Preventive Effect of Polynucleotide on Post-Thyroidectomy Scars: A Randomized, Double-Blinded, Controlled Trial

Ji Hee Kim,[1,2] Jong Ju Jeong,[3] Young In Lee,[1] Won Jai Lee,[2,4] Chorok Lee,[3] Woong Youn Chung,[3] Kee-Hyun Nam,[3] and Ju Hee Lee[1,2]*

[1]*Department of Dermatology and Cutaneous Biology Research Institute, Yonsei University College of Medicine, Seoul, Korea*

[2]*Scar Laser and Plastic Surgery Center, Yonsei University College of Medicine, Yonsei Cancer Hospital, Seoul, Korea*

[3]*Department of Surgery, Institute of Endocrine Research, Yonsei University College of Medicine, Seoul, Korea*

[4]*Department of Plastic and Reconstructive Surgery, Institute for Human Tissue Restoration, Yonsei University College of Medicine, Seoul, Korea*

Background and Objective: Polynucleotide (PN) provides a structural scaffold to induce anti-inflammatory and enhanced wound healing properties, and this study aimed to assess the efficacy of PN administration in the prevention of post-operative scars after conventional open total thyroidectomy.

Study Design Materials and Methods: Forty-two patients with thyroid carcinoma who underwent total thyroidectomy were randomly assigned to the study (PN administration) or control (normal saline) group. All patients underwent a single session of combined ablative and non-ablative fractional laser. The Vancouver Scar Scale (VSS), global photographic assessment, and objective scar were assessed using three-dimensional (3D) camera at baseline and at 2, 4, 8, and 16 weeks after surgery.

Results: Patients who underwent PN injection demonstrated better surgical scar quality outcome. Participants in the PN administration group had lower VSS scores than the control group (2.09 ± 0.47 vs. 4.01 ± 0.55, respectively) and lower scar height (0.23 ± 0.03 vs. 0.29 ± 0.03, respectively), as measured using 3D imaging. Furthermore, in the PN injected group, the degree of erythema, and pigmentation of the scar were less prominent. No patient developed hypertrophic scar or keloids on the surgical site. No other adverse events, including post-inflammatory hyperpigmentation, scarring, or infection, were observed.

Conclusion: Adjuvant administration of PN along with conventional fractional laser treatment led to more favorable effect in wound healing and post-operative scar prevention after thyroidectomy. Lasers Surg. Med. © 2018 Wiley Periodicals, Inc.

Key words: post-operative scar; thyroidectomy; scar; laser

INTRODUCTION

Conventional open thyroidectomy is commonly performed along the anterior neck crease, resulting in noticeable scars, which are particularly problematic for patients in the socially active age group [1]. Attempts to improve and prevent surgical scar is not confined to cosmetic aspects, as hypertrophic scars can cause significant patient morbidity because of pain, hyperesthesia, and swallowing discomfort in severe cases [1,2]. Among the current measures to prevent hypertrophic surgical scar, topical agents with growth factors or natural plant extracts and regular application of silicon sheet showed efficacy in various clinical trials and reports [3–7]. Being in a tertiary institution and capable of multidisciplinary management, our group has adapted multiple modalities in surgical scar management for the past decade [8–13]. Previously, our group has demonstrated the effect of early treatment ablative fractional laser (AFL) system and introduced the concept of prophylactic approach in the early post-operative period [8,9].

Normal wound healing process consists of sequentially overlapping phases of coagulation, inflammation, and remodeling. Meanwhile, up-regulation of pro-inflammatory cytokines prolongs the inflammatory phase, which induces abnormal fibroblast activity, causing hypertrophic scar or keloids [2,14,15]. To date, various treatment options are suggested to prompt mechanical destruction of scar tissue. However, the improvement measures show variable outcome depending on the measures selected [14]. Especially

Abbreviations: AFL, ablative fractional laser; ECM, extracellular matrix; HSP, heat shock protein; MMP-9, matrix metalloproteinase-9; MTZ, microscopic treatment zones; NFL, non-ablative fractional laser; PDRN, Polydeoxyribonucleotide; PN, polynucleotide; TGF-β, transforming growth factor beta

Ji Hee Kim and Jong Ju Jeong contributed equally to this work.

Conflicts of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and have disclosed the following: The authors have stated explicitly that there are no conflicts of interest in connection with this article.

*Correspondence to: Ju H. Lee, MD, PhD,Department of Dermatology and Cutaneous Biology Research Institute, Yonsei University College of Medicine, 250 Seongsanno, Seodaemun-gu, Seoul, Korea. E-mail: juhee@yuhs.ac

Accepted 20 February 2018

Published online in Wiley Online Library (wileyonlinelibrary.com).

DOI 10.1002/lsm.22812

for the post-operative scars, intervention in immature state, before or during the remodeling phase resulted in more favorable outcome in final scar assessments [16,17].

