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Randomized Controlled Trial

Atelocollagen vs. Prolotherapy in Partial-Thickness Supraspinatus Tears: A Prospective Randomized Controlled Trial with MRI-Confirmed Outcomes

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Background: Partial-thickness rotator cuff tears (PTRCTs) are a common cause of shoulder pain. The treatment options for this condition vary by tear characteristics and patient needs. Prolotherapy using a hypertonic dextrose solution promotes tissue regeneration by triggering an inflammatory response but may yield variable results. Recently, atelocollagen injections have emerged as a novel treatment for PTRCTs, offering pain relief and functional improvement by serving as a scaffold for tissue repair without causing additional tissue damage.

Objectives: This study aims to compare the efficacy of prolotherapy with hypertonic dextrose to that of atelocollagen injections for managing pain, improving shoulder functionality, and enhancing structural healing at the tear site in patients with PTRCTs. The efficacy of these methods will be evaluated by follow-up magnetic resonance imaging (MRI).

Study Design: A prospective, randomized, observational study.

Setting: Interventional pain management center at a university-affiliated hospital.

Methods: Thirty-four patients with partial-thickness supraspinatus tears (PTSTs) were enrolled and randomly assigned to 2 groups: Group P received prolotherapy, and Group C received atelocollagen injections. The treatments (ultrasound-guided injections) were administered in 3 sessions at one-week intervals. The primary outcome was pain reduction, measured immediately after treatment and at 2 weeks, one month, and 3 months. Secondary outcomes were functional improvements measured with the Korean Shoulder Pain and Disability Index (K-SPADI) and the Shoulder Constant-Murley Scoring System (SCSS) at one and 3 months, as well as comparative MRI evaluations of the supraspinatus tear between the baseline and the 3-month marks.

Results: Of the 34 patients, 28 completed the study. Group C (n = 15) showed significant pain relief from the baseline at both one and 3 months ($P = 0.04$ and $P < 0.01$) post-injection, whereas Group P (n = 13) showed significant pain reduction only at 2 weeks after the injection. MRI findings indicated better healing outcomes in Group C, in which improvements were observed in 4 patients as opposed to 0 patients in Group P. Similarly, 10 patients in Group P exhibited aggravated tear signs in follow-up MRI scans, while only 2 patients in Group C showed such aggravations. Functional scores improved in both groups ($P < 0.01$); however, no significant differences were observed.

Limitations: The 3-month follow-up period was relatively short.

Conclusions: In patients with PTSTs, atelocollagen injections provided more efficient pain relief and demonstrated greater structural improvements than did prolotherapy, as confirmed by MRI. While both treatments were associated with improved shoulder function, atelocollagen seemed to offer the additional benefit of promoting tissue healing. This study supports atelocollagen as a potential therapeutic option for PTST management.

Keywords: atelocollagen, injection, magnetic resonance imaging, prolotherapy, regeneration, rotator cuff injuries, shoulder pain, tears

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Among the most frequent causes of shoulder pain are partial-thickness rotator cuff tears (PTRCTs), which vary in reported prevalence (1). The treatment options for PTRCTs differ depending on the size, location, and severity of each tear and the individual's symptoms and activity levels (2). Conservative treatments include medication, physical therapy, corticosteroid and platelet-rich plasma injections, and prolotherapy to reduce the pain caused by inflammation around the tear (3). Among these, corticosteroid injections are not recommended for prolonged use due to their limited effectiveness and safety (4), the short duration of their benefits (5,6), and their potential long-term harmful effects, such as ligament atrophy and reductions in connective tissue, including collagen (4,7).

Prolotherapy with a hypertonic dextrose solution triggers inflammation in damaged or weakened tendons and induces the growth of new tissues (8). The hypertonic dextrose solution can stimulate fibroblast proliferation and promote extracellular matrix development in the treated tendons (9). However, this technique involves inducing tissue damage to trigger the natural healing process, and the outcomes may vary depending on individual regenerative capacity and the extent of the patient's injury. The efficacy of prolotherapy has been reported in previous studies, with varying results. Martins et al reported that prolotherapy did not help in tissue healing in a rat model of injured Achilles tendons (10). In another study, prolotherapy was found to be more beneficial than exercise alone in decreasing pain and improving shoulder function in patients with chronic rotator cuff injuries (11). A recent review suggested that prolotherapy worked better than nonsurgical treatments for shoulder tendon issues but was less effective than injections of steroids or platelet-rich plasma (12).

