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Does polydeoxyribonucleotide has an effect on patients with tendon or ligament pain?

A PRISMA-compliant meta-analysis

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Abstract

Background: Pain in the tendons or ligaments is extremely common, accounting for 30% of the causes of visiting general practitioners. Polydeoxyribonucleotide (PDRN) is emerging as a new treatment for musculoskeletal pain. However, the effects of PDRN in patients with tendon or ligament pain are unclear. Therefore, this study aimed to determine the impact of PDRN in patients with tendon or ligament pain through a meta-analysis.

Methods: Electronic literature search of PubMed, Embase, SCOPUS, and Cochrane Library databases of all articles on PDRN treatment for patients with tendon or ligament pain published in the English language from inception until January 31, 2020. The search identified 262 citations.

Results: One randomized controlled trial and 3 retrospective observational studies were included. Pain due to tendon or ligament disorders showed significant improvement after PDRN injection (standardized mean difference [SMD] = −1.43, 95% confidence interval [CI] = −1.80 to −1.06, $P < .00001$). In the subanalysis of patients with rotator cuff tendinopathy, rotator cuff tendinopathy-induced pain significantly improved (SMD = −2.34, 95% CI = −3.61 to −1.07, $P = .0003$) after PDRN injection. However, there was no difference in shoulder pain and disability index score and strength of shoulder abduction in patients with rotator cuff tendinopathy (shoulder pain and disability index score, SMD = 1.16, 95% CI = −1.20 to 3.52, $P = .34$; strength of shoulder abduction, SMD = 0.42, 95% CI = −0.03 to 0.88, $P = .07$).

Conclusion: Effective pain relief was achieved in patients with tendon or ligament disorders after PDRN injection. To more precisely determine this effect, a meta-analysis with a larger number of clinical trials is warranted.

Abbreviations: PDRN = polydeoxyribonuclide, SPADI = shoulder pain and disability index, VAS = visual analog scale.

Keywords: ligamentopathy, musculoskeletal pain, polydeoxyribonucleotide, tendinopathy

1. Introduction

Musculoskeletal pain affects the bones, muscles, ligaments, tendons, and nerves. Among these, pain in the tendons or ligaments is often caused by injuries, including sprains, overuse, and repetitive motions.[1,2] The multifactorial pathologies of the tendons and ligaments, such as unregulated apoptosis, mechanical overload, genetic factors, neuronal proliferation, and inflammation, induced by such injuries lead to pain and edema and functional deterioration.[3] These conditions are extremely common in athletes and workers with overuse injuries, accounting for approximately 30% of all causes of medical care by general practitioners.[4] In the treatment of tendon and ligament pain, conventional methods, including physical therapy, nonsteroidal anti-inflammatory drug and analgesic administration, and extracorporeal shockwave therapy, have known effects.[5]

Recently, several studies have reported that polydeoxyribonucleotide (PDRN) has an effect on musculoskeletal pain, especially in the tendons or ligaments, such as rotator cuff tendinopathy, lateral epicondylitis, pes anserinus, and plantar fasciitis.[6–11] PDRN is a compound formed by deoxyribonucleotide polymers of different lengths ranging from 50 to 2000 base pairs and nucleosides derived from salmon sperm.[12,13] The structure of PDRN consists of a low molecular weight fraction of deoxyribonucleic acid, which is composed of a linear polymer of deoxyribonucleotides with phosphodiester bonds, in which the monomer units are represented by purine and pyrimidine nucleotides.[12] In addition to the effect of PDRN on musculoskeletal pain, PDRN promotes regeneration of tendon or ligament injuries in animal models.[14,15]

However, to the best of our knowledge, the effects of PDRN in patients with tendon or ligament pain are unclear. To evaluate the

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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effectiveness of PDRN injection in patients with tendon or ligament pain, we performed a meta-analysis of all available clinical studies of PDRN treatment in patients with tendon or ligament pain.

2. Methods

2.1. Search strategy

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines. Ethical approval was waived by the local Ethics Committee of Kyungpook National University Hospital in view of the retrospective nature of the study and all the procedures being performed were part of the routine care. The PubMed, Embase, SCOPUS, and Cochrane Library databases were systematically searched for relevant studies published from inception until January 31, 2020. Search terms included (MeSH term "tendinopathy," "tendon," or "ligament," and keyword "tendinitis") and (MeSH "polynucleotide" and keywords "polynucleotide" and "PDRN") or (MeSH term "clinical trial" and keyword "trial") and (MeSH term "polynucleotide" and keywords "polynucleotide" and "PDRN").