To facilitate normal wound healing after injury, balancing between the early inflammation and remodeling phases is crucial [18,19]. Polydeoxyribonucleotide (PDRN), a novel component derived from the germ cells of salmon species (Oncorhynchus keta), is composed of a mixture of deoxyriboneucleotides with molecular weights between 50 and 1,500 kDa [20]. Owing to its molecular property of binding to adenosine A2A receptor, PDRN shows anti-ischemic and anti-inflammatory properties in various *in vitro* clinical models [21–23]. Enhanced wound healing and angiogenesis are well-established pharmacologic characteristics of PDRN [20,22]. Nonetheless, owing to its aqueous property, its application is fairly insufficient in providing structural scaffold. To fortify its effect by increasing viscosity to mimic the *in vivo* composition of the dermis and extracellular matrix (ECM), polynucleotides (PNs) are developed by molecular cross-linking by controlled depolymerization from highly polymeric DNA chain. As PN presents with higher molecular weight up to 8,000 kDa with viscoelastic texture, we expect it to provide structural scaffold to induce more favorable milieu along with conventional AFL for scar prevention.

To date, no prospective and randomized controlled clinical trials have been conducted for the application of PN in post-operative scar. Hypothetically, we suggest that adjuvant supplementation of polymer hydrogel on post-operative scar may assist optimal wound healing by providing scaffold for collagen and ECM derivative regeneration. The authors report clinical outcomes of safety and efficacy of PN to facilitate normal wound process and prevent abnormal scarring.

MATERIALS AND METHODS

Design and Study Population

Patients who underwent open total thyroidectomy with central compartment node dissection (CCND) between June 2015 and January 2016 were considered eligible for this study. This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University (IRB No. 1-2015-0057), and written and informed consent was obtained from each patient. The exclusion criteria were age younger than 20 years or older than 60 years, history of keloid scarring, pregnancy or cervical surgeries, or uncontrolled medical illness. The patients were randomized to the study (PN; Rejuran®, Pharma Research Products, Seongnam, Korea) and control (normal saline) groups. Forty-four patients (36 women and eight men; mean age, 37.0 years; range, 22–50 years; Fitzpatrik skin types III and IV) were enrolled (Table 1).

Patients visited the Scar Laser and Plastic Surgery Center 4 weeks after surgery. On the initial visit, all patients underwent combination fractional laser treatment and concomitant PN injection or normal saline injections. Then, injection of the study component was performed in two additional visits, with 2-week interval. Afterwards, patients visited the clinic for scar assessment after 4 weeks and 8 weeks. The final assessment was made on visit 5, 16 weeks after initiation of the study. Patients were followed up for 16 weeks after the initiation of scar treatment.

Surgical Procedure

All patients underwent open total thyroidectomy with CCND by a single surgeon (K.H.N.). A 5- to 7-cm cervical collar incision was made, and if possible, the incision follows the natural wrinkle lines of the neck for optimal final cosmesis. Then, subplatysmal flap dissection was performed from the sternal notch inferiorly to the thyroid cartilage superiorly and laterally to both medial borders of the sternocleidomastoid muscle. The midline was divided, and the thyroid gland was exposed. Dissections of the thyroid gland and central neck compartment were performed in all patients.

Laser Treatment and Injection

In the study, all patients underwent combination treatment with non-ablative fractional 1550 nm erbium glass laser (Mosaic HP^{TM}, Lutronic, Ilsan, Korea) and ablative fractional 10600 nm CO2 (eCO_2^{TM}, Lutronic, Ilsan, Korea). Topical anesthetic lidocaine and prilocaine cream was applied around the thyroidectomy scar under occlusion 1 hour before laser treatment. The NFL settings used were 30 mJ/pulse, with a spot density of 100 spots/cm^2 over a 16-cm^2 treatment area and with minimal overlapping of passes. Afterwards, AFL system was applied on the linear scar area. The settings were similar to those used for NFL, but with increased pulse width, which was set to 70 mJ/pulse. After optimal cooling of the laser-treated area with icepack, injection of 2 ml PN, or normal saline was done with 32-gauge microneedle on the laser-treated area. After the procedure, mild compression was applied, and patients were instructed to use moisturizer several times daily with regular applications of sunscreens.

Method of Randomization

A random number generator was used to generate 0 and 1s using Microsoft Excel (2010 version; Microsoft, Redmond, WA). Each random assignment was sealed individually in a non-transparent envelope. Assignments were made consecutively, with subjects receiving PN injection or normal saline.

Blinding

Participants and dermatologists were blinded as to whether the prepared injectable is PN. Clinical assessments were performed in the Scar Laser and Plastic Surgery Center by two dermatologists (J.H.K. and J.H.L.) who were blinded. Investigators involved in the clinical assessments were not present during surgery and were blinded regarding allocation.

Assessment of Clinical Efficacy

The final assessment was made 16 weeks after the initial treatment. Digital photographs were obtained using

identical digital camera settings, lighting conditions, and patient positioning on every visit. Vancouver Scar Scale (VSS) and patients' subjective perception of the scar improvement were the primary outcome measures of the study. To determine the success of treatment outcome, reduction in VSS score by 50% was expected. Additionally, we measured objective parameters to analyze the scar height and pigmentation which were designed as the secondary endpoint of the study.

Vancouver Scar Scale (VSS)

Two independent dermatologists (J.H.K. and J.H.L.) graded the treatment outcomes using the Vancouver Scar Scale (VSS), which includes pigmentation (0 = normal, 1 = hypopigmented, 2 = mixed pigmentation, 3 = hyperpigmented), pliability (0 = normal, 1 = supple, 2 = yielding, 3 = firm, 4 = ropes, 5 = contracture), height (0 = flat, 1 ≤2 mm, 2 = 2–5 mm, 3 ≥5 mm), and vascularity (0 = normal, 1 = pink, 2 = red, 3 = purple). The score for each parameter was assessed separately, and then all four scores were summed and recorded at every visit.