The atelocollagen injection, a novel treatment modality, reduces pain and improves function in patients with PTRCTs (13,14). Atelocollagen is a form of collagen from which telopeptides—amino acid sequences with antigenicity at both the N- and C-terminals—have been removed using proteases or pepsins, which can reduce immunogenicity and improve biocompatibility (15,16). At the site of injury, atelocollagen acts as a scaffold, inducing tissue repair and regeneration directly (17). An important step in tissue regeneration is tendon-to-bone healing, which follows a 3-phase process: inflammation, repair, and remodeling. In the last phase, scar tissue transitions from type III to type I collagen, marking tissue maturation and strengthening. Atelocollagen, which is derived from type I collagen, plays a pivotal role in facilitating this last phase of healing (18). This technique is not identical to prolotherapy, which works by damaging tissue intentionally to promote regeneration. Superior results may be anticipated with atelocollagen because it ultimately promotes tissue remodeling.

Despite the distinct mechanisms of these 2 injection therapies, it is clinically important to compare the relative effectiveness and potential complications of prolotherapy, a commonly utilized regenerative treatment for PTRCTs, with those of atelocollagen, an emerging therapy of interest. The present study aimed to compare the effects of prolotherapy to those of atelocollagen injections in reducing pain, enhancing functionality, and improving healing outcomes at the tear sites in patients with PTRCTs. Structural improvements at the tear sites were evaluated through follow-up magnetic resonance imaging (MRI), the findings of which were compared to preoperative MRI scans obtained before the injections were administered.

Methods

Study Design and Patients

This prospective randomized controlled clinical trial was approved by the Institutional Review Board of the Seoul National University Bundang Hospital (No. B-1911/579-002). All patients received written and verbal information about the trial before providing written informed consent. The inclusion criteria were as follows: (1) an age of 18-65 years, (2) exhibiting symptoms of PTRCTs over the course of 3 months, (3) having received a PTST diagnosis on an MRI scan in the past 3 months, (4) having tears involving less than 50% of the tendon depth, and (5) possessing at least one of the following types of supraspinatus tears: bursa-side, articular-side, or intra-tendinous. The exclusion criteria were as follows: (1) the presence of adhesive capsulitis, (2) the presence of full-thickness supraspinatus tears, (3) having received treatment using corticosteroid injections or prolotherapy, (4) having received previous surgery on the affected shoulder, and (5) the presence of traumatic rotator cuff tears.

Before the procedure, patients were sorted into 2 groups using a computer-generated randomization list: Group P received prolotherapy, and Group C received atelocollagen injections at the supraspinatus tear site.

Procedures

Procedures in both groups were performed by pain physicians with > 10 years of experience, using ultrasonography (HS 80®, Samsung Medison Co.) and a linear high-frequency probe (12 MHz). Patients in both groups were asked to modify the crass position by projecting the flexed elbow joint posteriorly while externally rotating and extending the glenohumeral joint by resting the palm of the hand on the ipsilateral iliac wing. First, the physician checked the supraspinatus tear site with ultrasoonography and disinfected the injection site. After infiltration of 1 mL of 1% lidocaine, a 23G, 6 cm needle (KOREAVACCINE) was advanced toward the supraspinatus tear site. Patients in Group P received 2 mL of 20% dextrose water, and those in Group C received one mL of atelocollagen (Tendoregen®, Phammode) with lidocaine (1 mL). After the first injection, the process was repeated twice at an interval of one week, for a total of 3 injections.

Outcome Measurements

The primary outcome was the difference in pain levels between 3 months after the treatment and the pain levels experienced at the baseline. Pain relief was assessed using visual analog scale (VAS, range 0-10) scores at the baseline (before the first injection) and at 2 weeks, one month, and 3 months after the injections. All complications and adverse events were recorded. The clinical outcomes for each patient were analyzed by 2 experienced pain physicians who were not involved in the treatment.