2.2. Eligibility criteria

Articles were included in this study based on the following criteria:

1) patients' pain was induced by tendon or ligament lesions;
2) "injection of PDRN near the lesion" was used to manage the pain;
3) pain levels were evaluated before and after PDRN treatment; and
4) studies involved human subjects.

The present meta-analysis included studies published in the English language, conducted using any study design, and not limited to randomized controlled trials (RCT). Review articles, letters, case reports, and studies that reported insufficient data or results were excluded from this meta-analysis.

2.3. Study selection and data extraction

After the exclusion of duplicate publications, 2 independent reviewers (DP and DK) evaluated potential eligible studies to be included in the meta-analysis. For eligibility, articles were screened based on a review of the title and abstract. Disagreements between 2 independent reviewers were resolved by consensus. After the primary screening, the full text of the eligible studies was independently checked by the 2 reviewers (DP and DK). Subsequently, data including the first author, year of publication, sample size, cause of pain, demographic data, method of PDRN injection, outcome measures, follow-up period, and major adverse effects were independently extracted from each eligible study.

2.4. Quality assessment

The methodological quality of the included studies was assessed using 2 different assessment tools. For RCTs, the Cochrane Collaboration's Handbook was used to determine adequate sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias.[16] The bias judgments were divided into "low risk," "high risk," and "unclear risk." For observational studies, the Newcastle-Ottawa scale was used for quality assessment of the prospective observational studies, with 3 aspects of selection: selection of subjects, comparability of groups, and assessment of outcome.[17] The quality of each study was graded as low (0–3), moderate (4–6), and high (7–9). All disagreements were resolved by consensus.[17]

2.5. Statistical analysis

RevMan version 5.3 software (http://tech.cochrane.org/revman) and R software were used in the statistical analysis of pooled data. Heterogeneity tests were performed in each analysis to measure the degree of discrepancy between the results. *P*-values $<.05$ were considered to have substantial heterogeneity, and a random-effects model was used in the data analysis.[18] In contrast, when the *P*-value was $>.05$, the pooled data were considered homogeneous, and a fixed-effects model was applied.[18] We analyzed the standardized mean difference (SMD), and 95% confidence interval (CI) was used in the analysis. A *P*-value $<.05$ indicated statistical significance.

3. Results

3.1. Study selection

The preliminary search of all databases provided a total of 262 potentially relevant studies (Fig. 1). After the elimination of duplicate studies, 92 publications were excluded based on a review of the titles and abstracts. An assessment of the remaining studies was conducted through a review of the full text of the articles. After a systematic review, 4 articles were included in the final analysis, which consisted of 1 RCT and 3 retrospective observational studies.[19–22] In the RCT by Kim et al,[21] patients in the control group received saline injections. In the retrospective case–control study by Yoon et al,[22] patients in the control group received conservative treatment.

3.2. Study characteristics

The selected studies included 123 cases. The study duration ranged from 3 to 6 months. The basic characteristics of the included studies are shown in Table 1.

3.3. Risk of bias

The study by Kim et al[21] was a RCT. Thus, based on the *Cochrane Handbook 5.1 Assessment Tool*, the risk of bias was evaluated. The study had an unclear risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment. A low risk of bias was observed on incomplete outcome data, selective reporting, and other biases. The other 3 studies included in our meta-analysis were assessed using the Newcastle-Ottawa scale: Yoon et al's studies[22] were rated as 9 stars, which indicate a low risk of bias (selection of subjects, 3 stars; comparability of groups, 3 stars; assessment of outcome, 3 stars). Do et al's[20] and Ryu et al's[19] studies were rated as 7 stars, which indicate a low risk of bias (selection of subjects, 3 stars; comparability of groups, 1 star; assessment of outcome, 3 stars).

