr. Rajesh Sajjan Shetty, Dr. Sridhar DK and Dr. Jaipalsinh R Mahida

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Abstract
Background: Recent studies have shown that local injection of autologous blood in treatment of lateral epicondylitis results in significant benefit by virtue of various growth factors contained in the blood. The objective of our study was assessment of efficacy of autologous blood injection versus local corticosteroid injection in the treatment of tennis elbow.
Aims and Objectives: To compare pain outcome measures, number of patients completely relieved of pain, post injection exacerbation of pain, recurrent rates and complication rates in both the groups.
Methods and Trial Design: A single blinded randomized controlled trial was undertaken.61 patients of untreated *lateral epicondylitis* were enrolled. A randomization coding system derived from a computer generated randomization table was followed. Both groups were evaluated at 1st week, 4th week and 12th weeks for pain relief and stage of disease, complete relief of pain, recurrent rates, post injection exacerbation of pain, complication rates.
Results: Follow-up done for total 12 weeks divided in to intervals at 1st week, 4th week, and 12th week. At 1st week corticosteroid injection group showed a statistically significant decrease in pain compared to autologous blood injection group. At 4th week both group patients had decrease in pain but statistically not significant when compared to each other. At 12th week follow up autologous blood injection group showed statistically significant decrease in pain compared to corticosteroid injection group.
In corticosteroid injection group at 12th week 6.89% had complete relief of pain and in autologous blood group 19.35% patients had complete relief of pain. Rate of recurrence 21.42% in corticosteroid group, no patient had recurrence in autologous blood group.
26% patients in corticosteroid group had post injection exacerbation of pain and in autologous blood injection group 58.06% had pain, which was statistically significant.
Conclusions: Autologous blood injection was more effective than steroid injection in the short term follow up in tennis elbow.

Keywords: Tennis elbow, autologous blood injection, corticosteroid injection

Introduction
Lateral epicondylitis is frequently diagnosed condition seen in orthopaedic practice.
It has an incidence of 4-7 per 1000 per year in general practice, with a peak between the ages of 35 and 54 years, with a mean age of approximately 42 years [1]. Prevalence among both the gender is same in many literature.
Lateral epicondylitis has been reported to be the because of overuse from many activities, hence the dominant arm is commonly affected. Patients usually present with pain over elbow and there will be tenderness over lateral epicondyle. Even though it has been termed tennis elbow and called same routinely, but non-athletes are commonly affected rather than athletes.
Exact pathophysiology of tennis elbow is not known, currently degeneration of the origin of the extensor carpi radialis brevis (ECRB), repeated micro trauma and incomplete healing response has been accepted as the cause of lateral epicondylitis by most of the researchers [2].
There are many treatment methods for lateral epicondylitis both conservative as well as operative. Most conservative methods such as local corticosteroid injection have focused on suppressing inflammatory process that does not actually exist. A recent review article concluded that for short term outcomes (6 weeks), statistically significant and clinically relevant differences were found on pain and global improvement with corticosteroid injection

Compared to placebo, local anaesthetic, or other conservative treatments [3]. For intermediate (6 weeks to 6 months) and long term outcomes (more than 6 months), no statistically significant or clinically relevant results in favour of corticosteroid injections were found. So it is not possible to draw a firm conclusion on the effectiveness of corticosteroid injection [4].

Recently an injection of autologous blood has been reported to be effective for both intermediate and long term outcomes for the treatment of lateral epicondylitis. There was a significant decrease in pain [5, 6]. It is hypothesized that mitogens such as platelet derived growth factor induce fibroblastic mitosis and chemotactic polypeptides such as transforming growth factor cause fibroblasts to migrate and specialize and have been found to cause angiogenesis. A specific humoral mediator may promote the healing cascade in the treatment of tendinosis as well. These growth factors trigger stem cell recruitment, increase local vascularity and directly stimulate the production of collagen by tendon sheath fibroblasts [7].