The secondary outcome was improvement in supraspinatus tears as seen in MRI scans. Follow-up MRI of the shoulder was performed using a 3T MRI system (Achieva, Ingenia, and Ingenia CX, Philips Healthcare) with dedicated shoulder receiver coils (8 channels; Sense Shoulder Coil, Philips Healthcare) 3 months after the last injection in both groups. The results were compared to the initial MRI findings. Fat-suppressed fast spin-echo T2-weighted images were acquired in oblique coronal and sagittal planes (repetition time/echo time, 2000-5000/80-100; field of view 140 × 140; matrix 256 × 256). The MR images were analyzed to assess the integrity of the supraspinatus tendon on oblique coronal and oblique sagittal images by an experienced radiologist who was not involved in the study procedures. A tear was defined as a fiber discontinuity in the tendon with a hyperintense signal intensity on fat-suppressed T2-weighted images. The mediolateral dimension of the tear was measured on an oblique coronal image as a straight line from the most lateral point to the most medial point of the intra-tendinous hyperintense signal. Similarly, the anteroposterior dimension of the tear was measured on an oblique sagittal image. The supraspinatus tear site was analyzed to determine whether its condition had improved (decreased dimensions of the tear site and/or tendinitis), unchanged, or worse (increased dimensions of the tear site and/or tendinitis) since the pre-procedure MRI scan.

We also used the Korean Shoulder Pain and Disability Index (K-SPADI, range 0-100, best-worst function) and Shoulder Constant-Murley Scoring System (SCSS, 0-100, worst-best function) for assessing functional improvement at the baseline and at one and 3 months after the injections. Data regarding age, gender, weight, height, diagnosis, complications, and injection pain were collected.

Statistical Analysis

In a previous study comparing the effects of prolotherapy injection and conventional treatment for focal supraspinatus rotator cuff disorder, the changes in VAS scores at 3 months after the procedures were 1.86 and 2.40 in the prolotherapy-injection and conventional-treatment groups, respectively (19). The effect size was calculated as 1.08, and a total sample size of 30 achieved 80% power, with a type I error of 0.05. The final sample size was 15 patients per group, and when a 10% dropout rate was considered, 17 patients per group were initially calculated. Age, gender, weight, height, diagnosis, complication, patient satisfaction, and shoulder MRI findings (type and size of supraspinatus tear) were compared between the groups using the t-test, the χ^2 test, or Fisher's exact test. Continuous numerical data over time pertaining to the VAS scores for shoulder pain and the K-SPADI and SCSS scores were compared using repeated-measures analysis of variance. SPSS version 27.0 (IBM Corp.) was used for statistical analyses. The results are expressed as the mean (standard deviation). Statistical significance was set at $P < 0.05$. Post hoc analysis was performed using the G*power 3.1.9.7 program (Heinrich-Heine-Universität Düsseldorf).

Results

Thirty-four patients (n = 17 per group) were enrolled. However, 6 patients (Group C = 2, Group P = 4) were lost to follow-up. Ultimately, 15 patients in Group C and 13 patients in Group P were analyzed (Fig. 1).

Patients' demographic and clinical characteristics are shown in Table 1. Patient characteristics did not differ significantly between the 2 groups. In both groups, bursa-side and intra-tendinous tears appeared more often than did articular-side tears in preprocedural MRI scans. In Group C, the initial medial-to-lateral supraspinatus tear size was 1.7 ± 0.5 mm, and the initial anterior-to-posterior tear size was 1.6 ± 0.6 mm; the initial tear size did not differ significantly between the groups (Table 1).

Group C exhibited significant pain relief from the baseline levels (5.3 ± 2.0) at one (4.0 ± 1.2, $P = 0.04$) and 3 (3.2 ± 1.2, $P < 0.01$) months after the injections (Fig. 2-A). Group P did not exhibit significant pain reduction from the baseline measurements (4.9 ± 1.6) until 2 weeks (4.2 ± 1.9, $P = 0.01$) after the injections. Pain reduction was significantly greater in Group C (3.2 ± 1.2) than in Group P (4.7 ± 1.5) at 3 months following the injections ($P < 0.01$). In the post hoc analysis of results for pain evaluation, the power (1-β) was calculated to be 0.824, with sample sizes of n1 = 15 and n2 = 13, an effect size (Cohen's d) of 0.5, and an α error probability of 0.05. No complications were reported in either group, and the injection pain intensity experienced by the patients was not significantly different between the groups (Fig. 2-B).