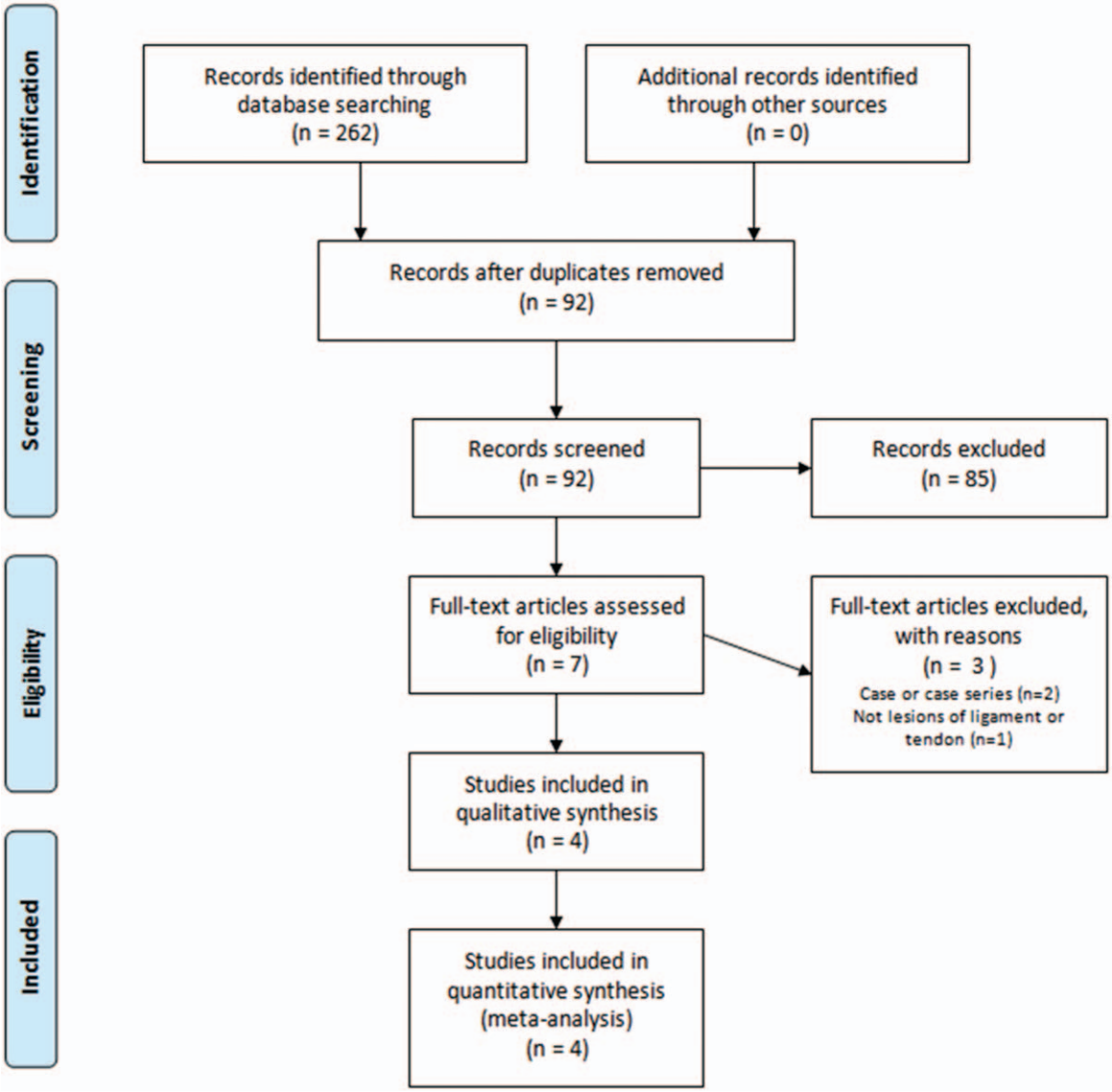

Figure 1. Flowchart showing the search results of the meta-analysis.

3.4. Meta-analysis results

To analyze the effect of PDRN injection in patients with pain due to ligament or tendon lesions, 2 different methods were used. First, the effect of PDRN injections was analyzed in patients with tendon or ligament pain after 12 weeks compared to a control group (normal saline injection or conservative treatment) using a visual analog scale (VAS). In addition, the effect of PDRN injection was evaluated in patients with tendon or ligament pain after 4 to 6 and 12 weeks (without comparison to the control group). Moreover, the effect of PDRN injection in patients with rotator cuff tendinopathy was analyzed after 12 weeks using VAS, shoulder pain and disability index (SPADI), and strength of shoulder abduction.

In the analysis of the effect of PDRN injection in patients with tendon or ligament pain after 12 weeks using VAS compared to the control group, the fixed-effects model was adopted since the *P*-value for heterogeneity of the assessment was >.05 ($P=.97$, $I^2=0\%$, $chi^2=0.00$, $df=1$). An analysis of the variation in VAS scores after 12 weeks of PDRN injection revealed that there was a significant reduction in VAS score (SMD = −1.43, 95% CI = −1.80 to −1.06, $P<.00001$) (Fig. 2). In the analysis of PDRN injection in patients with tendon or ligament pain after 4 to 6 and 12 weeks using the VAS, the random-effects model was adopted since the *P*-value for heterogeneity of the assessment was <.05 (12 weeks, $P=.006$, $I^2=76\%$, $Tau^2=0.67$, $df=3$; 4–6 weeks, $P<.00001$, $I^2=92\%$, $Tau^2=1.99$, $df=2$). Analysis of the variation in VAS scores after 4 to 6 and 12 weeks of PDRN injection revealed that there was also a significant reduction in VAS score (12 weeks, SMD = −2.20, 95% CI = −3.13 to −1.26, $P<.00001$; 4–6 weeks, SMD = −2.08, 95% CI = −3.176 to −0.40, $P=.02$) (Fig. 3).