Autologous blood was selected as the medium for injection because (1) its application is minimally traumatic, (2) it has a reduced risk for immune-mediated rejection, devoid of potential complications such as hypoglycemia, skin atrophy, tendon tears associated with corticosteroid injection (3) it is simple to acquire and prepare, easy to carry out as outpatient procedure and (4) it is inexpensive.

There are very few studies done to evaluate injection of autologous blood for lateral epicondylitis as treatment modality. Hence it is evaluated by comparing with the corticosteroid injection which is a commonly practiced conservative treatment modality [7, 8].

The purpose of this study is to evaluate the efficacy and role of autologous blood injection at lateral epicondylitis by comparing with local corticosteroid injection.

Materials and Methods

Injection of autologous blood is independent variable and pain at lateral epicondyle is dependent variable.

Study site: All confirmed patients of lateral epicondylitis willing for the treatment attending Sridevi Institute of Medical Sciences And Research Hospital, Tumkur.

Study design: Single blinded randomized control trial comparing the efficacy of autologous blood injection with local corticosteroid injection.

Sample size: A sample size of 30 patients per group is needed to detect a mean difference of 4 unit in DASH score between the two (independent) treatment and assumed common standard deviation of 5 units with 80% power, two-sided α (type I error) of 0.05 and 15% of loss to follow up.

Time frame of study: 1st September 2015 to 1st May 2016.

Inclusion Criteria

Cases of lateral epicondylitis, men and women above fifteen years of age with a pain in the lateral aspect of elbow, tenderness over the common extensor origin, a positive Mills' sign, were included in the study. Mill's sign is more specific because wrist is flexed and hence extensor origin is under tension while doing test.

Exclusion Criteria

- Patients received steroid injections within three months.
- A history of substantial trauma.
- Previously treated by surgery for lateral epicondylitis.
- Other causes of elbow pain such as osteochondritis dissecans of capitellum, lateral compartment arthosis, varus instability, radial head arthritis, posterior interosseous nerve syndrome, cervical disc syndrome, synovitis of radiohumeral joint, cervical radiculopathy, fibromyalgia, Osteoarthritis of elbow, Carpel tunnel syndrome.

Method of Collection of Data

- By interview and examination.
- By follow-up of total 12 weeks. It is divided in to intervals at 1st week, 4th week, and 12th week.

Single blinding was done where person who gives injection and person who follow up the cases for evaluation are different. Cases are injected with intralesional autologous blood injection and controls are injected with local Corticosteroid injection at lateral epicondyle.

Randomization

A randomization coding system derived from a computer generated randomization table was followed.

Procedure

Group A/autologous blood injection group

Patients were infiltrated with injection of 2 millilitres autologous blood drawn from contralateral cubital vein and 1 millilitre of 2% lignocaine, at the lateral epicondyle according to the below mentioned technique.

Group B/Local steroid with local anaesthetic injection group

Patients were infiltrated with 2 millilitres of local corticosteroid (Methyl prednisolone acetate 80mg) mixed with 1 millilitre of 2% lignocaine, at the lateral epicondyle according to the below mentioned technique.

Injection technique: The elbow is flexed to 90° with forearm pronated. With patient in supine posture, elbow will be painted and draped. The bony anatomical landmarks are identified. Two millilitres of autologous blood drown from the contralateral upper extremity vein and mixed with 1 millilitre of 2% lignocaine. The elbow is flexed to 90° with the palm facing down. The needle introduced proximal to the lateral epicondyle along the supracondylar ridge and gently advanced in to the under surface of the extensor carpi radialis brevis while infusing the blood-anaesthetics mixture. Then after two minutes Mill's manipulations were done. With forearm in maximum pronation and wrist in maximum palmar flexion the elbow was repeatedly extended and stretched six to seven times and then a small adhesive sterile dressing was given at the injection site, which was advised to be removed after 2 days. Patients were advised to give rest to the upper limb for 3 days and after that no restriction of activity is advised.

Controls were injected with 2 millilitre local corticosteroid (Methyl prednisolone acetate 80mg) mixed with 1milliliter of 2% lignocaine in the same technique as described above.

Outcome evaluation

Outcome is measured using 'DASH' score and 'Nirschl staging of lateral epicondylitis' [11].