In the follow-up MRI, none of the patients in Group P showed improvements in the tear sites, but 4 patients (3 patients with bursa-side and one patient with intra-tendinous tears in the initial MRI) in Group C did exhibit improvements. Additionally, 10 patients in Group P (2 patients with bursa-side, 7 patients with intra-tendinous, and one patient with articular-side tears in the initial MRI) exhibited aggravated signs in subsequent MRI scans (Table 2); in Group C, only 2 patients exhibited aggravations (and those patients had articular-side tears in the initial MRI) .

In Group C, K-SPADI scores improved significantly at 3 months after the injections (30.1 ± 12.1, $P < 0.01$) from the baseline (46.9 ± 12.7) (Fig. 3-A), and SCSS scores improved significantly at both one (77.8 ± 10.1) and 3 months (79.6 ± 9.9, $P < 0.01$) after the injections compared to the baseline levels (72.3 ± 7.8) (Fig. 3-B). In Group P, K-SPADI scores decreased at both one (33.5 ± 18) and 3 months (34.8 ± 16.9, $P < 0.01$) from the baseline amounts (46.9 ± 12.7) (Fig. 3-A), with significant improvement over the baseline SCSS scores (68 ± 11.9) at one month (77.1 ± 13.8, $P = 0.02$) after the injections (Fig. 3-B). Functional improvement was not significantly different between the 2 groups.

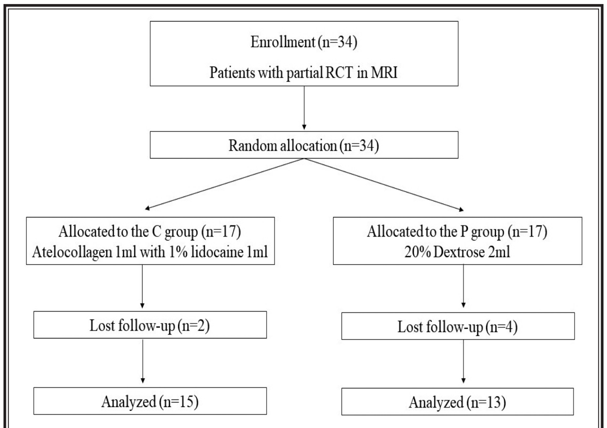

Fig 1. *Flow diagram of patients included in the study.* RCT, rotator cuff tear.

Table 1. ***Comparison of patient demographic and clinical characteristics between the atelocollagen injection (Group C) and prolotherapy (Group P).***

Characteristic	**Group C (n = 15)**	**Group P (n = 13)**	***P* values**
Gender (Male/Female)	5/10	4/9	0.6
Age (years)	61.7 ± 8.3	57.9 ± 7.6	0.21
Height (cm)	159.9 ± 7.7	164.1± 8.3	0.17
Weight (kg)	62.3 ± 12.9	70.9 ± 9.0	0.05
Tear site in initial MRI			0.79
Bursa-side, n (%)	6 (40)	4 (35.7)	
Intra-tendinous, n (%)	7 (46.7)	7 (57.1)	
Articular-side, n (%)	2 (13.3)	2 (7.1)	
Tear size in initial MRI (mm)			
Mediolateral	1.7 ± 0.5	1.6 ± 0.5	0.62
Anteroposterior	1.6 ± 0.6	1.48 ± 0.5	0.69

Data are reported as the mean ± SD or number (%) of patients.
MRI, magnetic resonance imaging

Discussion

In this study, we found that Group C exhibited significant pain relief from the baseline to 3 months after the injections, whereas Group P showed no significant pain reduction until 2 weeks after the injections. In the follow-up MRI scans, obtained 3 months after the injections were administered, 4 out of 15 patients in Group C showed improvements in their tear sites, but Group P did not show any tear-site improvement. Furthermore, both groups showed functional improvements after the injections, with no significant differences. Previous

