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Platelet-rich plasma versus meloxicam for biceps tendonitis as alternative to steroids with IL6 as a marker

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Abstract

Background: Both platelet-rich plasma and non-steroidal anti-inflammatory drugs have proven their efficacy in the management of soft tissue inflammatory disorders. This study was conducted aiming to compare PRP and NSAID injections in the management of biceps tendinitis.

Patients and methods: We included a total of 88 cases, who were divided into two equal groups; the PRP group (44 cases), and the Meloxicam group (44 cases). All cases were subjected to history taking, examination, and routine investigations (including IL-6). Ultrasound-guided injection of PRP and meloxicam 15 mg inside the biceps sheath was performed in both groups respectively.

Results: No significant difference was detected regarding demographic or clinical parameters. Interleukin-6 showed an early increase in the PRP group, then it decreased to significantly lower levels compared to the meloxicam group after 2 weeks. Likewise, the VAS score showed a mild increase during the initial 3 days in the PRP group but it improved significantly in the subsequent visits. Although the Oxford score improved in both groups, the improvement was significantly better in the PRP group on the later follow-up assessment.

Conclusions: Ultrasound-guided injection of PRP and meloxicam is effective in managing biceps tendinitis symptoms. However, a more significant improvement is achieved with PRP.

Keywords: Anti-inflammatory drugs, Biceps tendinitis, Platelet-rich plasma, non-steroidal.

Introduction

Biceps tendinitis is an inflammatory disorder of the tendon around the long head of the biceps muscle. Primary tendinitis, which means inflammation of the tendon within the bicipital groove, accounts for 5% of these cases [1]. The remaining majority of cases usually have a concomitant lesion (like rotator cuff tear), and they are known as Superior Labrum Anterior Posterior (SLAP) lesions [2].

Such cases are typically complaining of deep throbbing pain located at the anterior shoulder (mainly at the site of the bicipital groove) and radiating to deltoid muscle insertion or down to the hand with a radial distribution. The pain usually becomes worse at night, especially if the subject slept over the affected shoulder [3, 4].

The management of this disorder includes conservative methods (rehabilitation, stretch therapy, and rest), medications (oral NSAIDs, paracetamol), local injections (steroids), and surgery if all the previous measures have failed [5, 6].

Multiple studies have reported the efficacy of local steroid injection in painful musculoskeletal conditions [7, 8]. However, there is still an increased risk for tendon atrophy, rupture, or decreases bone strength [9]. Moreover, changes in blood glucose could be problematic in diabetic persons [10]. Due to these side effects, it was recommended to seek an effective alternative to steroids in managing these conditions [11].

Non-steroidal anti-inflammatory drugs are commonly prescribed for pain resulting from soft tissue injury or tendinopathy [12]. Although it has multiple side effects (e.g. peptic ulceration and bleeding), this risk of adverse events is decreased significantly when these medications are injected locally. Even if systemic these rare effects are encountered, they will be less severe compared to steroid effects [11].

Furthermore, local NSAID injection is not associated with significant cartilaginous soft tissue changes [13, 14].

Multiple reports have stated that Platelet-rich plasma (PRP) has an accelerating role in response to injury. Cellular response to the injurious agent is composed of four stages; hemostasis, inflammation, proliferation, as well as remodeling [15, 16].

Mos and his associates reported that in vivo application of PRP in tendon injuries resulted in angiogenesis and fibrovascular callus formation, which in turn may have a beneficial effect on the catabolic demarcation of the injured tendon matrix [17].

This study was conducted at Mansoura University Hospitals aiming to compare PRP and NSAID injections in the management of biceps tendinitis.

Patients and methods

This is a prospective randomized study that was conducted at pain clinics, Mansoura University Hospitals during the period between January 2019 and January 2020. This study was designed for cases diagnosed with biceps tendinitis who are prepared for local injections. We included a total of 88 cases that were divided into two equal groups; the first group (PRP group) included 44 cases that underwent PRP injection, whereas the other group included the remaining 44 cases that underwent NSAID (meloxicam) injection.

Cases older than 18 years, who reported no improvement with physical therapy, oral pain killers, or local steroid injection were included in the study. On the other hand, cases with rheumatoid arthritis, uncontrolled systemic comorbidity, previous shoulder surgery, pregnancy, or steroid injection within the last 3 months were excluded.

Informed written consent was obtained from all cases before participating in the study, after a complete explanation of the benefits and drawbacks of each treatment method. In addition, the study was approved by the local ethical committee of Mansoura University.