Statistical analysis

Paired t test was used for serial analysis in both groups and unpaired t test for comparison between the two groups. The

chi-squared test was used to compare categorical variables between the groups. A p-value < 0.05 is considered to indicate statistical significance.

Observations and Results

Total 61 patients were included under the present study. Clinical evaluation done for all patients. A baseline DASH scores and Nirschl staging of the pain at lateral epicondyle was recorded. Cases were treated with autologous blood injection and controls with local corticosteroid injection. After the procedure patients were asked to report immediately if any increase in pain was there and were asked to follow up at 1 week, 4 weeks, 12 weeks interval after the intervention. If pain persisted analgesics were given and was advised to be taken only if there is severe pain.

In autologous blood injection group 2 patients were lost to follow up, one after 1st week and one after 4th week. One patient had persisting pain after 4 weeks, he opted for corticosteroid injection at 4th week follow up.

In corticosteroid injection group, two patients lost to follow up after 4th week.

Age group encountered in the study ranged from 22 years to 60 years, with a mean age of 42.6. Peak incidence at fourth decade of life was seen.

The mean age of patients in autologous blood injection group was 38.9 and in corticosteroid injection group was 40.8, p value= 0.428 which was non-significant. Thus, age of patients in both the groups was comparable.

Out of the 61 participants, 29 were males and 32 were females. In corticosteroid injection group, 15 were males and 15 were females. In autologous blood injection group, 15were males and 17 were females. p value= 0.800 which is non-significant. Thus, both the groups were comparable in terms of number of males and females in each group.

Out of the 61 participants, 42 participants had their right side elbow affected and 19 had their left side affected. p value=0.582 which is non-significant. Thus, both the groups were comparable in terms of side of elbow involved.

Out of the 61 participants, 51 participants had their dominant elbow affected and 10 had their non-dominant elbow affected. p value=1 which is non-significant. Thus, both the groups were comparable in terms of dominance of elbow involved.

The mean duration of the condition in all 61 patients suffering from lateral epicondylitis was 8.62 weeks.

The mean duration of the condition in corticosteroid injection group was 8.4 weeks. The mean duration of the condition in corticosteroid injection group was 11.4 weeks. p value= 0.035 which is significant. In autologous blood group patient mean duration was more.

Based on the type of work the patient does at work place, the occupation is categorized as either manual work or non-manual work**.** p value=1 which is non-significant. Thus, both the groups were comparable in terms of type work they do at workplace.

p value for DASH Score is 0.624 and p value for Nirschl score is 0.107 which are statistically not significant. Hence, the outcome values before the injection are comparable.

p value for DASH score is 0.050 and p value for Nirschl score is 0.008 which are statistically significant. Hence, the decrease in pain at 1st week is statistically significant in corticosteroid injection group compared to autologous blood injection group.

p value for DASH Score is 0.0022 and p value for Nirschl score is 0.003 which are statistically significant. Hence, the decrease in pain at 4th week is statistically significant in corticosteroid injection group compared to autologous blood injection group.

p value for DASH Score is <0.0001 and p value for Nirschl score is <0.0001 which are statistically significant. Hence, at 12th week the decrease in pain is statistically significant in autologous blood injection group compared to corticosteroid injection group.

Upto 4th week there was significant improvement with 63.3% of patients completely relieved of pain in patients treated with a corticosteroid injection and 16.66% in autologous blood injection group.

Many of these patients reported recurrences at 12th week follow up. The rate of recurrence was 21.42% in corticosteroid injection group.

The rate of recurrence was 0% in autologous blood injection group. $p \leq 0.001$ which is significant. Thus, corticosteroid injection group showed statistically significant high recurrence rate compared to autologous blood injection group.

After 12 weeks of follow up, 2 (6.89%) patients in corticosteroid injection group were

completely relieved of pain whereas 6 (19.35%) participants in autologous blood injection group were completely relieved of pain. p value≤0.001 which is significant. Thus, autologous blood injection group had statistically significant more number of patients completely relieved of pain.

