Efficacy and Safety of Polynucleotide Injection for Preventing Post-surgical Scars

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Abstract

Scar formation shows a disorganized collagen structure and a loss of dermal appendages. Scars can have lasting physical and psychological effects. Polynucleotides (PNs) offer anti-inflammatory effects in laboratory models, which enhance small blood circulation and stimulate DNA synthesis. PNs are likely to enhance the protective barrier of the skin, reduce inflammation, and help alleviate redness. This study was a prospective-controlled trial that aimed to assess the safety and effectiveness of polynucleotide injections in preventing post-surgical scars. Methods: A total of six patients who had undergone excision were included. Immediately after excision, PN was injected into the scar, while the other side was left untreated to serve as the control. The primary outcome was evaluated by assessing the severity of the scar using the Vancouver Scar Scale (VSS) and Antera 3D. The secondary outcome evaluation assessed patient satisfaction and side effects using the 5-point global assessment score (5-point GAS) and the visual analog scale (VAS). Outcome assessment was carried out until 3 months after excision. Results: Three months after treatment, the mean EI score in the PN group was 1.809 ± 0.056, which was lower than the score of 1.978 ± 0.073 for the control group. This difference was statistically significant ($p = 0.006$). While the objective assessment showed a greater reduction in scar volume in the PN group compared to the control group, the statistical analysis did not reveal a significant result. Therefore, the study suggests that including more participants may be necessary. Conclusion: PN is effective in preventing post-surgical scars, particularly in terms of reducing redness.

Keywords**:** *scar, polynucleotides*

1. Introduction

The biological processes driving the overall healing response generally encompass overlapping phases, including hemostasis and inflammation, proliferation (which includes granulation, vascularization, and wound closure via contraction or epithelialization), and remodeling. Scar formation is the body's natural response to tissue injury, aimed at restoring tissue strength and integrity. However, this process is not perfect and is influenced by a balance between organizations. As a result, scar tissue often differs in structure from normal tissue. A mature scar, which represents the final stage of wound healing, typically shows a disorganized collagen arrangement and a loss of dermal appendages. It is crucial to note that scar formation is a dynamic process that begins with the injury and progresses through various stages of wound healing, ultimately leading to the development of a mature scar.

PDRN (Polydeoxyribonucleotide) has been used to enhance wound healing due to its ability to stimulate cell migration and growth, promote proper extracellular matrix (ECM) deposition, support angiogenesis, and reduce inflammation. This multifaceted approach offers several advantages, including non-invasiveness, various routes of administration, strong therapeutic effects, low immunogenicity, and no toxicity. As a result, PDRN is gaining popularity over conventional treatments. It also effectively lowers levels of pro-inflammatory mediators, suggesting that it may help inhibit scar formation by suppressing inflammatory reactions and reducing HMGB-1 production (Yun et al., 2023).

Polynucleotides (PNs), which are produced through a controlled depolymerization process, have an increased molecular size and a texture that combines viscosity and elasticity. Although the exact pharmacological mechanism of PNs is not fully understood, their structural resemblance to PDRN suggests they may have similar effects. PNs have been shown to have hydration qualities, drawing moisture, revitalizing the ECM, and enhancing skin elasticity and tone. Furthermore, PNs increase the levels of vascular

endothelial growth factor (VEGF) in skin tissues, improving microcirculation and promoting DNA synthesis, which aids in the regeneration of skin tissue. Consequently, PNs are expected to fortify the skin's barrier, reduce inflammation, and help diminish erythema (Lee et al., 2023).

Post-surgical scars can leave marks of trauma, and some individuals may struggle with the scars left behind. This study aims to evaluate the potential of polynucleotides in preventing future scarring, as the mechanism of polynucleotides plays a role in the wound healing process. To date, this method has not been used before. One study applied PDRN on days 1 and 2 after surgery, and the results showed its effectiveness in reducing scarring. PDRN injections on surgical wounds have proven be effective in preventing hypertrophic scars. These injections quickly reduced scar erythema by controlling inflammation in the early stages of healing, without any side effects. As a result, both clinical outcomes and subjective symptoms were significantly improved. This suggests that PDRN injections could offer an affordable, effective, and safe option for preventing hypertrophic scars and improving scar healing (Kim et al., 2023).

The text also suggests that PN treatment may prevent post-surgical scar formation with minimal serious side effects. The motivation for this study arises from previous research where PDRN injections were used to prevent hypertrophic scars, though PNs have not been widely explored for this purpose. This study aims to investigate whether PN injections can prevent scar formation at a particular concentration.

