The effectiveness of 2 consecutive intra-articular polydeoxyribonucleotide injections compared with intra-articular triamcinolone for hemiplegic shoulder pain

A STROBE-complaint retrospective study

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Abstract
The aim of this study was to investigate the effects of intra-articular injection of polydeoxyribonucleotide (PDRN), compared with intra-articular triamcinolone (TA) injection, in subacute stroke patients with hemiplegic shoulder pain (HSP).

Participants were subacute stroke patients with HSP who had undergone 2 consecutive intra-articular injections of TA or PDRN.

In the results, there were significant improvements in all PROM measures 2 weeks after the second injection, compared with pre-injection results, in both groups (P < .05). In the PDRN group, however, none of the PROM measures were significantly improved at 3 and 4 weeks after the second injection, compared with pre-injection results (P ≥ .05). When comparing pre-injection results with those at 4 weeks after the second injection, all PROM and NRS measures in the TA group were more improved than in the PDRN group, but this was not statistically significant (P ≥ .05).

In conclusion, considering the systemic side effects of steroids, especially among patients with diabetes or metabolic syndrome, PDRN seems to be a worthwhile treatment option for HSP, although PDRN does not seem to have an equivalent persistence effects when compared with TA.

Abbreviations: CRPS = complex regional pain syndrome, HSP = hemiplegic shoulder pain, NRS = Numeric rating scale, PDRN = polydeoxyribonucleotide, PROM = passive range of motion, TA = triamcinolone

Keywords: adenosine, hemiplegic shoulder pain, polydeoxyribonucleotide, steroid side effects, triamcinolone

1. Introduction
Hemiplegic shoulder pain (HSP) is one of the most common musculoskeletal complications after acute stroke. Moreover, it can interfere with rehabilitative treatment and has been associated with poorer functional outcomes and prolonged hospital stays.[2–4] With regard to treatment, nothing has yet been proven effective, although different treatment methods, such as physical therapy,[5] functional electrical stimulation,[6,7] and intra-articular steroid injection,[8,9] are employed. In clinical practice, physicians frequently treat HSP using steroid injections,[9] although their effects remain controversial.[8–10]

Although there are many causes of HSP, articular inflammation is one of the important pathophysiology of HSP.[11] From this perspective, intra-articular steroid injection can help relieve pain,[8,9] but the systemic side effects of steroid injection, such as suppression of the hypothalamus-pituitary-adrenal (HPA) axis and increased blood glucose,[12,13] as well as local side effects, such as tissue degeneration and tendon rupture,[14–16] can also occur. In particular, the increased blood glucose level that can occur as a side effect of steroid injections limits their selection as a therapeutic agent, especially considering the fact that diabetes and metabolic syndrome are often combined with stroke.

Recently, there have been studies investigating the effects of polydeoxyribonucleotide (PDRN) in patients with plantar fasciitis,[17] lumbar sacral radiculopathy,[18] supraspinatus tendinopathy,[19] and the effects of PDRN in rheumatoid arthritis animal models.[20] Unlike steroids, PDRN has anti-inflammatory effects without metabolic side effects such as elevated blood sugar levels, making it a possible alternative to steroids for the treatment of musculoskeletal disorders in those studies. To the best of our knowledge, however, there have been no studies on the effect of PDRN for HSP to date. Therefore, in this study, we...
tried to investigate the effects of intra-articular injections of PDRN, compared with intra-articular triamcinolone (TA) injections, in patients with HSP.

2. Method

2.1. Participants

This study received Institutional Review Board approval of Daegu Fatima Hospital. A written informed consent was not necessary for this retrospective study, and patient anonymity was preserved. Among the stroke patients who were admitted to our hospital, those with HSP were investigated retrospectively. We compared the effect of PDRN injection with TA injection instead of the control group due to ethical issues. Patients who had undergone 2 consecutive TA or PDRN intra-articular injections, and who had been clinically evaluated (passive ROM and NRS) after these 2 consecutive injections, were included. Patients who had limitation in passive external rotation of the hemiplegic shoulder of at least 20°, compared with the unaffected side, were included.[4] Patients who had any of the following were excluded: history of shoulder surgery, prior steroid injection, autoimmune diseases such as rheumatoid arthritis or ankylosing spondylitis, complex regional pain syndrome (CRPS), and chronic stroke patients (≥6 months). On the basis of these criteria, 64 subacute stroke patients, who were admitted to our hospital with HSP between March 2016 and March 2017, were initially included. Among them, 44 patients were excluded due to the exclusion criteria. Therefore, a total of 20 patients (10 patients with TA injections vs 10 patients with PDRN injections) were included for analysis in this study (Fig. 1A, B).