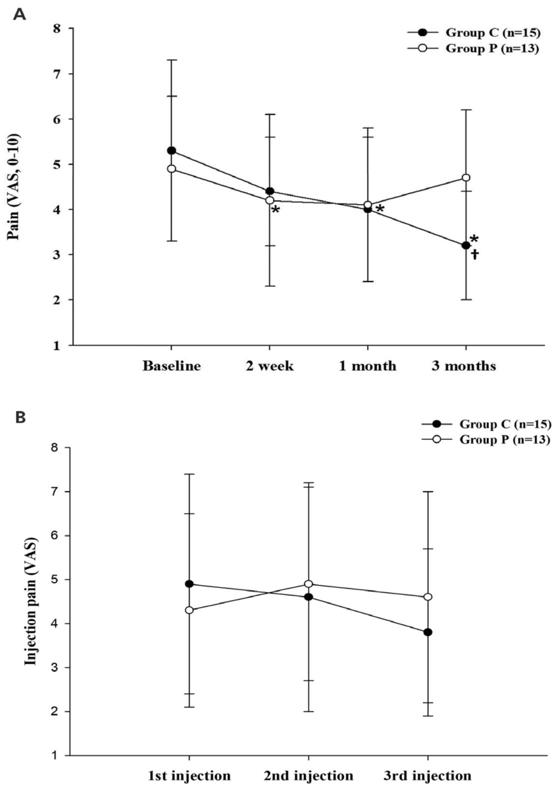

Fig. 2. *(A) Changes in shoulder pain between Groups C (atelocollagen injection) and P (prolotherapy) (VAS score, 0 = no pain, 10 = the worst pain imaginable). Group C exhibited significant pain relief from the baseline to one ($P = 0.04$) and 3 ($P < 0.01$) months after the injections. In Group P, significant pain reduction was not observed until 2 weeks ($P = 0.01$) after the injections. Group C had a significantly lower VAS score than Group P at 3 months ($P < 0.01$). (B) Differences in injection pain between both groups. Error bar indicates standard deviation.*

*Significant at $P < 0.05$, compared to the baseline. †Significant at $P < 0.05$, between both groups. VAS, visual analog scale.

studies have explored the effectiveness of atelocollagen injections compared to simple observation (13) and other conservative treatments (14) for patients with rotator cuff tears. However, no earlier study has compared the effects of atelocollagen injections to those of prolotherapy, a traditional regenerative therapy. Although prolotherapy and atelocollagen have distinct mechanisms, we selected prolotherapy as the control because of its well-established effectiveness in tendon healing and wide application. Consequently, despite the different mechanisms, a clinical comparison was required between prolotherapy and the new therapeutic option, atelocollagen injections, as forms of PTRCT treatment. Additionally, this study demonstrated that atelocollagen may offer potential in PTRCT treatment in the areas of pain reduction, function enhancement, and structural integrity enhancement.

Surgical indications for PTRCTs are controversial; however, if the extent of a partial tear is less than 50% of the tendon depth, nonoperative management is recommended (20). PTRCT management aims to reduce pain, restore function, and inhibit tear progression. PTRCTs are associated with a high risk of tear progression; incidence rates range from 8 to 26% (15,20). In our study, we included patients who were diagnosed with PTSTs and had a tear less than 50% of the tendon depth. Notably, PTSTs are associated with a higher likelihood of retear than are full-thickness tears. Therefore, achieving structural improvements is crucial for enhancing the long-term efficacy of treatments.

Table 2. *Comparison of improvement in tear site in follow-up magnetic resonance imaging between the atelocollagen injection (Group C) and prolotherapy (Group P).*

Changes in Tear site in Follow-up MRI	**Group C (n = 15)**	**Group P (n = 13)**	***P* values**
			<0.01
Improved, n (%)	4 (26.7)	0 (0)	
Bursa-side/intra-tendinous/ articular-side tear	3/1/0	0	
No change, n (%)	9 (60)	3 (23.1)	
Bursa-side/intra-tendinous/ articular-side tear	3/4/2	2/1/0	
Aggravated, n (%)	2 (13.3)	10 (76.9)	
Bursa-side/intra-tendinous/ articular-side tear	0/2/0	2/7/1	

Data are reported as number of patients or number (%) of patients.