2. Objectives

1) To evaluate the efficacy and safety of polynucleotide injection for preventing post-surgical scars
2) To evaluate the satisfaction of patients after treatment
3) To evaluate the adverse effects after treatment

3. Materials and Methods

Study Design and Population

This is a prospective, assessor-blinded, controlled trial conducted at two centers, comparing the outcomes of post-excision scars following the injection of PN with those of untreated control scars. The criteria for inclusion were as follows: 1) Immediate to 1 day post-excision patients, size more than 2 cm, aged older than 18 years; 2) Healthy individual; 3) Capable of visiting OPD and following the method; 4) Agree with informed consent; 5) Fitzpatrick skin type III-IV. The criteria for exclusion were as follows: 1) Allergic to Sodium polynucleotide; 2) Using NSIAD, immunosuppressive drugs; 3) Phobia from injection; 4) The presence of inflammation or infection on the skin around the site of the injection; 5) Pregnancy.

Randomization and blinding

The patients were not assigned randomly. Those receiving 20% PN had it injected on either the right or lower side of the wound, while the left or upper side of the wound was designated as the control side. The patients knew which intervention they received, which could introduce a positive placebo effect as a potential confounder. However, the placebo effect was minimized in this study by using objective measures and blinding the outcome assessments, except for the subjective symptoms of patients. The treating doctor was not blinded and did not participate in the evaluation. In addition, the Vancouver Scar Scale and 5-point GAS were assessed by a blind dermatologist on every visit.

Study intervention

Patients in the treatment group of this study received one session of polynucleotide composed of 20% sodium polynucleotide divided into 2 syringes, with each syringe containing 2 ml of contents.

1) Patients were placed in a supine position.
2) Non-sterile gloves were worn and sterilized with chlorhexidine.
3) Targeted lesions were cleaned with alcohol.
4) Before treatment, surgical scar was divided in half.
5) Surgical scar site was cleaned and wiped with cotton that was soaked with normal saline.
6) Application of 5% Lidocaine cream (Emla) was carried out on the entire lesion and left for 30 minutes.
7) Lidocaine cream was covered with sealing films.

8) Lidocaine cream was used to clean with cotton and normal saline.
9) Sodium polynucleotide was obtained from Rejuran healer, South Korea.
10) Polynucleotide was injected into the whole lesion with a sharp needle number 33 gauze.
11) Injection used the intradermal technique.
12) The amount of each mark was 0.1 ml, with each site 0.5 cm apart.
13) The area of treatment contained around 0.2- 2 ml of sodium polynucleotide depending on the size of the surgical scar.
14) After treatment, the lesion was cleaned with chlorhexidine.
15) The left half was set as the control side.
16) Anaphylaxis symptoms such as dyspnea, chest discomfort, and rash were observed for 20 minutes.
17) A total of 1 session was conducted.
18) Follow up was done at baseline, 1, 4, 8, and 12 weeks.

This study includes one session because, upon reviewing the mechanism of PN, it assists in the inflammation phase of wound healing by inhibiting pro-inflammatory cytokines like IL-6 and stimulating growth factors such as VEGF. This process occurs over the course of several hours to 3 days during wound healing. As with Kim et al., (2023), this study administered PDRN injections 1 and 2 days after surgery, and the results demonstrated that scar height was less pronounced. The clinical characteristics of hypertrophic scars, including elevation, erythema, and symptoms, were all significantly reduced in the PDRN group.

Statistical analysis

To assess changes over time compared to baseline, a linear mixed model (LMM) was used with the patient as a random effect, and time and treatment as fixed effects. For comparisons between groups at baseline and at three months, a paired t-test was conducted for each parameter. Continuous data are presented as mean ± standard error of the mean (SEM), while categorical data are presented as proportions. All statistical analyses were performed using Python, with the stats models package for the linear mixed model (LMM) and the SciPy stats module for the paired t-test. A p-value of <0.05 was considered statistically significant.

4. Results and Discussion

4.1 Results

A total of 6 patients were screened for eligibility. Baseline patient characteristics are shown in Table 1. The baseline assessment scores between the two groups showed no significant differences, as presented in Table 2.

Baseline Patient Characteristics

Table 1 shows the basic characteristics of patients. Among the participants, one patient had a history of PCOS and MDD. One patient had underlying urticaria, hypothyroid, dyslipidemia, and impaired fasting glucose. One patient had obstructive uropathy, and another patient had coronary artery disease. Additionally, all patients had Fitzpatrick phototypes 3, 4, and 5. None of the patients had a prior history of keloid formation.