2.2. Intervention

All patients included in this study underwent ultrasound-guided intra-articular TA or PDRN injections in the hemiplegic shoulder. The TA group received intra-articular injections of TA 40 mg/1 mL (Dong Kwang Pharm., Seoul, Korea) and normal saline (N/S) 14 mL (total 15 mL). The PDRN group received intra-articular injections of PDRN (Rejuvenex, PharmaResearch Products, South Korea) 1 ampoule (PDRN sodium 5.625 mg/3 mL) and N/S 12 mL (total 15 mL). In this study, patients with diabetes mellitus (DM) and HSP were excluded, because 20 mg of TA was usually injected in DM patients with HSP in our department. Success of intra-articular shoulder injections was judged by checking drug flow into the articular cavity using color Doppler (Fig. 2).[21]

2.3. Outcome measurement

The primary outcome measures were pain measured using a numeric rating scale[22] (NRS; on a scale of 0–10, where 0 = no pain and 10 = highest level of pain) during passive ROM of the shoulder in 4 planes (forward flexion, abduction, external, and internal rotation); and passive ROM of the shoulder in four planes (forward flexion, abduction, external rotation, and internal rotation) using goniometry.[4] All ROMs were measured in the seated position. Assessment was performed just before the first injection, 1 day after the first injection, 1 week after the first injection, 1 week after the second injection, 2 weeks after the second injection, 3 weeks after the second injection, and 4 weeks after the second injection (Fig. 1B).
Table 1
Clinical characteristics of the stroke patients in the TA and PDRN groups.

|                  | TA group       | PDRN group     | P     |
|------------------|----------------|----------------|-------|
| Age, y           | 64.70 ± 15.31  | 67.90 ± 11.57  | .616  |
| Sex ratio (female: male) | 4:6            | 7:3            | .370  |
| Stroke type, n (%)|                |                | .370  |
| Infarction, n (%) | 6 (60%)        | 3 (30%)        |       |
| Hemiparesis, n (%)| 4 (40%)        | 7 (70%)        |       |
| Brunnstrom motor recovery stage | 3.00 ± 1.70    | 3.70 ± 1.16    | .183  |
| Hemi-side (right:left) | 7:3            | 3:7            | .179  |
| Duration since stroke, mo | 3.10 ± 0.88    | 4.15 ± 1.97    | .149  |
| Initial status    |                |                |       |
| NRS               | 4.80 ± 0.79    | 4.50 ± 1.08    | .487  |
| Passive flexion, degree | 125.50 ± 9.85  | 129.50 ± 19.64 | .572  |
| Passive abduction, degree | 124.50 ± 10.12 | 121.00 ± 14.30 | .535  |
| Passive external rotation, degree | 48.00 ± 6.33  | 54.00 ± 8.10   | .081  |
| Passive internal rotation, degree | 60.00 ± 15.28  | 64.00 ± 5.16   | .443  |

Values: mean ± standard deviation.
NRS = numeric rating scale, PDRN = polydeoxyribonucleotide, TA = triamcinolone.

2.4. Statistical analysis
Statistical analyses were performed using SPSS for Windows and R package for Windows (version 2.15.2; R Foundation for Statistical Computing, Vienna, Austria). The initial statistical analysis was carried out using a one-way analysis of variance (ANOVA) with a Tukey post-hoc test to compare the passive ROM and NRS measures across the time of assessments, and to evaluate the effectiveness of the treatments in each group. An independent t test was used to compare between-group differences in the degree of improvement in NRS and passive ROM after treatment. The results are presented as the mean ± standard deviation. Chi-square tests were used to compare categorical variables (e.g., sex ratio, hemi-side) between the groups. P values of < .05 were considered statistically significant.

3. Results
3.1. Characteristics of patients
There were no statistically significant differences in patients’ age, gender, hemi-side, duration since stroke, stroke type (infarction or hemorrhage), Brunnstrom motor recovery stage, NRS, and passive ROMs (flexion, abduction, external rotation, and internal rotation) between the 2 groups, before the injections (P ≥ .05) (Table 1).