Table 1: Mean Nirschl score at baseline, 1week, 4th week and 12th week follow up

	Autologous group			Corticosteroid group				
Follow up period	**N**	**Mean Nirschl**	**SD**	**n**	**Mean Nirschl**	**SD**	**p value**	**Inference**
Pre injection	31	4.3	1.90	30	3.8	1.30	0.107	NS
1st week	31	4.0	1.25	30	3.1	1.21	0.008	S
4th week	30	2.6	1.01	30	2.23	0.85	0.133	NS
12th week	28	0.9	0.60	28	1.7	0.67	<0.0001	S

Table 2: Mean DASH score pre- and post-procedure at 1week, 4weeks, 12weeks

	Autologous group			Corticosteroid group				
Follow up period	**n**	**Mean DASH**	**SD**	**n**	**Mean DASH**	**SD**	**p value**	**Inference**
Pre injection	31	30.8	8.21	30	29.8	7.00	0.624	NS
1st week	31	28.6	9.16	30	24.4	7.17	0.050	S
4th week	30	15.8	6.99	30	15.2	6.33	0.707	NS
12th week	28	3.0	2.73	28	12.5	6.28	<0.0001	S

Local skin atrophy: Only two patients (6.6%) had local skin atrophy in corticosteroid injection group while no patient in autologous blood injection group had this problem. p value=0.0150 which is non-significant. There was no statistical significance related to post intervention local skin atrophy.

In corticosteroid injection group 8 participants (26%) patients complained of post-intervention exacerbation of pain while in autologous blood injection group 18 participants (58.06%) complained of increase of pain after local injection. And these patients with this increase of pain after the procedure had to be given analgesics for pain relief as a co-intervention. p value=0.009 which is significant. Thus, autologous blood injection group had statistically significant more post injection exacerbation of pain compared to corticosteroid injection group. Pain usually occurred till 1st week.

No patients reported elbow stiffness, infection, reflex sympathetic dystrophy, post-injection flare, facial flushing, neurovascular damage or tendon rupture or other untoward complications.

Discussion

Tennis elbow is a common problem encountered in orthopaedic practice. Majority of the treatment modalities used for its management lack scientific rationale [9] The role of local steroid is debatable because pathology is not inflammation at the lateral epicondyle.

Recently, an injection of autologous blood has been reported to be effective for both intermediate and long term outcomes for the treatment of lateral epicondylitis. There was a significant decrease in pain. It is hypothesized that mitogens such as platelet derived growth factor induce fibroblastic mitosis and chemotactic polypeptides such as transforming growth factor cause fibroblasts to migrate and specialize and have been found to cause angiogenesis. A specific humoral mediator may promote the healing cascade in the treatment of tendinosis as well. These growth factors trigger stem cell recruitment, increase local vascularity and directly stimulate the production of collagen by tendon sheath fibroblasts [10]

In this current study, the mean age encountered was 39.8 years (Range: 20 to 60years); the peak incidence was seen from 35 to 50 years. This was seen similar in one study which observed mean age of 42 years [11] Another study observed the mean age to be 46.7 years [12] Probably this is working age group, hence mostly affected.

In this current study, out of the 61 participants, 29 (47.5%) were male patients and 32 (52.5%) were female patients. Two other studies had more number of male patients [10, 12]. This study has slightly more number of female patients may be because their involvement in household activities which involve repetitive activities.

In this current study, out of the 61 participants, 42(68.8%) participants had their right side elbow affected and 19 (31.14%) had their left side affected. Out of the 61 participants, 51(83.6%) participants had their dominant elbow affected and 10 (16.39%) had their non-dominant elbow affected. In other two studies, one had 84% of the patients with their dominant elbow affected, while in another 78.6% of the patients with their dominant side affected [13]. It is caused by repetitive activity, hence dominant side involved more.