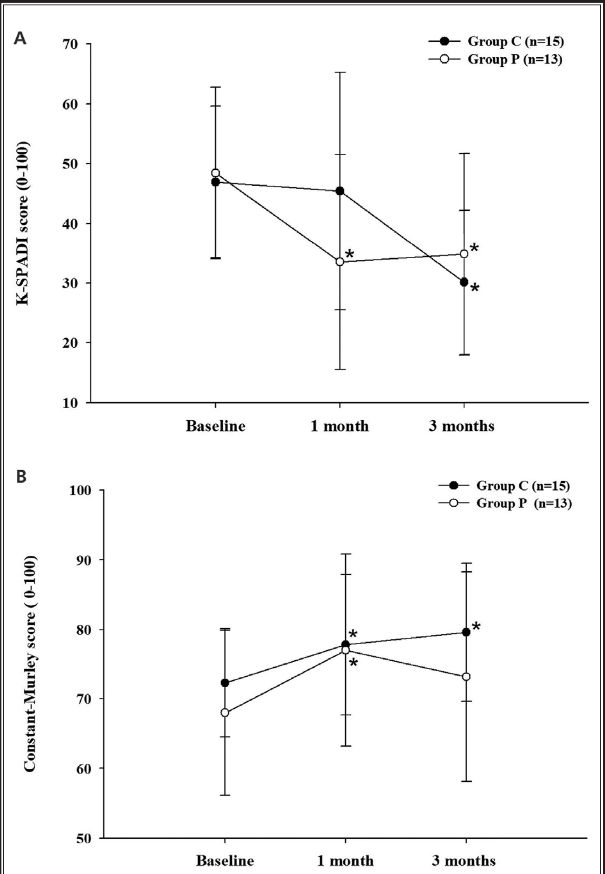

Fig. 3. *Changes in K-SPADI (A) and SCSS (B) scores, between Groups C (atelocollagen injection) and P (prolotherapy). Group C showed significant improvement in K-SPADI scores at 3 months (P < 0.01) and SCSS score at one and 3 months (P < 0.01) after injections compared to the baseline. Group P showed significant improvement in K-SPADI scores at one and 3 months (P < 0.01) and SCSS score at one month (P = 0.02) after the injections compared to the baseline. No significant difference in functional improvement was observed between the 2 groups. The error bar indicates standard deviation.*
*Significant at $P < 0.05$, compared to baseline scores.
K-SPADI, Korean Shoulder Pain and Disability Index; SCSS, Shoulder Constant-Murley Scoring System

Prolotherapy, also known as proliferative or regenerative injection therapy, is an effective treatment for ligament and tendon injuries. This treatment involves injecting an irritating solution, such as a liquid based on hypertonic dextrose, into injured connective tissues, such as ligaments or tendons, to promote the repair and strengthening of those tissues (21). The therapeutic efficacy of prolotherapy is controversial, and post-prolotherapy structural improvements have not been assessed with MRI or other modalities. In our study, the pain-reducing effect of prolotherapy lasted for a shorter duration than in previous studies. However, in a development similar to previous study results, functional improvement lasted for up to 3 months. The MRI scans revealed minimal structural improvement, and in more than 70% of patients, the supraspinatus tears had progressed beyond the states shown in their initial scans. This finding indicates that while prolotherapy helps with pain relief and functional improvement, it does not heal the rotator cuff tear site structurally.