Objective Measurements: Scar Height and Pigmentation

For objective measurement of surgical scar texture and height, the Antera 3D® three-dimensional (3D) image capture system (Miravex, Dublin, Ireland) was used, which allows multispectral analysis measurement.

To evaluate the adverse effect of the study, narrow-band reflectance spectrophotometry was used to assess color changes. The Erythema Index (EI) and the Melanin Index (MI) of scars were obtained using narrow-band reflectance spectrophotometry (DermaSpectrometer II; Cortex Technology, Hadsund, Denmark) using 568- and 655-nm probe wavelengths at every visit. The EI and MI were measured at the left margin, center, and right margin of the scar, and the mean EI and MI values were used for comparison.

Patient Perception of the Scar

For the subjective evaluation, patients were surveyed at the final visit (16 weeks after treatment) about their overall level of satisfaction using the following response choices in a quartile grading scale: grade 1 (<25%), minimal to no improvement; grade 2 (26–50%), moderate improvement; grade 3 (51–75%), marked improvement; grade 4 (>75%), near-total improvement. Patients also reported any side effects of treatment, including bleeding, oozing, post-therapy dyschromia, scaling or crusting, erythema, and scarring.

Tolerability

Adverse events related to the procedure were assessed by the investigator through physical examination and patients were questioned at each visit during the treatment and follow-up period. Adverse events were recorded regarding the severity, onset, or duration, if any, were recorded at each visit, and follow-up was planned until complete resolution.

Statistical Analysis

Data from clinician and machine assessments were analyzed for statistical significance using *t*-test, Mann–Whitney U test, or analysis of variance. The differences were considered significant if $P < 0.05$. All statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL).

RESULTS

Degree of Clinical Improvement

Vancouver scar scale. The mean values of the VSS scores for the PN administration group was 6.05 ± 0.52 before treatment and 2.09 ± 0.47 at 16 weeks of follow-up (Fig. 1A–D). In the control group, the VSS was 6.25 ± 0.59 initially and 4.01 ± 0.55 at 16 weeks (Fig. 1E and F). PN

TABLE 1. Demographic Characteristics at Baseline

	Treatment group			
Demographic characteristics	PN $n = 22$		Control $n = 20$	
Age (yr)				
Mean(SD)	36.55 (8.48)		37.45 (6.75)	
Median (min, max)	37.5 (22,50)		38.5 (25,49)	
Age, *n* (%)	*n*	%	*n*	%
19–29 yr	6	27.27	3	15
30–39 yr	6	27.27	9	45
40–49 yr	9	40.91	8	40
50–59 yr	1	4.55	0	
Gender, *n* (%)				
Male	2	9.09	5	25
Female	20	90.91	15	75
VSS				
Mean (SE), initial	6.05 (0.52)		6.25 (0.59)	
Mean (SE), 16 weeks	2.09 (0.47)		4.01 (0.55)	

injected group demonstrated more than 50% of decrease in VSS score after the treatment and the outcome was considered successful. The degree of improvement over 16 weeks was more significant in the PN administration group ($P < 0.05$) (Fig. 2). As for individual scar characteristics, pigmentation and vascularity further decreased in the PN administration group (pigmentation: initial, 1.64 ± 0.10; after treatment, 0.77 ± 0.13; $P < 0.05$; vascularity: initial, 1.41 ± 0.14; after treatment, 0.32 ± 0.12; $P < 0.05$; pliability: initial, 1.73 ± 0.16; after treatment, 0.59 ± 0.16; $P = 0.07$; height: initial, 1.27 ± 0.22; after treatment, 0.41 ± 0.16; $P = 0.06$).

Objective improvement by 3D image analysis. Images obtained on every visit were reconstructed to calculate the difference in height. The average scar height for the PN administration group was 0.46 ± 0.06 before treatment and decreased to 0.23 ± 0.03 at 16 weeks (Fig. 3A–D). In the control group, the average scar height was 0.38 ± 0.04 before treatment and decreased to 0.29 ± 0.03 after 16 weeks (Fig. 3E and F). The degree of improvement over 16 weeks was more significant in the PN administration group ($P < 0.05$) (Fig. 4). Notably, the improvement rate in height after a single session of combination treatment with laser and injection was more pronounced in the PN administration group ($P < 0.05$). Additionally, the average scar width was measured in both groups: for the test group, the initial average width of 4.45 ± 0.44 decreased to 2.67 ± 0.30 after 16 weeks, and in the control group, the initial average width of 4.41 ± 0.45 decreased to 2.89 ± 0.27 after 16 weeks ($P = 0.27$).

Objective improvement by spectrophotometry: Erythema index (EI), Melanin index (MI). Patients in the PN administration group showed a significant decrease in post-treatment erythema (EI) compared with the control group after 12 weeks (PN treated group: 381.09 ± 10.68 to 367.47 ± 11.48; Control group: 400.03 ± 21.69 to 400.05 ± 23.71 $P < 0.05$). Although both group demonstrated improvement in MI, the change were not proiminent in PN injected group (PN treated group 148.06 ± 10.037 to 134.76 ± 8.57; Control group 147.56 ± 9.79 to 113.41 ± 9.37; $P < 0.05$).

