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Title:	Temporary ectropion correction after lower blepharoplasty using Polydeoxyribonucleotide (PDRN) and platelet-rich-plasma (PRP) injection.
Type of Manuscript:	Original Article
Running Title:	Temporary ectropion correction

Abstract

Background : Ectropion is a common complication after lower blepharoplasty, often causing patient discomfort and dissatisfaction. While various surgical methods have been proposed to prevent ectropion, there is a lack of effective treatments for its management once it occurs. This study aimed to evaluate the efficacy of intradermal injection of polydeoxyribonucleotide (PDRN) and platelet-rich-plasma (PRP) for scar regeneration and rapid recovery of temporary ectropion following lower blepharoplasty. **Methods :** This retrospective study included 21 cases of ectropion among 420 transcutaneous lower blepharoplasty patients between January 2020 and October 2022. PDRN and PRP were injected intradermally into the lower eyelid, and patients were followed up at one- or two-week intervals. The outcomes were assessed based on patient satisfaction, total injection count, and time to complete ectropion improvement. **Results :** The average time for complete ectropion improvement was 9.3 weeks, and patient satisfaction was relatively high (average 4.3 out of 5). 10 primary cases showed good effects with only one injection, while all 6 patients with previous surgeries required two or more injections. The improvement was faster than the usual 3-6 months reported in the literature, likely due to the increased collagen synthesis and anti-inflammatory effects of PDRN, as well as the tissue repair and angiogenesis effects of PRP. **Conclusions :** Intradermal injection of PDRN and PRP demonstrated promising results in the rapid recovery of ectropion after lower blepharoplasty, reducing patient discomfort and increasing satisfaction. Further comparative studies and research on the individual effects of PDRN and PRP are necessary to better understand and optimize this treatment approach.

Key Words: Ectropion / Lower blepharoplasty / Polydeoxyribonucleotide (PDRN) / Platelet-rich-plasma (PRP)

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Introduction

The periorbital region is a structure that displays facial expressions and is often considered the most important area for aesthetic surgery due to its impact on people's impressions [1-3]. With the recent global pandemic, mandatory mask-wearing has heightened interest in the exposed eyes, leading to an increase in eye-related cosmetic surgery. As aging progresses, the periorbital area becomes more sensitive to change, resulting in a rise in anti-aging surgery, particularly upper and lower blepharoplasty [1-3]. Among of them, complications from lower blepharoplasty, such as ectropion, occur more frequently in older patients, with weak lower lid support being a common cause [3,4]. While ectropion can be caused by excess skin removal, hematoma, swelling, or postoperative contracture, it often resolves over time. However, ectropion can cause discomfort, such as eye irritation and dryness, and can occasionally persist, leading to malposition [3-6]. Several surgical methods have been proposed to prevent ectropion [7,8], but few have been suggested to treat it once it occurs. Non-surgical approaches such as taping, massage, and steroid injections have been attempted, but their outcomes remain inconclusive. In this study, we aim to report on the benefits of intradermal injection of polydeoxyribonucleotide (PDRN) and platelet-rich-plasma (PRP) for scar regeneration and rapid recovery of ectropion after lower blepharoplasty.

Patients and Methods

This retrospective study was reviewed and approved by our Institutional Review Board (approval No. 2023-03-037). Informed consent was submitted by all subjects when they were enrolled. We analyzed 21 cases of ectropion that occurred out of 420 cases of transcutaneous lower blepharoplasty performed between January 2020 and October 2022. The study excluded patients who underwent lateral canthoplasty, other canthopexy, tarsal sling operation, or transconjunctival lower blepharoplasty. We retrospectively investigated the patients' gender, age, history of lower blepharoplasty, accompanying diseases, smoking status, location of ectropion, timing of injection for ectropion, additional injection timing, total injection count, patient satisfaction scale, and follow-up period. Detailed patient information is provided in Table 1.

Injection and Follow-Up

Patients were monitored for complications during outpatient follow-up visits at one-week intervals after lower blepharoplasty, and injection therapy was immediately administered when ectropion was observed. First, 15ml of blood, including 1.5cc of anticoagulant, was collected intravenously from the patient's arm. The blood sample was then transferred to a kit (Ycellbio PRP; Ycellbio medical), containing 12.5ml for women, 13.5ml for men, and

14.5ml for anemic patients. After centrifugation for four minutes, the buffy coat in the center of the kit was extracted using an adjustable lever. Then, 1.5-2.0cc of PRP was collected using a long needle. The prepared PRP and PDRN (PLACENTEX ®; PharmaResearch) were evenly injected intradermally into the lower eyelid using a 30-gauge needle. After injection, outpatient follow-up was conducted at one- or two-week intervals to monitor the patient's condition. If symptoms persisted or improvement was slow, additional PDRN with PRP therapy was administered using the same method previously described. Outpatient observation continued until the ectropion was completely corrected. Long-term follow-up was conducted at 12 and 24 weeks to monitor the patient's condition, and patient satisfaction was assessed using a 5-point scale at 24 weeks (1-very dissatisfied, 2-dissatisfied, 3-neither satisfied nor dissatisfied, 4-satisfied, 5-very satisfied).