In general, African American and Asian patients are more prone to hypertrophic scarring and keloid formation compared to Caucasian patients. Regarding hyperpigmentation, individuals with Fitzpatrick skin types IV and higher have a greater incidence of hyperpigmentation (Lee Peng, & Kerolus, 2019).

Table 1 Baseline patient characteristics

Characteristics	n(%)
Age, years, mean (SD)	48.83 (19.35%)
Sex	
Male	2 (66.67%)
Female	4 (33.33%)
Comorbidities	
Yes	2 (66.67%)
No	4 (33.33%)
History of keloid/hypertrophic scar in other areas of the body	
Yes	0 (0.00%)
No	6 (100%)
Current medication	
Yes	5 (83.33%)
No	1 (16.67%)
Fitzpatrick's skin type	
Type 3	1 (16.67%)
Type 4	2 (33.33%)
Type 5	3 (50.00%)
Alcohol drinking	
Yes	0 (0.00%)
No	6 (100%)
Smoking	
Yes	0 (0.00%)
No	6 (100%)

Abbreviations: SD, standard deviation

Table 2 Baseline assessment scores before intervention of PN and control group

Assessment tools	**PN n=6 Mean (SD)**	**Control n=6 Mean (SD)**	**p-*value***
Vancouver scar scale			
Vascularity	0.500 (0.223)	0.500 (0.223)	0.363
Height	0.666 (0.210)	0.500 (0.223)	0.363
Pliability	0.167 (0.167)	0.000 (0.000)	0.363
Pigmentation	0.000 (0.000)	0.000 (0.000)	-
Antera 3D			
Scar volume	1.277 (0.200)	1.211 (0193)	0.753
Redness	1.457 (0.186)	1.450 (0.128)	0.944
Hyperpigmentation	0.531 (0.089)	0.541 (0.086)	0.345

Abbreviations: PN, polynucleotide; SD, standard deviation.

Vancouver Scar Scale

With regard to each component of VSS, the vascularity score within the control group tends to decrease for 2 months, as in Table 3. Meanwhile, the PN group tends to decrease for 1 month with statistical significance. The height score in each group was not significant. The pliability score in the control group after 3 months decreased from 1 week (1.167 ± 0.477, $p = 0.03$). On the other hand, the mean value of the PN group after 3 months was 1.000 ± 0.516, $p=0.025$. For pigmentation, both groups were increased significantly at 3 months. There was no notable difference in the scores of any components between the groups. None of the parameters showed statistical significance, which may be due to an insufficient sample size, and the duration of follow-up may have been insufficient.

Table 3 Vancouver Scar Scale at the 3-month follow-up

	PN	Control	p-*value*
VSS total, mean ± SD			
Vascularity	0.833 ± 0.166	1.000 ± 0.258	0.363
Height	0.833 ± 0.307	0.833 ± 0.307	1
Pliability	1.000 ± 0.516	1.167 ± 0.477	0.741
Pigmentation	0.500 ± 0.341	0.500 ± 0.341	1

VSS: Vancouver Scar Scale

Subjective Symptoms

Figures 1 and 2 show the VAS scores of both groups for subjective symptoms at the 3-month follow-up. The mean VAS scores for pain and itching were not significant in either group. The 5-point GAS of both doctors and participants in PN treatment was better than the control side with no statistical significance.

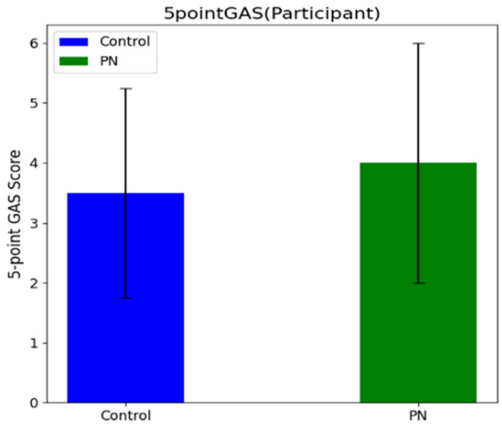

Figure 1 5-point GAS (Participant)