In the analysis of the effect of PDRN injection in patients with rotator cuff tendinopathy, the random-effects model was adopted in VAS after 12 weeks of PDRN injection since the *P*-value for heterogeneity of the assessment was <.05 ($P=.002$, $I^2=84\%$, $Tau^2=1.03$). An analysis of the variation in VAS scores after 12

Table 1

Characteristics of included studies.

Study	Disease	Group	N	Age, yr	Sex (M:F)	Intervention	Injection volume	Times of injection	Outcome measures	Follow-up	Adverse effects
Do et al (2018)	Partial thickness tear of SST tendon	PDRN	17	57.9±9.1	(9:8)	PDRN (5.625 mg/3 mL) after local anesthesia (0.5% lidocaine 2 mL)	150% of tear volume estimated by US	3 times (every 2 wks)	1. VAS at shoulder resting 2. VAS on shoulder acting 3. DASH 4. ROM 5. Shoulder strength 6. Tear volume of SST	Initial: 6, 12 wks	Abdominal pain and diarrhea
Ryu et al (2018)	Rotator cuff tendinopathy	PDRN	32	53.4±10.0	(17:15)	PDRN (5.625 mg/3 mL) 3 mL with 1% lidocaine 1 mL	Total 4 mL	Max 5 times* (every 1 wk)	1. VAS 2. SANE 3. SPADI	Initial: 1, 4, 12 wks	None
Yoon et al (2016)	Chronic SST tendinopathy	PDRN	55	54±6.6	(25:30)	PDRN (5.625 mg/3 mL) 3 mL with 1% lidocaine 1 mL	Total 4 mL	3 times (every 1 wk)	1. VAS 2.SPADI 3. Shoulder strength 4. ROM 5. Tear size of SST	Initial: 12, 24 wks	None
		Control	51	52.4±7.6	(21:30)	Conservative treatment without injection					
Kim et al (2015)	Plantar fasciitis	PDRN	20	52±16	(7:13)	PDRN (5.625 mg/3 mL) 1.5 mL	Total 1.5 mL	3 times (every 1 wk)	1. VAS 2. MOXFQ	Initial: 4, 12 wks	None
		Control	20	55±16	(4:16)	Normal saline	Total 1.5 mL	3 times (every 1 wk)			

DASH = disabilities of the arm, shoulder and hand; MOXFQ = Manchester-Oxford Foot Questionnaire; PDRN = polydeoxyribonucleotide; ROM = range of motion; SANE = single assessment numeric evaluation; SPADI = shoulder pain and disability index; SST = supraspinatus; US = ultrasonography; VAS = visual analog scale.

* Injections were discontinued if the pain score decreased to at least one-quarter of preinjection levels, if the patient received the maximum of 5 injections, or if decided to withdraw from treatment.

weeks of PDRN injection in patients with rotator cuff tendinopathy revealed that there was a significant reduction in VAS score (SMD = −2.34, 95% CI = −3.61 to −1.07, $P = .0003$) (Fig. 4). In the analysis of SPADI score and strength of shoulder abduction after 12 weeks of PDRN injection, the fixed-effects model was adopted since the *P*-value for heterogeneity of the assessment was >.05 (SPADI score, $P = .73$, $I^2 = 0\%$, $chi^2 = 0.12$; strength of shoulder abduction, $P = .06$, $I^2 = 72\%$, $chi^2 = 3.54$). However, the analysis did not show significant improvement in both SPADI score and strength of shoulder abduction after 12 weeks of PDRN injection in patients with rotator cuff tendinopathy (SPADI score, SMD = 1.16, 95% CI = −1.20 to 3.52, $P = .34$; strength of shoulder abduction, SMD = 0.42, 95% CI = −0.03 to 0.88, $P = .07$) (Fig. 4).