Parameters like age, sex, side of elbow involved, dominance of upper limb involved, duration of symptom and type of occupation of the patients were comparable. The pre injection mean DASH score in both groups were not comparable, autologous blood injection group had more score. Nirschl staging before injection in both the groups were comparable. Mean DASH score for steroid injection group was 29.8, mean DASH score for autologous blood injection group was 30.8, p value was 0.624; mean Nirschl staging for steroid injection group was 3.8, mean Nirschl staging for autologous blood injection group was 4.3, p value was 0.107.

Till 1st week follow up, statistically significant difference between the two groups with DASH scoring and Nirschl staging was seen. Corticosteroid injection group showed statistically significant decrease in DASH score and Nirschl stage at 1st week compared to autologous blood injection group. One study showed similar results with local corticosteroid injection group, when compared with oral naproxen [14].

At 4th week no much significant difference in results between both groups were noted. But both group result showed decrease in pain.

At 12th week follow up autologous blood injection group showed statistically significant decrease in DASH score and Nirschl staging compared to corticosteroid group.

At the end of 12th week 6.89% patients in corticosteroid injection group and 19.35% patients in autologous blood injection group were completely relieved of pain. This was not statistically significant with a p value of 0.2554.

One study reported that 22/28 patients (79%) responded to autologous blood injections with average Nirschl scores decreasing from 6.5 to 2.0 with a mean follow up of 9.5 months [15].

In corticosteroid injection group, till 4th week there was significant improvement, compared to autologous blood injection group. 3 (10.34%) of these patients reported recurrences at 12 weeks follow up. The rate of recurrence was 10.34% in corticosteroid injection group. Similar recurrence rate was seen in one study where 14% patients worsened in their symptoms with corticosteroid injection [14].

In autologous blood injection group at 4th week follow up, many patients were relieved of some pain. At the end of 12weeks there was no recurrence. This was not statistically significant compared to autologous blood injection group with a p value of 0.2377.

This study cannot prove conclusively whether the blood itself induced an inflammatory cascade or whether the injury created by the injection was responsible. It is theorized that the beneficial effects of steroid injection result from the bleeding caused by forcing fluid through tissue planes at high pressures.

It was seen that there was a significant increase in post intervention pain for few days in autologous blood injection group. In corticosteroid injection group 8 participants (26%) patients complained of post-intervention exacerbation of pain while in autologous injection group 18 participants (58.06%) complained of increase of pain after local injection. This was statistically significant with a p value of 0.009. And these patients had to be managed with oral analgesic for varying period of days (2 to7days) for pain relief.

61.29% patients in ABI had same level of pain as baseline at 1 week, in CST all patient at 1 week had some relief of pains.

Only two patients (6.6%) had local skin atrophy in corticosteroid injection group while no patient in autologous injection group had this problem. Between two groups there was no statistical significance related to post intervention local skin atrophy. (p = 0.150) showing that the local steroid infiltration done with proper investigations and care gives rise to negligible complication.

Corticosteroid group had significant recurrence rate, compared to autologous blood group. One study showed significant recurrence rate at the end of 6 months of follow up.

Pre-injection mean DASH score was more in autologous blood injection group compared to corticosteroid group, but final results were better in autologous blood group. Hence this study not biased in view of pre injection DASH score.

Conclusion

To conclude, autologous blood injection is beneficial for the treatment of lateral epicondylitis. Advantages of autologous blood injection are-highly acceptable, efficacious, economic, easy to carry out as outpatient procedure, devoid of potential complications such as hypoglycemia, skin atrophy, tendon tears associated with corticosteroid injection and low recurrence rate.

Clinical findings such as those presented should be correlated with histologic specimens showing evidence of healing such as organization of collagen bundles and return to normal cellular activity after injections of autologous blood into areas of tendinosis. Most patients are reluctant to donate blood that may be discarded and not used for their benefit. Nonetheless this study offers encouraging results of an alternative treatment that addresses the pathophysiology of lateral epicondylitis that has failed traditional nonsurgical modalities. Further clinical studies may prompt other investigators to further define substances that may enhance tendon healing for lateral epicondylitis and other disabling tendinosis

Limitation of this study is short term follow up. Larger study with more number of patients and long term follow up required to conclude firmly about benefit of autologous blood injection over corticosteroid injection

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