3.2. Changes in NRS and passive ROM
In both groups, a significant improvement in NRS was observed 1 day after the first injection (Table 2). Both groups also showed significant improvement at 1 week, 2 weeks, and 3 weeks after the second injection, as compared with their initial status. However, in both groups, there was no statistically significant improvement 4 weeks after the second injection, as compared with their initial status (Fig. 3A–E).

Both groups showed statistically significant improvements in terms of flexion, abduction, and internal rotation 1 day after the first injection, compared with their pre-injection results (P < .05). In addition, both groups showed statistically significant improvement in terms of all passive ROM measures 2 weeks after the second injection, compared with their pre-injection results (P < .05). However, at 3 and 4 weeks after the second injection, only the TA group showed significant improvements in terms of flexion, external rotation, and internal rotation, compared with their pre-injection results (P < .05). In the PDRN group, all passive ROM measures were not significantly improved 3 and 4 weeks after the second injection, compared with their pre-injection results (P ≥ .05) (Table 2).

3.3. Degree of improvement in NRS and passive ROM
We analyzed the degree of improvement in 6 intervals (interval 1–) (Fig. 1B). In all intervals, there was no significant difference between the TA and PDRN groups. When comparing 4 weeks after the second injection with the pre-injection results (interval 6), all passive ROM and NRS measures in the TA group were more improved than the PDRN group, but these differences were not statistically significant (P ≥ .05) (Fig. 4) (Table 3).

4. Discussion
To the best of our knowledge, there has been no published study investigating the effects of intra-articular inject of PDRN in musculoskeletal disorders. Recently, studies of PDRN in patients with musculoskeletal pain have suggested the possibility of use of PDRN for musculoskeletal disorders, but to date, there has been

Table 2
Comparison of the physical findings in the TA and PDRN groups.

| Group | Pre-injection | 1 d after 1st injection | 1 wk after 1st injection | 1 wk after 2nd injection | 2 wks after 2nd injection | 3 wks after 2nd injection | 4 wks after 2nd injection | P     |
|-------|---------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------|
| NRS   | A 4.80 ± 0.79  | 2.10 ± 0.88††          | 3.60 ± 1.17             | 2.20 ± 1.32*            | 1.90 ± 1.10††          | 2.20 ± 3.30            | 3.30 ± 1.06             | <.001 |
|       | B 4.50 ± 1.08  | 2.30 ± 0.48‡‡          | 2.80 ± 1.32‡‡          | 1.70 ± 1.25‡‡          | 2.10 ± 1.20‡‡          | 2.60 ± 1.35††          | 3.10 ± 1.29             | <.001 |
|       | A 125.00 ± 9.85| 148.00 ± 10.06         | 143.50 ± 13.75†         | 155.00 ± 7.07*          | 154.00 ± 6.99†         | 146.50 ± 10.12         | 143.50 ± 10.01*         | <.001 |
|       | B 120.00 ± 19.55| 154.00 ± 14.30        | 151.50 ± 15.28         | 155.00 ± 14.34‡         | 153.50 ± 14.92‡         | 141.00 ± 21.19         | 137.50 ± 19.33‡         | .005  |
| Abduction, degree | A 124.50 ± 10.12| 150.00 ± 9.13           | 143.00 ± 13.78§        | 150.00 ± 11.55§         | 148.50 ± 13.34§        | 145.50 ± 5.90          | 139.50 ± 11.66§         | <.001 |
|       | B 121.00 ± 14.30| 148.50 ± 17.01       | 142.50 ± 13.39         | 152.50 ± 15.50†         | 146.00 ± 19.55         | 140.00 ± 18.71         | 137.00 ± 16.19          | .002  |
| ER, degree | A 48.00 ± 6.33  | 59.50 ± 5.99           | 60.50 ± 6.85 ††        | 63.50 ± 10.55 ††       | 62.50 ± 7.91 ††        | 65.60 ± 9.56 ††        | 62.50 ± 11.37 ††        | .001  |
|       | B 54.00 ± 8.10  | 69.00 ± 8.76 ††        | 71.00 ± 9.94 ††        | 71.00 ± 8.76 ††        | 67.50 ± 9.80 ††        | 65.00 ± 6.50 ††        | 63.00 ± 8.23 ††         | .001  |
| IR, degree | A 55.00 ± 8.13  | 73.00 ± 11.60          | 70.00 ± 12.47          | 70.00 ± 8.17           | 76.00 ± 12.65          | 73.00 ± 14.18          | 72.00 ± 15.49 ††        | .009  |
|       | B 64.00 ± 5.16  | 80.00 ± 11.55          | 77.00 ± 10.59          | 82.00 ± 9.19           | 79.00 ± 8.76           | 76.00 ± 6.43           | 74.00 ± 6.99 ††         | .001  |