3.5. Publication bias

A funnel plot analysis was performed in all assessments. The graphical funnel plot that involved the change in VAS scores after 12 weeks of PDRN injection in patients with tendon or ligament pain compared to the control group appeared to be symmetrical (Fig. 5A). However, the graphical funnel plots that involved the change in VAS scores after 4 to 6 and 12 weeks of PDRN injection in patients with tendon or ligament pain appeared to be slightly asymmetrical (Fig. 5B and C). However, in the Egger's test, statistically significant publication bias was unlikely to occur (12 weeks, $P = .9464$; 4 weeks, $P = .1531$).

In the analysis of the effect of PDRN injection in patients with rotator cuff tendinopathy, the graphical funnel plots that involved the change in VAS scores after 12 weeks of PDRN

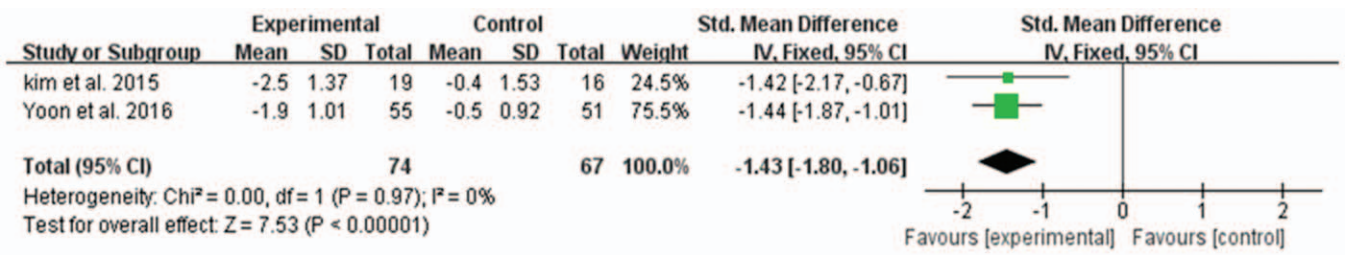

Figure 2. Analysis of visual analog scale (VAS) score changes in patients with tendon or ligament pain compared to the control group after polydeoxyribonucleotide injection.

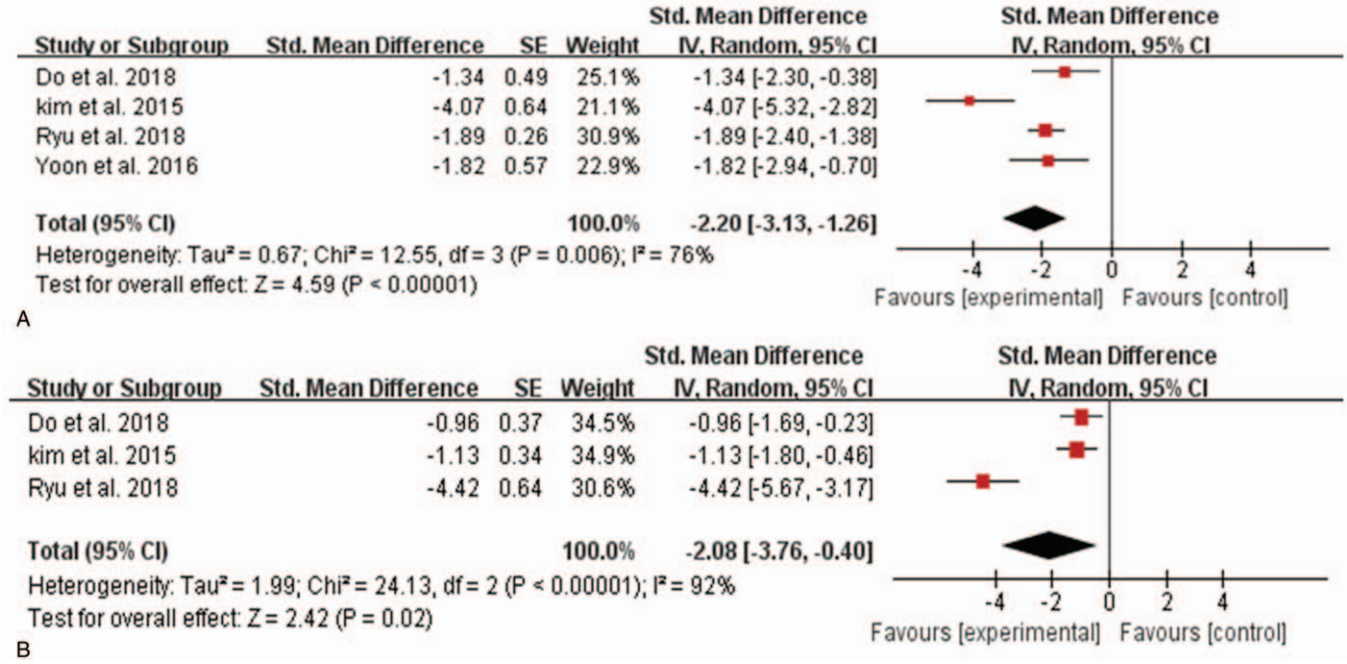

Figure 3. Analysis of visual analog scale (VAS) score changes after polydeoxyribonucleotide (PDRN) injection in patients with tendon or ligament pain. (A) After 12 wks of PDRN injection. (B) After 4–6 wks of PDRN injection.