Side Effects

All patients reported post-treatment edema, erythema, and scaling, which resolved within 1 week. However, no patient developed hypertrophic scar or keloids on the thyroidectomy site after 16 weeks. No other adverse events due to laser treatment or PN injection, including

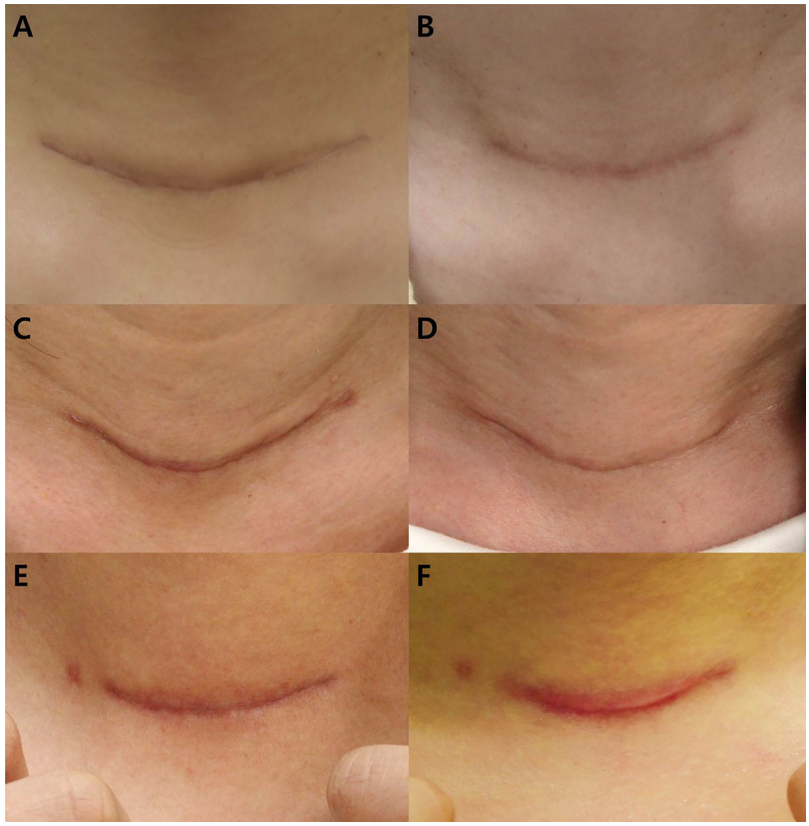

Fig. 1. Digital photograph of a thyroidectomy scar before (A and C: PN injected group, E: control group) and 16 weeks after treatment (B and D: PN injected group, F: control group). Overall VSS showed more significant improvement in PN injected group while control group showed more prominent scar height and pigmentation.

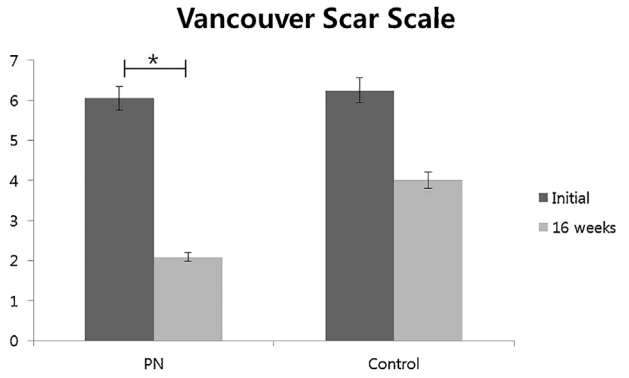

Fig. 2. The mean values of the VSS scores for the PN administration group showed further improvement over 16 weeks and was more significant in the PN administration group ($P < 0.05$).

post-inflammatory hyperpigmentation, scarring, or infection, were observed.

Subjective Analysis

From the patients' perspective, the average scar perception score after the treatment improved from 2.86 ± 0.18 to 3.27 ± 0.18 in the treatment group. The control group reported minimal improvement from 2.91 ± 0.16 to 2.90 ± 0.23, respectively, with no significant differences ($P = 0.23$) (Fig. 5).

DISCUSSION

In this prospective, randomized, controlled study, we evaluated the effect of PN injection in adjunction to conventional AFL treatment to surgical stars. Participants who underwent adjuvant PN injection demonstrated a better outcome in scar quality. PN administration group demonstrated lower VSS scores and lower scar height, as measured by 3D imaging. Furthermore, the degree of erythema and pigmentation were less prominent after PN administration.

As for scar quality assessment, we adapted clinical scale as well as 3D image analysis to evaluate both clinical perception and quantitative measurement. Among various clinical scar analysis tools, VSS has been classically used and it is subdivided into categories to incorporate individual scar characteristics; yet it still relies on subjective assessment by the physician [24,25]. There have been increasing efforts to improve the quantitative measurement of skin and its related structures for objective assessment of clinical outcome. For instance, spectrophotometers have been classically used to assess chromaticity such as hemoglobin and melanin load. In recent years, shift from two-dimensional measurements to three-dimensional structures demonstrated its accuracy in objective measurement of aesthetic outcomes [26]. We coupled the 3D imaging technique to monitor the height and width of the post-operative wound. Beyond the classic photographic analysis or clinical scales, 3D measurement system enabled quantitation of scar. For linear scars that presents with elevation or depression, a 3D imaging system can especially provide accurate measurement of stereoscopic parameters [27].