Values: mean ± standard deviation.
ER = external rotation, IR = internal rotation, NRS = numeric rating scale, PDRN = polydeoxyribonucleotide, TA = triamcinolone.
*P < .05 compared with pre-injection.
†P < .05 compared with 1 wk after 1st injection (just before 2nd injection), Group A, triamcinolone 40 mg group; Group B, PDRN group.
no study of its effects on HSP.\textsuperscript{[17,19]} PDRN is obtained from sperm trout through an extraction process.\textsuperscript{[23]} The compound holds a mixture of deoxyribonucleotide polymers with chain lengths ranging from 50 to 2000bp.\textsuperscript{[23]} PDRN acts through stimulation of the A2A receptor under pathologic conditions of low tissue perfusion.\textsuperscript{[23]} Adenosine is a purine nucleoside that is released from a variety of cells in response to several types of stress.\textsuperscript{[24,25]} It has been suggested that adenosine regulates inflammation via interaction with 1 or more of its 4 known receptors (A1, A2A, A2B, and A3). Although adenosine receptor stimulation has been shown to have a differential effect on the release of pro-inflammatory cytokines, stimulation of the adenosine A2A receptor has been shown to inhibit tumor necrosis factor (TNF)-\(\alpha\) production in human peripheral blood mononuclear cells (PBMCs).\textsuperscript{[19]} Moreover, in a previous study, PDRN lowered the circulating levels and cartilage expression of the inflammatory cytokines TNF-\(\alpha\) and interleukin-6 in a rheumatoid arthritis animal model.\textsuperscript{[20]} These effects of PDRN, in markedly reducing the production of inflammatory cytokines, point to its potential as an alternative treatment option to steroids.

The findings of the current study indicated that both the TA group and the PDRN group experienced improvements immediately, from the first day after the injection. This immediate effect of the TA group was similar to previous studies.\textsuperscript{[26,27]} In addition, there was no significant difference in the degree of improvement between the TA and PDRN groups until 4 weeks after the second injection, compared with their pre-injection results. These results may indicate that PDRN and TA have similar onset time and duration of therapeutic effects for HSP, until at least 4 weeks after 2 consecutive injections.

However, for passive ROMs, the PDRN group did not show a significant improvement in all passive ROM measures from the third week after the second injection, unlike the TA group. This presumably due to the following 2 reasons. First, the potency of the anti-inflammatory effect of PDRN (PDRN sodium 5.625mg) may be smaller than that of TA 40 mg. Second, it may be due to the difference in the form of PDRN and TA. Particulate TA may remain in the joint space for a longer time than soluble PDRN. In summary, our results suggest that there was no significant difference in the degree of improvement in the TA and PDRN groups until 4 weeks after the second injection, compared with their pre-injection results. These results may indicate that PDRN and TA have similar onset time and duration of therapeutic effects for HSP, until at least 4 weeks after 2 consecutive injections.

There are some limitations of our study. First, the number of patients was small and the study period was not long. To understand more about long-term therapeutic effects of PDRN, further studies with more patients and a longer period of time for follow-up will be necessary in the future. Second, this study is limited by its retrospective design. However, to date, there is no published study investigating the effects of PDRN on HSP. Moreover, in this study, PDRN was shown to have similar therapeutic effects to TA (which is widely used as a treatment for shoulder pain in clinical practice) for HSP. Considering these 2 points, this study seems to have sufficient significance as a
preliminary study. Considering the anti-inflammatory effect of PDRN, the possibility of its use as an alternative therapy seems to be justified, especially in patients with diabetes or metabolic syndrome who are expected to have systemic side effects from frequent steroid injections. In addition, it is worth considering the effect of various doses of PDRN in future prospective, randomized controlled studies, and comparing the effects of TA and PDRN over a longer time period.

5. Conclusion

Even though PDRN seems not to have an equivalent persistence effect compared with TA, considering the systemic side effects of steroids, especially in patients with diabetes or metabolic syndrome, it appears that PDRN is worthwhile to be used as an option for treatment of HSP. As it is known that PDRN has a dose-dependent effect,[10] it is also necessary to study the therapeutic effects of various doses of PDRN in the future.

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