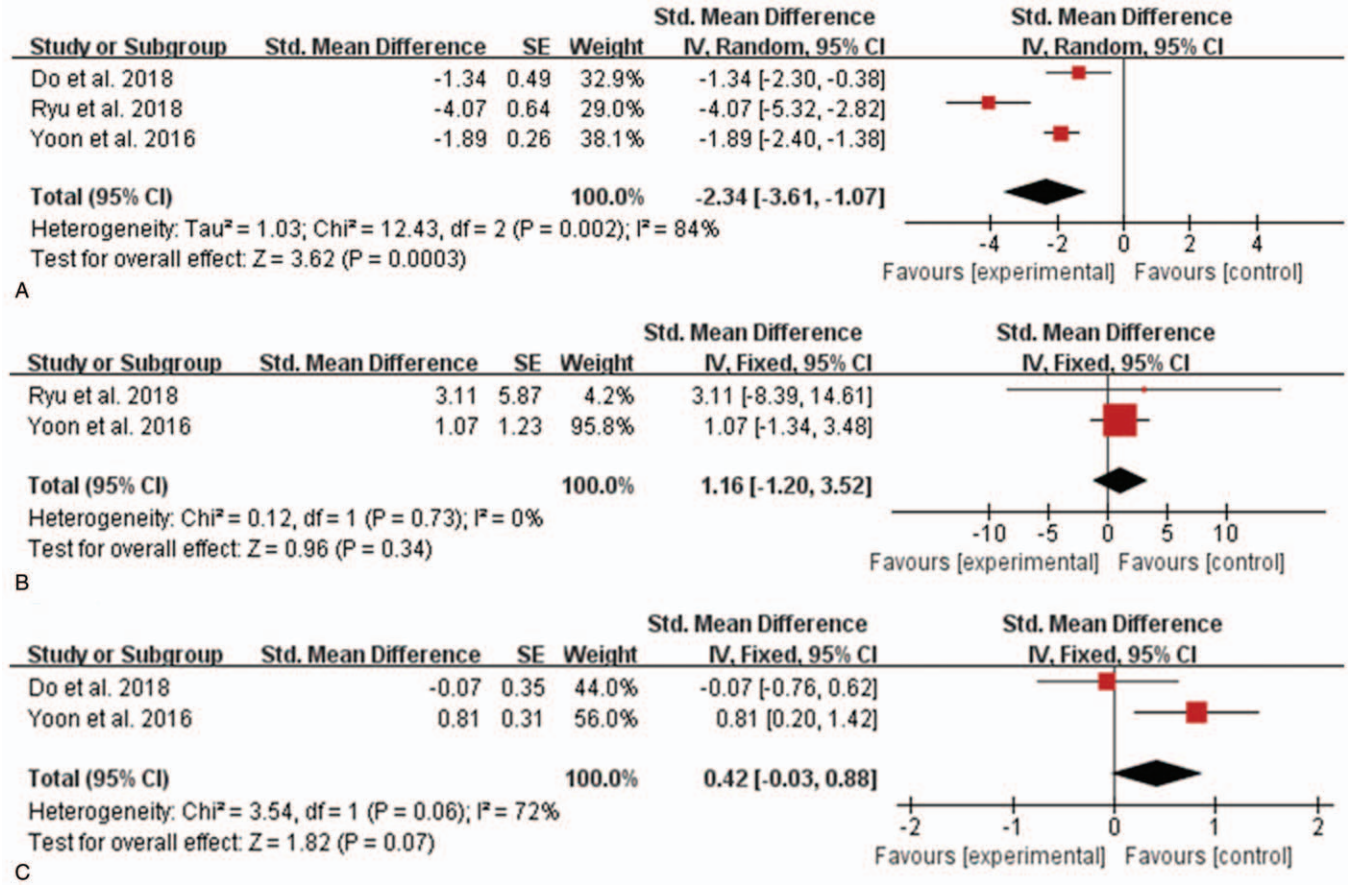

Figure 4. Results of the analysis of the visual analog scale (VAS) score, shoulder pain and disability index (SPADI) score, and strength of shoulder abduction in patients with rotator cuff tendinopathy. (A) VAS score changes after 12 wks after PDRN injection. (B) SPADI score changes after 12 wks of PDRN injection. (C) Strength of shoulder abduction after 12 wks of PDRN injection. PDRN = polydeoxyribonucleotide.