There have been numerous options suggested in the literatures to treat established or matured hypertrophic scars [3,14,28,29]. Once developed, the treatment requires multiple session with variable clinical outcomes [30]. The etiology and clinical spectrum of scars is very broad [31]. Without a doubt, even with technical and procedural progress, development of hypertrophic scars is inevitable in majority of cases. Moreover, proposing a standardized treatment protocol is challenging due to the difficulty in eliminating every possible deviations during the surgical manipulation itself. On the other hand, with close collaboration with surgeons and dermatologists, we've identified patients who are prone to develop hypertrophic scar after elective surgical procedure with standardized operational procedure. In previous cohort study in our institution, young age and high BMI are the metabolic factors identified to be prone to hypertrophic scar development after thyroidectomy [32,33]. Additionally, prolonged itching sensation, induration, and cervical adhesion were common manifestations of post-operative scars that result in hypertrophic or keloid scars [14,32].

Intraoperatively, hydrogel polymers have been used to prevent post-operative adhesion due to surgical manipulation [34,35]. Barrier-based synthetic polymer membranes have shown effectiveness in surgical procedures involving internal organs [36]. Common components include cross-linked hydrogels derived from hyaluronic acid act as barrier organelle and structural scaffold for appropriate ECM accumulation during the wound healing process [37]. Recently, we have demonstrated the efficacy of the intraoperative use of acellular dermal matrix in the prevention of post-operative adhesion and improvement of functional outcome [11]. Meanwhile, laser devices and topical agents hitherto available allow external modulation of scar properties, but adjustment or manipulation of underlying dermal or ECM structures is difficult afterward.

When applied to early remodeling phase of wound healing, AFL induces arrays of microscopic treatment zones (MTZs) in controlled dermal depth without surrounding tissue injury [38,39]. Around the regularly spaced microscopic thermal wounds, wound healing is promoted with subsequent ECM remodeling [40,41]. In molecular level, expression of heat shock proteins (HSPs), transforming growth factor beta (TGF-β), and matrix metalloproteinase-9 (MMP-9) were increased in post-operative scar tissue after AFL [9]. HSP s TGF-β are crucial mediators during scar remodeling due to its anti-inflammatory effect and both can mutually induce accelerated wound healing [42,43]. Notably, HSPs induced by AFL systems can both act as early responders to promote anti-inflammatory effect and long-term remodeling promoting neocollagengenesis [44]. Additionally, the increased level of collagenases is expected to maintain

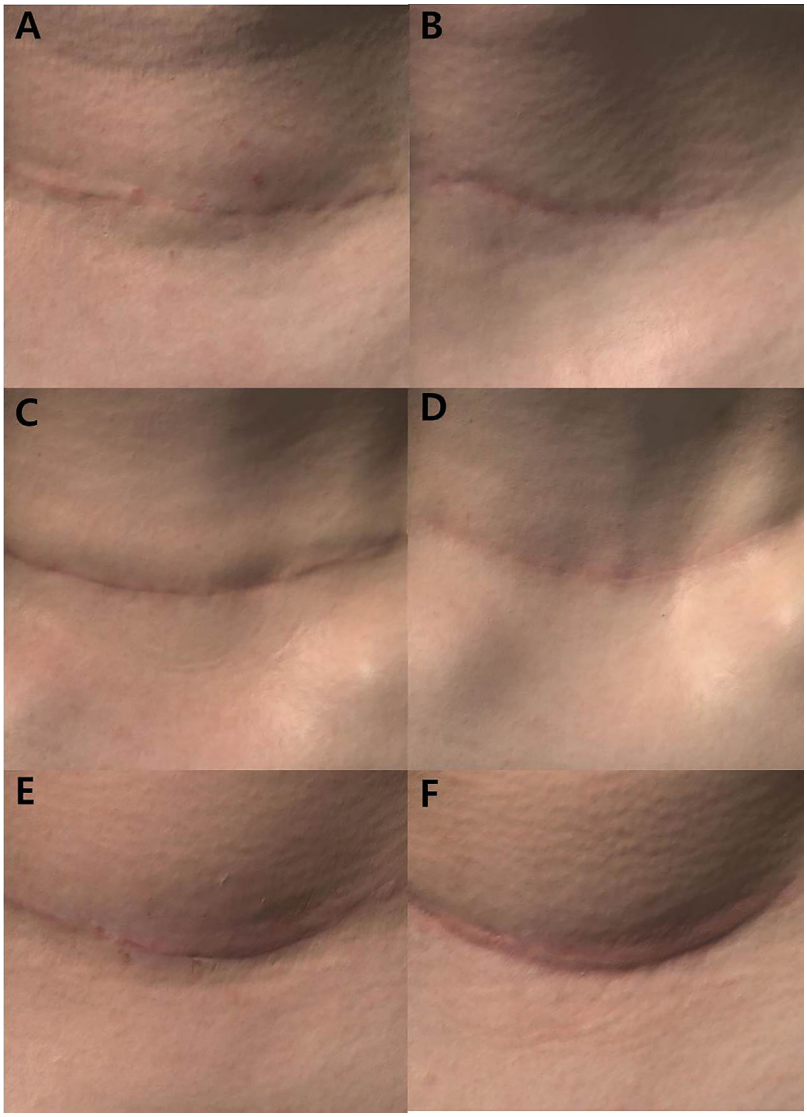

Fig. 3. Three-dimensional image analysis of a thyroidectomy scar before (A and C: PN injected group, E: control group) and 16 weeks after treatment (B and D: PN injected group, F: control group). Scar height measure by 3D image were further decreased in PN injected group compared to the control group.

equilibrium between collagen overproduction and regulated accumulation of ECM components for normal wound healing [9,45].