All cases were subjected to complete history taking, thorough shoulder examination, and routine radiological investigations. Moreover, the visual analogue scale (VAS) [18], and Oxford Shoulder Score [19] were determined before intervention. Plain shoulder radiography was ordered for all cases to exclude the primary causes of impingement. Moreover, shoulder ultrasonography (US) and/or magnetic resonance imaging (MRI) were used to confirm the diagnosis.

Enzyme-linked immunosorbent assay (ELISA) was used to measure the levels of interleukin-6 (IL-6) according to manufacturers' instructions (Ray Bio Eliza Kits, Ray Biotech Life, Georgia, USA). It was measured before the procedure, then 36 hours, 1 week, and 2 weeks following the procedure.

Ultrasound-guided technique

The procedure was performed using a Toshiba Xario device. The linear transducer was placed over the bicipital groove, and the biceps tendon was identified. Then, a 25-gauge needle was introduced into the biceps tendon sheath. Care was taken not to inject the medication inside the tendon itself to avoid rupture..5-1 ml of saline was initially injected to confirm the presence of peri-tendinous flow. After that, 2 ml of autologous PRP was injected in the PRP group, while 15 mg of meloxicam dissolved in 2 ml saline was injected in the Meloxicam group.

A technically successful procedure was identified by distention of the biceps tendon sheath and circumferential coating of the biceps tendon by the injectate.

After the procedure, the patient was advised to rest for at least 3 days and to apply a plastic bandage for 10 hours. Both VAS and Oxford scores were assessed 1 and 4 weeks after injection.

Sample size calculation

The sample size was calculated using Power Analysis and Sample Size software program (PASS) version 15.0.5 for windows (2017) using data obtained from a pilot study conducted on 10 patients at Mansoura university hospital with short term effect of PRP on biceps tendinitis one week after treatment measured by Interleukin-6 levels as the primary outcome. Patients were allocated into two groups: PRP Group and meloxicam (as control) Group.

Interleukin-6 levels at one week were 7.81 ± 1.039 (pg/mL) for the PRP group and 8.39 ± 0.782 for the control group. A sample size of 41 patients in each group is needed to achieve 80% power (1-β or the probability of rejecting the null hypothesis when it is false) in the proposed study using a two-sided two-sample unequal-variance t-test with a significance level (α or the probability of rejecting the null hypothesis when it is true) of 5%. 10% drop-out is expected, so 44 patients will be enrolled in each group.

Statistical analysis

IBM's SPSS Statistics (Statistical Package for the Social Sciences) for Windows (version 25, 2017) was used for statistical analysis of the collected data. Shapiro-Wilk test was used to check the normality of the data distribution. Quantitative variables were expressed as mean and standard deviation while categorical variables were expressed as frequency and percentage. Independent sample T and Mann Whitney tests were used for inter-group (between subjects) comparison of parametric and non-parametric continuous data with no follow-up readings respectively. Fisher exact and Chi-square tests were used for inter-group comparison of nominal data using the crosstabs function. All tests were conducted with a 95% confidence interval. P (probability) value < 0.05 was considered statistically significant.

Results

The mean age of the included cases was 34.95 and 33.27 years for PRP and NSAIDs groups respectively. Males represented 75 and 86.4% of cases in both groups respectively. As regard occupation, most of the included cases were manual workers (47.7% of cases in both groups), followed by the employee (40.9 and 43.2% of cases respectively), and housewives (11.4 and 9.1% of cases in both groups respectively).

Participation in sports was reported by 59.1 and 75% of cases in both groups respectively. Although all cases had tendonitis affecting the long head of the biceps, some cases had concomitant supraspinatus, subacromial, or subscapularis tendinitis.

All the previous parameters did not differ significantly between the two study groups ($p > 0.05$). These data are illustrated in table (1).

Table (1): Demographic characteristics, history of sports participation, and affected tendons in the studied groups.

		PRP group (n= 44)	**Meloxicam group (n= 44)**	**95% CI**	**p**
Age (year)		34.95 ± 8.934	33.27 ± 8.582	-2.03, 5.39	0.370
Gender	Male	75.0% (33)	86.4% (38)	-0.05, 0.28	0.177
	Female	25.0% (11)	13.6% (6)		
Occupation	Housewife	11.4% (5)	9.1% (4)	-	1
	Manual worker	47.7% (21)	47.7% (21)		
	Employee	40.9% (18)	43.2% (19)		
Sport participation		59.1% (26)	75.0% (33)	-0.03, 0.35	0.112
Long head of biceps tendinitis		100.0% (44)	100.0% (44)	-	1
Supraspinatus tendinitis		20.5% (9)	22.7% (10)	-0.15, 0.2	0.796
Subacromial bursitis		15.9% (7)	2.3% (1)	-0.25, -0.02	0.058
Subscapularis tendinopathy		27.3% (12)	15.9% (7)	-0.28, 0.06	0.195

Data is expressed as mean and standard deviation or as percentage and frequency. 95% CI: 95% confidence interval of the mean difference between both groups. P is significant when < 0.05.