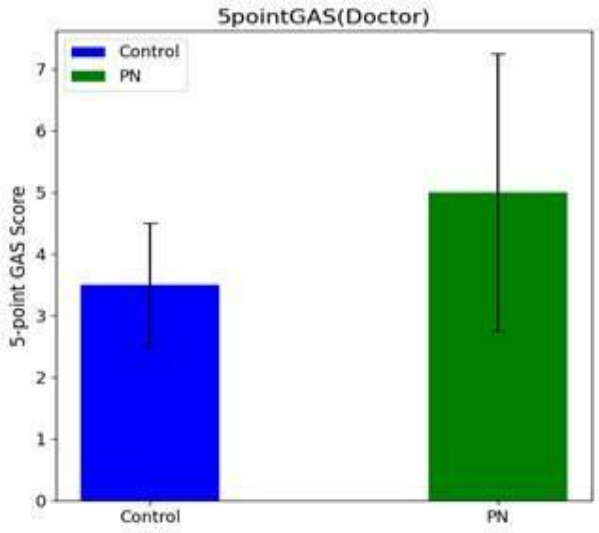

Figure 2 5-point GAS (Doctor)

Erythema and Pigmentation

The mean value of EI scores 3 months after treatment was 1.809 ± 0.056 in the PN group, as shown in Figure 3, which was lower than that in the control group (1.978 ± 0.073). Further, the difference between the two groups was statistically significant (p = 0.006). As shown in Figure 3, the EI decreased more slightly in the PN group than in the control group from 1 week to 1 month after treatment. Conversely, MI measured at the 3-month follow-up was not different in the PN group and the control group with no statistical significance, as seen in Figure 4.

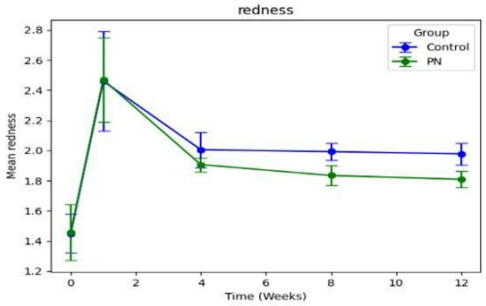

Figure 3 Redness

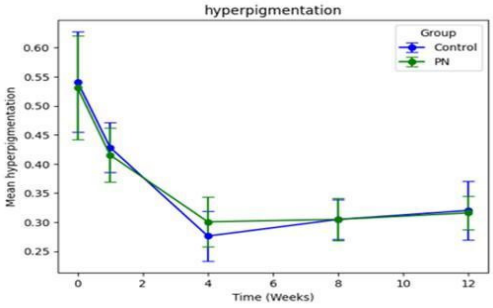

Figure 4 Hyperpigmentation

Scar Volume

Over time, scar volume increases as a part of the natural wound-healing process. However, the scar volume on the PN side was less prominent than on the control side from 1 month to 3 months. There was no significant difference in the volume at the 3-month follow-up between the two groups (1.054 ± 0.242 mm^3 in the PN group and 1.195 ± 0.311 mm^3 in the control group, p = 0.69; Figure 5).

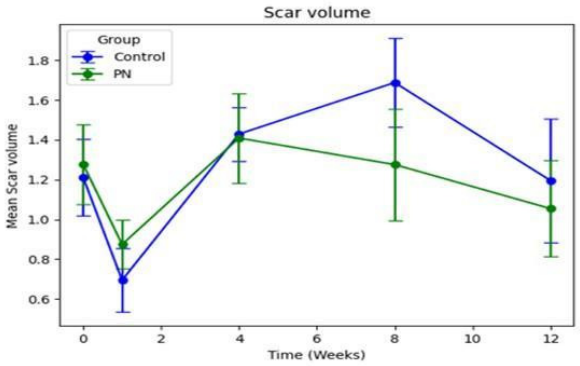

Figure 5 Scar volume

Adverse Effects

Most patients in the PN group reported tolerable and transient pain during the procedure. Five patients in both groups reported wound separation after off-stitch, which was resolved after attaching a sterile stitch. There were adverse events due to PN injection, such as delayed wound healing. One patient reported hypopigmentation. One patient was suspected of infection, which improved after topical and oral antibiotics.

4.2 Discussion

To the best of our knowledge, this is the first study to demonstrate the effectiveness of early postoperative PN injections in preventing hypertrophic scar formation through a randomized controlled trial. The findings revealed that early PN injections significantly decreased scar redness, with the injection group displaying a notably lower erythema index. However, no significant differences were found between the two

groups regarding scar height, pliability, vascularity, and pigmentation, as evaluated by the Vancouver scar scale.