The process by which collagen is added to tissues differs from that of prolotherapy. Prolotherapy irritates the wound to promote healing; however, collagen supplementation directly provides a healing material that supports the repair process. Atelocollagen, which is typically derived from type I collagen and is less immunogenic when telopeptides are removed, has various medical and cosmetic applications, including wound healing and tissue regeneration (16). Type I collagen constitutes most of the matrix in the supraspinatus tendon, accounting for more than 95% of its composition (22). The main mechanism of atelocollagen, tendon-to-bone healing, has been demonstrated in a rabbit model of supraspinatus tendon damage using a patch-type atelocollagen (23). At 12 weeks, the atelocollagen-injection group showed a healing process histologically and a considerably higher biomechanical tensile strength than the control group. Additionally, Stopak et al (24) found that adding type I collagen to chicken feather buds led to their integration into the feathers' normal connective tissue, demonstrating the easy assimilation of collagen into surrounding areas without impairing body function. In our results, pain relief and functional improvement experienced by PTST patients after their atelocollagen injections lasted up to 3 months, and the proportion of patients with a decrease in tear size was significantly higher than it was in patients who received prolotherapy injections ($P < 0.01$) (Table 2). According to the follow-up MRI scans in previous studies, the size of full-on PTRCTs spontaneously decreased in 6.8% of patients without any treatment (25). In our study, 26.7% of the patients who underwent atelocollagen injections showed a decreased tear size. This result is in line with the findings of Kim et al (14), who reported an improvement in tendon integrity in 36.7% of patients with intra-tendinous PTSTs after atelocollagen treatment, as confirmed by MRI. However, in the study conducted by Kim et al (14), the focus was specifically on treating intra-tendinous PTRCTs, which might account for the differences in outcomes compared to our study. In our study, most patients had bursa-sided PTSTs, which predominantly contributed to a decrease in tear size (Table 2). Of the 4 individuals with decreased tear size in Group C, 3 had bursa-sided tears, which constituted 50% of the total 6 bursa-sided tears in Group C. In contrast, of the 7 patients who had articular-sided tears, only one showed improvement in tear size. This result might have occurred because atelocollagen, when injected under ultrasound guidance, is most effectively administered at bursa-side. When the syringe that contains the atelocollagen is inserted into the skin, it is likelier to reach the bursa-side tear of the supraspinatus. Otherwise, Kim et al (14) insisted that injecting atelocollagen into the intra-tendinous area was more advantageous than injecting it into the bursa- or articular-sided tears because there was no leakage and the atelocollagen reached the target site. However, it is still unclear whether a particular subtype of PTSTs will see increased benefits from atelocollagen injections, and future research is needed to establish if it will.

Prolotherapy typically causes mild to moderate pain because it involves injecting an irritating solution, often hypertonic dextrose, into the damaged tissue. Atelocollagen can also induce injection pain due to its high concentration. In our study, however, no complications were reported after the procedure in either the prolotherapy or atelocollagen injection groups, and the level of pain patients experienced during the injections was similar for both groups, as shown in Fig. 2-B.

Limitations

This study has several limitations. First, we did not include a sham injection (saline or dry-needling) group, and we could not compare prolotherapy or atelocollagen injection groups with the natural progression of PTSTs. However, spontaneous healing of PTRCTs is rare (25,26), and previous studies have reported no significant differences in pain reduction and functional improvement between patients who received atelocollagen injections and patients who received sham injections (14). Second, the follow-up period of 3 months was shorter than those in other studies. Other studies have evaluated pain, function, or structural changes 6 months after the procedure (4,12,14). However, if no significant improvement in pain and function occurs after 3 months, it becomes ethically necessary to consider alternative treatments. Third, the sample size calculation was based on a prior pilot study, requiring at least 17 patients per group to achieve an 80% power. The final sample size did not meet this target, but it was demonstrated retrospectively that the power exceeded 80%.

Nonetheless, a notable strength of this study is its inclusion of patients with all types of tears, whereas previous studies have evaluated structural changes after atelocollagen injections only in intra-tendinous tears (14). Furthermore, MRI was used in both groups to establish the structural improvement that occurred after the surgery.

Conclusion

To our knowledge, this study is the first prospective, randomized, controlled clinical trial to comparatively analyze prolotherapy and atelocollagen injections for patients with PTSTs, evaluating pain relief, functional improvement, and structural improvement with MRI. Atelocollagen injections reduced pain significantly when compared to prolotherapy and might have contributed to some structural improvement. Therefore, a regimen of atelocollagen injections might be regarded as a novel regenerative therapy for the management of posttraumatic PTSTs.

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