Basal IL-6 levels did not differ significantly between the two groups. After 36 hours, there was a significant increase in IL-6 levels in the PRP compared to the meloxicam group ($p < 0.001$). However, after 2 weeks, IL-6 levels decreased significantly in the PRP group compared to the other group. Table (2) illustrated these data.

Table (2): Basal and follow-up values of Interleukin-6 in the studied groups.

Interleukin-6 (pg/mL)	PRP group (n= 44)	Meloxicam group (n= 44)	95% CI	p
Basal	7.94 ± 1.477	7.69 ± 1.214	-0.32, 0.83	0.382
36 hours	9.90 ± 2.046	7.18 ± 1.068	2.03, 3.41	0.000
One week	6.51 ± 1.438	6.72 ± 0.987	-0.73, 0.31	0.427
Two weeks	5.91 ± 1.387	6.59 ± 0.936	-1.18, -0.18	0.009

Data is expressed as mean and standard deviation. 95% CI: 95% confidence interval of the mean difference between both groups. P is significant when < 0.05.

Regarding the VAS score, it did not differ between the two groups before intervention. Nevertheless, the Meloxicam group showed significant improvement regarding pain relief compared to the PRP group within the early three days after injection. On the subsequent visits, there was more significant pain improvement in the PRP group. These data are illustrated in table (3).

Table (3): Basal and follow-up values of VAS score in the studied groups.

VAS score	PRP group (n= 44)	Meloxicam group (n= 44)	95% CI	p
Basal	5.52 ± 0.590	5.41 ± 0.658	-0.15, 0.38	0.396
Three days	5.86 ± 0.824	4.70 ± 0.851	0.80, 1.51	< 0.001
One week	2.64 ± 0.967	3.45 ± 0.589	-1.16, -0.48	< 0.001
Four weeks	1.14 ± 0.824	2.55 ± 0.589	-1.71, -1.11	< 0.001

Data is expressed as mean and standard deviation. 95% CI: 95% confidence interval of the mean difference between both groups. P is significant when < 0.05.

Oxford shoulder score showed the same improvement changes similar to VAS. It did not differ between the two groups before intervention. Although the Meloxicam group showed a significant improvement in the early three days, the PRP group had the upper hand on the subsequent follow-up visits. Table (4) illustrates these data.

Table (4): Basal and follow-up values of Oxford score in the studied groups.

Oxford score	PRP group (n= 44)	Meloxicam group (n= 44)	95% CI	p
Basal	27.91 ± 2.291	27.00 ± 2.588	-0.13, 1.94	0.085
Three days	31.20 ± 2.800	33.00 ± 2.909	-3.01, -0.59	0.004
One week	40.39 ± 3.021	38.32 ± 2.522	0.89, 3.25	0.001
Four weeks	44.16 ± 1.413	41.52 ± 1.759	1.96, 3.31	< 0.001

Data is expressed as mean and standard deviation. 95% CI: 95% confidence interval of the mean difference between both groups. P is significant when < 0.05.

Discussion

This study was conducted at Mansoura University Hospitals aiming to compare PRP and Meloxicam injections in the management of biceps tendinitis. We included a total of 88 cases who were randomly divided into two groups; the first group included 44 cases who underwent PRP injection, while the other 45 cases who underwent NSAID (meloxicam) injection was included in the second group.

To the best of our knowledge, there is a paucity of studies comparing the efficacy of these two injections in the current literature.

It was previously reported that biceps tendon pathologies are often encountered in patients whose age between 18 and 35 years, who are subjected to hard manual work or high-impact sports [6].

In the current study, basal IL-6 levels did not differ significantly between the two groups. After 36 hours, there was a significant increase in IL-6 levels in the PRP compared to the Meloxicam group ($p < 0.001$). However, after 2 weeks, IL-6 levels decreased significantly in the PRP group compared to the other group.

A previous study has reported that PRP decreased both gene expression and the production of IL-6 in tendon cells [20].

Interleukin 6 (IL-6), promptly and transiently produced in response to infections and tissue injuries, contributes to host defense through the stimulation of acute-phase responses, hematopoiesis, and immune reactions [21].

Unlike the information provided by the presence of inflammatory cells, current evidence on the inflammation markers shown in tendinopathic tendons does not show a consistent picture [22]. A previous study has reported that IL-6 expression is significantly increased in the synovium cases with supraspinatus tear [23].