Viscoelastic supplementation with exogenous hyaluronic acids or its derivatives was reported effective in degenerative or traumatic joint diseases [46]. PN is a unique biodegradable, biocompatible polymer with nontoxic and non-allergic properties [21,47]. It binds to water molecules easily and provides lubrication, which alleviates inflammation due to constant friction in osteoarthritis [46,48]. During the first 4–12 weeks, scar tissue displays increased the number of fibroblasts and yet immaturely formed ECM structure. In our study, PN is administered on the surgical wound after 2 weeks immediately after a single session of fractional laser resurfacing. Afterward, PN was injected regularly for two more sessions in 2-week intervals. PN is also used to mediate the remodeling phase of wound healing. The remodeling phase is marked by the maturation of elements and effects on the ECM, leading to proteoglycan and collagen deposits, which are closely related to scar formation [49]. PN is subjected to enzymatic cleavage, which enables progressive release of smaller oligonucleotides such as nucleosides, nucleotides, and nucleobases [50,51]. PN can be easily applied with external injection without any additional instrument. Exogenously administered PN may contribute to produce glycosaminoglycan, proteins, glycoproteins, and fibrils and help maintain their physiological functions.

Notably, no patient showed any sign of cervical adhesion or persistent lymphedema during the

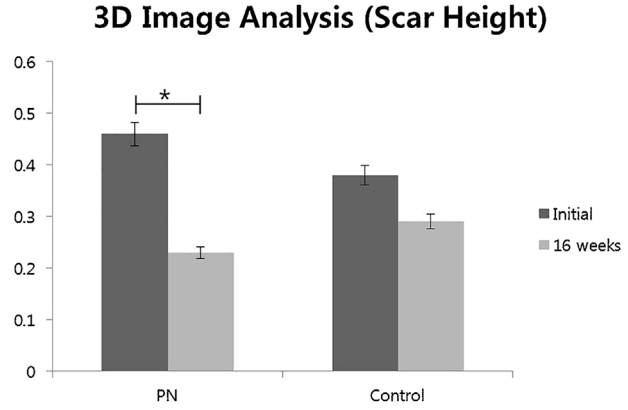

Fig. 4. The mean scar height measured with 3D image analysis was lower in the PN over 16 weeks and was more significant ($P < 0.05$).

16-week follow-up period. In an animal model, PDRN demonstrated anti-inflammatory property by down-regulating key pro-inflammatory mediators; tumor necrosis factor α (TNF- α), interleukin 6 (IL-6), and high-mobility group box 1 (HMGB1) [22]. Keloid and hypertrophic scars are the result of prolonged inflammatory phase, which leads to pathologic keloid fibroblast activity, resulting in abnormal ECM accumulation [14]. Therefore, we expect PN to induce a adjuvant effect along with fractional laser, which facilitates harmonized wound healing process.

A potential limitation of the study is that our study results cannot be applied to all kinds of scars because our patient group had controlled wounds on a limited anatomic position, performed by a single surgeon. Long-term follow-up is needed to compare the outcomes. Further studies are needed to evaluate the underlying molecular mechanism and wound healing properties of PN on other types of scars.

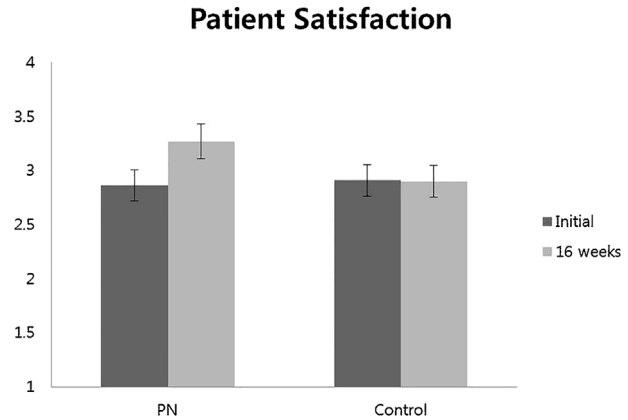

Fig. 5. Patient grading of the clinical efficacy and scar perception; grade 1 (<25%), minimal to no improvement; grade 2 (26–50%), moderate improvement; grade 3 (51–75%), marked improvement; grade 4 (>75%), near-total improvement.

CONCLUSION

PN, as a high-molecular weight biopolymer with its viscoelastic property, promotes a favorable milieu for wound healing in adjunction to conventional AFL treatment for hypertrophic scar prevention. Furthermore, we expect to propose a standardized approach that can be tailored to each patient's susceptibility to develop abnormal scarring after surgical procedure.