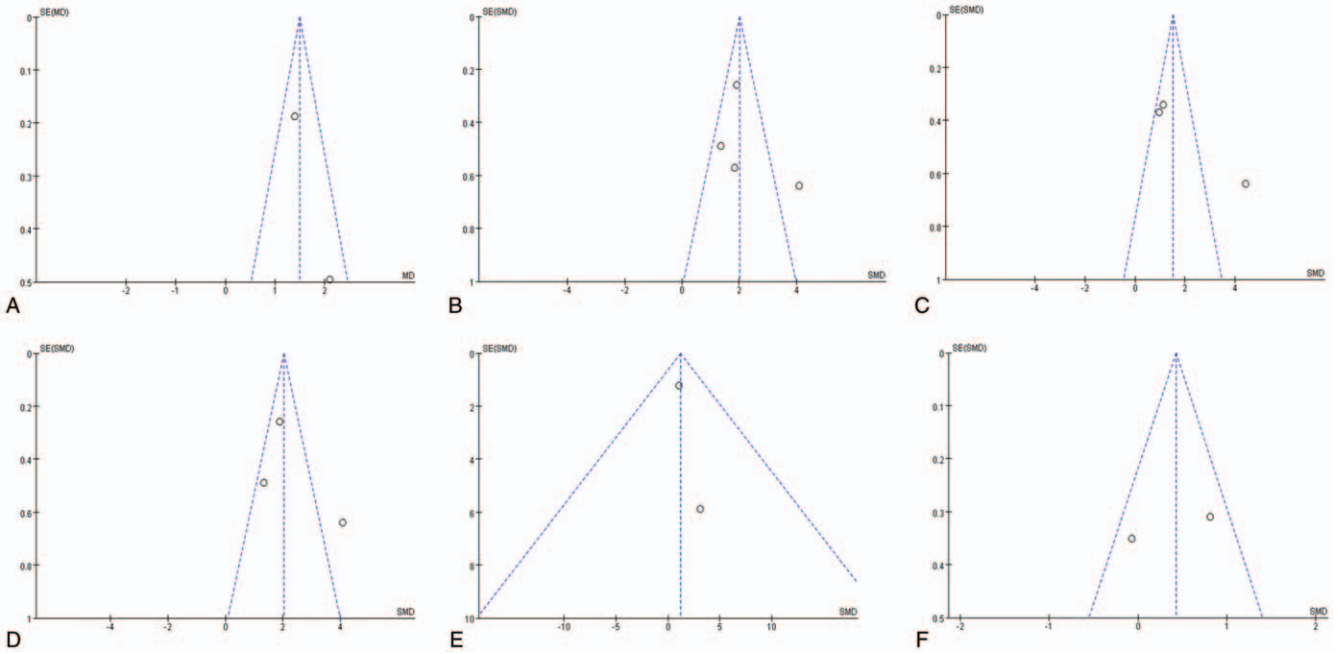

Figure 5. Graphical funnel plots. (A) Visual analog scale (VAS) score changes in patients with tendon or ligament pain compared to the control group after 12 wks of polydeoxyribonucleotide injection. (B) VAS score changes after 12 wks of PDRN injection in patients with tendon or ligament pain. (C) VAS score changes after 4–6 wks of PDRN injection in patients with tendon or ligament pain. (D) VAS score change after 12 wks of PDRN injection. (E) SPADI score change after 12 wks of PDRN injection. (F) Strength of shoulder abduction after 12 wks of PDRN injection. PDRN = polydeoxyribonucleotide.

injection appeared to be slightly asymmetrical (Fig. 5D). However, in the Egger's test, statistically significant publication bias was unlikely to occur ($P = .9727$). In contrast, the graphical funnel plots that involved the change in SPADI score and strength of shoulder abduction after 12 weeks of PDRN injection appeared to be symmetrical (Fig. 5E and F).