The initial increase in IL-6 levels in the PRP group could be attributed to immunological reaction or the initial inflammatory tissue response to PRP. This elevation was settled as local inflammation subsides. Also, the leucocytes present in the PRP preparation may cause IL-6 overexpression, and that may explain the initial increase encountered in our results [24]. Further studies handling the molecular levels need to be conducted to clarify the exact changes of serum IL-6 after PRP injections.

In the current study, the VAS score did not differ between the two groups before intervention. Nevertheless, the Meloxicam group showed significant improvement regarding pain relief compared to the PRP group within the early three days after injection. On the subsequent visits, there was more significant pain improvement in the PRP group. Oxford shoulder score also did not differ between the two groups before intervention. Although the Meloxicam group showed a significant improvement in the early three days, the PRP group had the upper hand on the

subsequent follow-up visits. Our results imply that Meloxicam can achieve a more rapid response, whereas PRP causes a delayed but more effective relief.

Oral NSAIDs are considered the main treatment prescribed for musculoskeletal pain due to their strong anti-inflammatory properties [25]. Besides, multiple studies have confirmed the efficacy of local application of these medications for multiple musculoskeletal conditions [7, 26, 27].

However, other authors reported that the response was more rapid in steroid injection compared to NSAID. They attributed that finding to the fact that steroids, along with their anti-inflammatory effect, can inhibit collagen, granulation tissue, and extracellular matrix formation, whereas NSAIDs do not [28].

One study compared between subacromial injection of steroids (triamcinolone 40 mg) versus NSAID (ketorolac 60 mg) in the management of shoulder impingement syndrome. After 1 month, there was significant improvement of pain and motion range in both groups. Nevertheless, the University of California at Los Angeles shoulder scale showed better improvement in the Meloxicam group (7.15 vs. 2.13 in steroids and Meloxicam groups respectively - $p = 0.03$). Other outcome parameters did not differ significantly between steroids and NSAID [29].

Other investigators conducted study to confirm the efficacy of NSAIDs in musculoskeletal conditions. Comparing, between triamcinolone and diclofenac injections in relieving symptoms of trigger finger. The complete symptomatic resolution was achieved in 70 and 53% of cases in steroid and Meloxicam groups, respectively. Moreover, no significant difference was detected between the two groups regarding Quinnell score 3 months after injection [28].

Furthermore, another study compared intraarticular steroids versus NSAIDs injections in knee osteoarthritis. VAS score showed a significant decrease in both groups for 24 weeks (from 6.3 to 4.6 in the Meloxicam group and from 5.2 to 3.6 in the steroid group). The difference between the two groups was statistically insignificant. Nevertheless, NSAIDs were found to save many financial costs compared to steroids [30].

All of the previous three studies confirmed that local NSAID injection is effective in relieving pain, and that agrees with our findings.

Regarding PRP application in tendinopathies in the literature, one study has reported the effectiveness of PRP in the management of biceps tendinitis. VAS score decreased from 6 before intervention down to 0.5 at the final follow-up ($p < 0.002$). In addition, elbow functional assessment score increased from 63 before intervention up to 90 after it ($p < 0.004$). The authors concluded that PRP injection may be a promising modality for biceps tendinitis resistant to the standard therapy [31].

Another study compared the efficacy of PRP injection versus physical therapy (PT) in partial supraspinatus tears. VAS, Disabilities of Arm, Shoulder, and Hand

questionnaire (DASH), and range of motion were improved significantly in both groups. However, the DASH score showed significantly better improvement in the PRP compared to the PT group [32].

Moreover, another study reported that PRP was significantly better than the dry needling from six weeks to six months after initial injection ($P < 0.05$). The mean Shoulder Pain and Disability Index was 17.7 in the platelet-rich plasma group while it was 29.5 in the dry needling group ($p < 0.05$) after 6 months [33].

Furthermore, PRP was found to be as good as steroid injections in patients with rotator cuff tears [34].

Conversely, other authors investigated the role of PRP in cases with chronic rotator cuff tendinopathy, and they reported that PRP injection was not effective in improving quality of life, pain, disability, and range of movement. VAS and other functional scores did not differ between the two groups at 1-year follow-up [35].

The present study has multiple limitations; first of all, it is a single-center trial. Besides, the follow-up period was limited to 4 weeks with a single injection. Therefore, more studies from different pain centers with longer follow-up periods should be conducted soon.

Conclusion

Based on our findings, Ultrasound-guided injection of PRP and Meloxicam are effective in managing biceps tendinitis symptoms. However, a more significant improvement was achieved with PRP.

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