REFERENCES

1. Arora A, Swords C, Garas G, et al. The perception of scar cosmesis following thyroid and parathyroid surgery: A prospective cohort study. Int J Surg 2016;25:38–43.
2. Song C. Hypertrophic scars and keloids in surgery: Current concepts. Ann Plast Surg 2014;73(Suppl 1):S108–S118.
3. Ohmori S. Effectiveness of silastic sheet coverage in the treatment of scar keloid (hypertrophic scar). Aesthetic Plast Surg 1988;12(2):95–99.
4. Gilman TH. Silicone sheet for treatment and prevention of hypertrophic scar: A new proposal for the mechanism of efficacy. Wound Repair Regen 2003;11(3):235–236.
5. Jenwitheesuk K, Surakunprapha P, Jenwitheesuk K, Kuptarnond C, Prathanee S, Intanoo W. Role of silicone derivative plus onion extract gel in presternal hypertrophic scar protection: A prospective randomized, double blinded, controlled trial. Int Wound J 2012;9(4):397–402.
6. Wananukul S, Chatpreodprai S, Peongsujarit D, Lertsapcharoen P. A prospective placebo-controlled study on the efficacy of onion extract in silicone derivative gel for the prevention of hypertrophic scar and keloid in median sternotomy wound in pediatric patients. J Med Assoc Thai 2013;96(11):1428–1433.
7. Alberti LR, Vicari EF, De Souza Jardim Vicari R, Petroianu A. Early use of CO2 lasers and silicone gel on surgical scars: Prospective study. Lasers Surg Med 2017;49(6):570–576.
8. Jung JY, Jeong JJ, Roh HJ, et al. Early postoperative treatment of thyroidectomy scars using a fractional carbon dioxide laser. Dermatol Surg 2011;37(2):217–223.
9. Shin JU, Gantsetseg D, Jung JY, Jung I, Shin S, Lee JH. Comparison of non-ablative and ablative fractional laser treatments in a postoperative scar study. Lasers Surg Med 2014;46(10):741–749.
10. Kim YS, Lee HJ, Cho SH, Lee JD, Kim HS. Early postoperative treatment of thyroidectomy scars using botulinum toxin: A split-scar, double-blind randomized controlled trial. Wound Repair Regen 2014;22(5):605–612.
11. Kim DY, Kang SW, Kim DS, et al. Preventive effect of human acellular dermal matrix on post-thyroidectomy scars and adhesions: A randomized, double-blinded. Controlled trial. Dermatol Surg 2015;41(7):812–820.
12. Shin S, Shin JU, Lee Y, et al. The effects of multi-growth factors-containing cream on post-Thyroidectomy scars: A preliminary study. Ann Dermatol 2017;29(3):314–320.
13. Chang EHE, Kim HY, Koh YW, Chung WY. Overview of robotic thyroidectomy. Gland Surg 2017;6(3):218–228.
14. Gauglitz GG, Korting HC, Pavicic T, Ruzicka T, Jeschke MG. Hypertrophic scarring and keloids: Pathomechanisms and current and emerging treatment strategies. Mol Med 2011;17(1-2):113–125.
15. Tuan TL, Nichter LS. The molecular basis of keloid and hypertrophic scar formation. Mol Med Today 1998;4(1):19–24.
16. Katz BE, Oca AG. A controlled study of the effectiveness of spot dermabrasion ("scarabrasion") on the appearance of surgical scars. J Am Acad Dermatol 1991;24(3):462–466.
17. Oliaei S, Nelson JS, Fitzpatrick R, Wong BJ. Laser treatment of scars. Facial Plast Surg 2012;28(5):518–524.
18. Arnold F, West DC. Angiogenesis in wound healing. Pharmacol Ther 1991;52(3):407–422.
19. Phillips GD, Whitehead RA, Knighton DR. Initiation and pattern of angiogenesis in wound healing in the rat. Am J Anat 1991;192(3):257–262.