4. Discussion

In the current study, we evaluated the effectiveness of consecutive PDRN injections in alleviating pain caused by tendon or ligament lesions. In the meta-analysis, 4 studies were included, and pain, which was measured using the VAS, was analyzed. Additionally, we also evaluated the effectiveness of PDRN injection in alleviating pain due to rotator cuff tendinopathy. In this meta-analysis, 3 studies were included, and pain (VAS), SPADI score, and strength of shoulder abduction were analyzed.

We analyzed all data in each included study, and the overall outcome showed that tendon or ligament pain was significantly reduced after consecutive PDRN injections. Moreover, at each evaluation time point (i.e., 4–6 and 12 weeks after PDRN injection), the pain was significantly alleviated. The effect size was found to range from −1.06 to −1.80 (VAS score after 12 weeks of PDRN injection compared to that in the control group), from −1.26 to −3.13 to −1.26 (VAS score after 12 weeks), and from −0.40 to −3.176 (VAS score after 4 weeks of PDRN injection). Based on Cohen's study, these effect sizes can indicate that consecutive PDRN injections have a large positive pain-reducing effect in patients with tendon or ligament pain.

In the analysis of the effect of PDRN injection using VAS on rotator cuff tendinopathy, the overall outcome showed that pain due to rotator cuff tendinopathy was also significantly reduced after consecutive PDRN injections. The effect size was found to range from −1.07 to −3.61 (VAS score after 12 weeks of PDRN injection). Based on Cohen's study, these effect sizes can indicate that consecutive PDRN injections have a large positive reducing effect on pain induced by rotator cuff tendinopathy. However, in the analysis using SPADI score and strength of shoulder abduction, there was no significant improvement. The effect size was found to range from −1.20 to 3.52 in SPADI score and −0.03 to 0.88 in strength of shoulder abduction.

Some possible mechanisms of PDRN injection in pain reduction have been proposed. Squadrito et al reported that PDRN stimulates one of the adenosine receptors ($A2_A$ receptors) under pathologic conditions, such as tendon or ligament injuries.[13] Adenosine, a purine nucleoside, has been reported to reduce excessive inflammation through binding with one or more of its 4 known receptors (A1, $A2_A$, $A2_B$, and A3).[23] Especially, the stimulation of adenosine A2A receptor specifically has been demonstrated to inhibit proinflammatory cytokine production in human peripheral blood mononuclear cells.[24] These anti-inflammatory effects of PDRN may be helpful in reducing pain induced by tendon or ligament disorders. Moreover, PDRN has been demonstrated to exert profibrinolytic and antithrombotic activities through stimulation of vascular prostacyclin and vascular endothelial growth factor production,[12] which may also promote regeneration of tendons or ligaments. Collectively, these effects of PDRN on anti-inflammation and promotion of tendon or ligament regeneration may contribute to the improvement of pain in patients with tendon or ligament lesions.

Our meta-analysis had few limitations. First, in the meta-analysis of patients with rotator cuff tendinopathy, we could not perform the analysis with data extracted from the placebo or control group. Of the 3 included studies on rotator cuff tendinopathy, only Yoon et al performed a study with a control

group. They compared the effect of PDRN injection with that of conservative treatment. The other 2 studies did not recruit placebo or control subjects. The recruitment of a placebo group may be complicated by ethical issues. Additionally, physicians may have limited options to manage pain conservatively other than medication administration, corticosteroid injection, or physical therapy. Therefore, it can be difficult to find an appropriate procedure for the control group. However, despite these difficulties, the absence of a placebo or control group is one of the limitations of the previous study. Second, although 1 retrospective case–control study, 2 retrospective observational studies, and 1 RCT had high quality, only 1 RCT was included in our meta-analysis. For a more qualified meta-analysis outcome, more strictly controlled RCTs with a placebo group would be necessary.

Therefore, consecutive PDRN injections were effective in relieving pain caused by tendon or ligament disorders. Moreover, the pain-reducing effect was significantly manifested at 4 to 6 weeks or 3 months after consecutive PDRN injections. Additionally, consecutive PDRN injections were also effective in patients with rotator cuff tendinopathy, although there was no improvement in disability and strength of shoulder abduction. Our study is the first meta-analysis to analyze the effect of PDRN injection on pain reduction in tendon or ligament disorders and rotator cuff tendinopathy. However, our meta-analysis had a limited number of included trials and sample size. Therefore, in the future, a meta-analysis with a larger number of clinical trials would be warranted.

Author contributions

Conceptualization: Donghwi Park.
Data curation: Donghwi Park.
Supervision: Jong-moon Hwang, Ae Ryoung Kim.
Writing – original draft: Dae-Won Gwak, Jong-moon Hwang, Donghwi Park.
Writing – review & editing: Donghwi Park.

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