Traditionally, scar treatment involves waiting until the scars are mature or in the process of maturing, typically around 2–3 months after the wound is formed. Nevertheless, recent studies have suggested that early intervention within the first month after suture removal can be more effective in minimizing scar formation. Excessive scar development is often linked to extended and excessive inflammation during the wound-healing process Kim et al., (2023).

Previous studies have shown that early embryonic wounds do not undergo a significant inflammatory phase, enabling them to heal quickly and without scarring. In contrast, wounds that occur later in fetal development involve intense inflammation and heal with scars, resembling the healing process in adult skin. Therefore, regulating the inflammatory response is essential for scar-free healing, and controlling the inflammatory phase (0-3 days) during the initial stages of wound healing is crucial for preventing scarring. However, no safe or effective methods are currently available for preventing scars and reducing inflammation Kim et al., (2023).

In keloids, there is a marked increase in collagen production by fibroblasts, along with elevated levels of transforming growth factor (TGF)-β. TGF-β plays a crucial role in the proliferative phase of wound healing, and its expression, especially TGF-β1 and TGF-β2, is linked to heightened scarring. In contrast, regenerative healing is characterized by the absence of scarring and inflammation. This connection is further supported by research showing that pro-inflammatory cytokines, such as interleukin-6 (IL-6) and IL-8, promote scarring, whereas the anti-inflammatory cytokine IL-10 reduces the formation of scar tissue (Lee et al., 2023).

As an adenosine receptor A2A agonist, PDRN promotes angiogenesis by increasing vascular endothelial growth factor, supports tissue repair by stimulating fibroblasts, and exerts anti-inflammatory effects by inhibiting various pro-inflammatory mediators. These mechanisms may help in preventing scar formation. They specifically confirmed that PDRN administration reduced scarring by suppressing the expression of high-mobility group box protein-1 (HMGB-1). HMGB-1 is a common nuclear protein released when necrotic cells lose membrane integrity, signaling tissue damage. It triggers inflammation by attracting inflammatory cells and stimulating pro-inflammatory cytokines such as TNF-α and IL-1 (Kim et al., 2023).

Based on the current study, objective assessments using Antera 3D revealed that the mean EI scores 3 months after treatment in the PN group were lower than those in the control group from 1 week to 1 month post-treatment. This aligns with previous studies suggesting that PN may inhibit pro-inflammatory cytokines during the inflammation phase.

Additionally, the subjective assessment using the Vancouver Scar Scale (VSS), which includes vascularity, height, pliability, and pigmentation, showed that vascularity and pliability were lower in the PN group compared to the control group. There was no difference in height and pigmentation between the two groups. However, none of the parameters reached statistical significance, likely due to the small sample size.

Overall, this study emphasizes that PN has the potential to alleviate redness. No serious adverse events were reported at any time during the study period.

However, there are some limitations that should be mentioned. First, the sample size in this study was small, and additional large-scale, long-term studies are needed to determine the optimal balance between the efficacy and safety of PN, as well as to confirm its long-term effectiveness in preventing hypertrophic scars over several months or even years.

Second, there was no placebo or vehicle control group in the study. Since wounds are particularly sensitive and painful in the immediate postoperative period, the control group should have received the same intervention as the experimental group (saline injections), which would have been unlikely to provide any therapeutic benefit. Instead, this study chose to observe the control group without treatment. This choice means that the patients were not blinded to their treatment assignment, which could have introduced a positive placebo effect as a potential confounder. However, the placebo effect was minimized in this study by focusing on objective parameters and blinding the outcome measurement process, excluding the patients' subjective symptoms.

Developing new strategies to improve wound healing and minimize scar formation remains crucial, especially by addressing inflammation in the early stages of healing. This is the first randomized controlled study to show the effectiveness of early postoperative PN injections in preventing hypertrophic scar formation. The findings of this study suggest that PN injections rapidly reduced scar erythema by modulating inflammation in the early phase of wound healing, with no side effects. Consequently, they significantly decreased both excessive scar formation and related symptoms.

5. Conclusion

In conclusion, this study demonstrated that early postoperative PN injections on surgical wounds had a positive effect on reducing scar erythema by modulating inflammation in the early phase of wound healing. However, the overall results lacked significant improvements in other scar characteristics when considering the broader goal of preventing hypertrophic scars. Future research should involve larger participant cohorts, explore different injection locations, and examine the timing of injections to further assess PN's potential for preventing hypertrophic scarring.

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7. References

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