20. Squadrito F, Bitto A, Irrera N, et al. Pharmacological activity and clinical use of PDRN. Front Pharmacol 2017;8:224.
21. Altavilla D, Bitto A, Polito F, et al. Polydeoxyribonucleotide (PDRN): A safe approach to induce therapeutic angiogenesis in peripheral artery occlusive disease and in diabetic foot ulcers. Cardiovasc Hematol Agents Med Chem 2009;7(4):313–321.
22. Bitto A, Oteri G, Pisano M, et al. Adenosine receptor stimulation by polynucleotides (PDRN) reduces inflammation in experimental periodontitis. J Clin Periodontol 2013;40(1):26–32.
23. Kim JY, Pak CS, Park JH, Jeong JH, Heo CY. Effects of polydeoxyribonucleotide in the treatment of pressure ulcers. J Korean Med Sci 2014;29(Suppl 3):S222–S227.
24. Sullivan T, Smith J, Kermode J, McIver E, Courtemanche DJ. Rating the burn scar. J Burn Care Rehabil 1990;11(3):256–260.
25. Tyack Z, Simons M, Spinks A, Wasiak J. A systematic review of the quality of burn scar rating scales for clinical and research use. Burns 2012;38(1):6–18.
26. Luebberding S, Krueger N, Kerscher M. Comparison of Validated Assessment Scales and 3D digital fringe projection method to assess lifetime development of wrinkles in men. Skin Res Technol 2014;20(1):30–36.
27. van der Aa T, Verhiel SH, Erends M, et al. A simplified three-dimensional volume measurement technique in keloid scars: Validity and reliability. J Plast Reconstr Aesthet Surg 2015;68(11):1574–1580.
28. Carr-Collins JA. Pressure techniques for the prevention of hypertrophic scar. Clin Plast Surg 1992;19(3):733–743.
29. Gold MH. Topical silicone gel sheeting in the treatment of hypertrophic scars and keloids. A dermatologic experience. J Dermatol Surg Oncol 1993;19(10):912–916.
30. On HR, Lee SH, Lee YS, Chang HS, Park C, Roh MR. Evaluating hypertrophic thyroidectomy scar outcomes after treatment with triamcinolone injections and copper bromide laser therapy. Lasers Surg Med 2015;47(6):479–484.
31. Del Toro D, Dedhia R, Tollefson TT. Advances in scar management: Prevention and management of hypertrophic scars and keloids. Curr Opin Otolaryngol Head Neck Surg 2016;24(4):322–329.
32. Shin JU, Park JH, Oh SH, et al. Early intervention in thyroidectomy scars: Demographics, symptoms, and prevention. J Wound Care 2015;24(4): 163–164, 166–168, 170–161.
33. Kim JH, Sung JY, Kim YH, et al. Risk factors for hypertrophic surgical scar development after thyroidectomy. Wound Repair Regen 2012;20(3):304–310.
34. Duron JJ. Postoperative intraperitoneal adhesion pathophysiology. Colorectal Dis 2007;9(Suppl 2):14–24.
35. Alpay Z, Saed GM, Diamond MP. Postoperative adhesions: From formation to prevention. Semin Reprod Med 2008;26(4): 313–321.
36. Lou W, Zhang H, Ma J, et al. In vivo evaluation of *in situ* polysaccharide based hydrogel for prevention of postoperative adhesion. Carbohydr Polym 2012;90(2):1024–1031.
37. Nguyen KT, West JL. Photopolymerizable hydrogels for tissue engineering applications. Biomaterials 2002;23(22):4307–4314.
38. Manstein D, Herron GS, Sink RK, Tanner H, Anderson RR. Fractional photothermolysis: A new concept for cutaneous remodeling using microscopic patterns of thermal injury. Lasers Surg Med 2004;34(5):426–438.
39. Bernstein EF, Schomacker KT, Basilavecchio LD, Plugis JM, Bhawalkar JD. Treatment of acne scarring with a novel fractionated, dual-wavelength, picosecond-domain laser incorporating a novel holographic beam-splitter. Lasers Surg Med 2017;49(9):796–802.
40. Laubach HJ, Tannous Z, Anderson RR, Manstein D. Skin responses to fractional photothermolysis. Lasers Surg Med 2006;38(2):142–149.
41. Lin JY, Warger WC, Izikson L, Anderson RR, Tannous Z. A prospective, randomized controlled trial on the efficacy of fractional photothermolysis on scar remodeling. Lasers Surg Med 2011;43(4):265–272.
42. Helbig D, Paasch U. Molecular changes during skin aging and wound healing after fractional ablative photothermolysis. Skin Res Technol 2011;17(1):119–128.
43. Helbig D, Moebius A, Simon JC, Paasch U. Nonablative skin rejuvenation devices and the role of heat shock protein 70: Results of a human skin explant model. J Biomed Opt 2010;15(3):038002.
44. Hantash BM, Bedi VP, Kapadia B, et al. In vivo histological evaluation of a novel ablative fractional resurfacing device. Lasers Surg Med 2007;39(2):96–107.
45. Fujiwara M, Muragaki Y, Ooshima A. Keloid-derived fibroblasts show increased secretion of factors involved in collagen turnover and depend on matrix metalloproteinase for migration. Br J Dermatol 2005;153(2):295–300.
46. Kwon YW, Eisenberg G, Zuckerman JD. Sodium hyaluronate for the treatment of chronic shoulder pain associated with glenohumeral osteoarthritis: A multicenter, randomized, double-blind, placebo-controlled trial. J Shoulder Elbow Surg 2013;22(5):584–594.
47. Noh TK, Chung BY, Kim SY, et al. Novel anti-melanogenesis properties of polydeoxyribonucleotide, a popular wound healing booster. Int J Mol Sci 2016;17(9):1448.
48. Rathbone MP, Christjanson L, Deforge S, et al. Extracellular purine nucleosides stimulate cell division and morphogenesis: Pathological and physiological implications. Med Hypotheses 1992;37(4):232–240.
49. Bloemen MC, van der Veer WM, Ulrich MM, van Zuijlen PP, Niessen FB, Middelkoop E. Prevention and curative management of hypertrophic scar formation. Burns 2009;35(4): 463–475.
50. Vanelli R, Costa P, Rossi SM, Benazzo F. Efficacy of intra-articular polynucleotides in the treatment of knee osteoarthritis: A randomized, double-blind clinical trial. Knee Surg Sports Traumatol Arthrosc 2010;18(7):901–907.
51. Jeong W, Yang CE, Roh TS, Kim JH, Lee JH, Lee WJ. Scar prevention and enhanced wound healing induced by polydeoxyribonucleotide in a rat incisional wound-healing model. Int J Mol Sci 2017;18(8).