Results

The study included 12 female patients and 9 male patients. The average age was 62 years old (range: 48-80), and the patients had accompanying conditions such as diabetes, hypertension, and hyperlipidemia. 15 patients underwent primary lower blepharoplasty, 5 patients underwent secondary lower blepharoplasty, and 1 patient underwent their third lower blepharoplasty. There were 5 patients who smoked, and the occurrence of ectropion was seen in 11 cases on the left side and 10 cases on the right side, with no cases occurring on both sides. The first injection was administered within 2-6 weeks of ectropion onset (average 3.8 weeks). 10 patients received a single injection, all patients developed symptoms after primary blepharoplasty. And 11 patients received two or more injections of PDRN with PRP. Among them, 5 patients developed ectropion after primary lower blepharoplasty, 5 after secondary blepharoplasty, and 1 after their third surgery. The average time for complete ectropion improvement after injection was 9.3 weeks (range: 6-14 weeks). Patient satisfaction survey results showed an average of 4.3 (range: 3-5). Average follow-up duration was 34.9 weeks (range: 24 -52 weeks). Table 2 was shown detailed results.

Case 1

A 63-year-old male patient, who had undergone two previous lower blepharoplasty surgeries but was still experiencing eyelid bags and was dissatisfied with the results, planned to undergo a third surgery with transcutaneous lower blepharoplasty. The patient had diabetes and was taking medication for high blood pressure, but his condition was relatively well controlled. During an outpatient visit 4 weeks after surgery, ectropion symptoms were observed on the right side, and the patient complained of discomfort. Therefore, PDRN one-ample and PRP were injected intradermally into the right lower eyelid, and even after 8 weeks of outpatient follow-up, the symptoms were significantly improved, but the lid position itself was still not normal, so additional PDRN + PRP injections were performed. During the follow-up period, an additional injection was performed at 12 weeks after surgery, and the patient's symptoms improved, and the ectropion was corrected by 14 weeks after surgery. At 20 weeks after surgery, the fat bulging under the eyes was improved with symmetry on both sides, resulting in a satisfactory outcome as scale 4 (Fig. 1).

Case 2

A 68-year-old male patient with no history of surgery, except for hyperlipidemia and no significant internal medicine diseases, underwent transcutaneous lower blepharoplasty. During the surgery, there was no excessive bleeding or skin excision. However, at the third week after surgery, the patient reported eye discomfort and asymmetry, and visited to the clinic. On the same day of the visit, PDRN + PRP injection therapy was performed. When the patient returned for an outpatient visit at 8 weeks after surgery, the symptoms had almost improved, and there was no discomfort, but slight ectropion and lid position abnormalities were observed in the left lower eyelid, so additional injections were performed. At 12 weeks after the injection, the eyelid had returned to normal, and the ectropion symptoms had completely improved. Despite undergoing two rounds of injection therapy, the patient had a high satisfaction scale of 5 (Fig. 2).

Discussion

The desire to appear younger and more attractive is universal among individuals of all ages and ethnicities. As people age, gravitational effects may cause fat bulging and decreased elasticity around the eyelids, resulting in an older appearance [1-3]. Various surgical methods have been proposed to improve this, including the relatively simple and attractive blepharoplasty technique, particularly lower blepharoplasty, which can remove fat bulging and sagging skin to create a younger and more attractive eye appearance [3-8]. However, there are potential complications, such as ectropion, especially in cases of severe lid laxity due to denervation of the orbicularis oculi muscle or excessive skin resection. Ectropion may also occur due to hematoma or inflammation after surgery [6-8]. The frequent occurrence of ectropion after facial bone fracture surgery, even without excessive skin excision, demonstrates that hematoma and traumatic traction can cause ectropion [9,10]. Additionally, heavy smokers may experience blood vessel constriction, leading to a significant increase in wrinkles due to an increased inflammatory response. While numerous reports have discussed the relationship between smoking and increased wrinkles, no specific research has examined the correlation between smoking and ectropion [11,12]. Various surgical techniques, such as lateral canthopexy, canthoplasty, sling operation or other procedure including transconjunctival approach, have been widely reported and modified to prevent ectropion in patients who are expected to develop it after surgery [4-7,12]. However, many cases occur where standard lower blepharoplasty and fat repositioning are performed without predicting ectropion, resulting in temporary ectropion. Although most cases improve over time, this process can take several months [13], causing significant discomfort for patients. Preventing these complications is important, but if they occur, it is essential to quickly restore lid position to reduce patient discomfort and increase satisfaction. Previous methods, such as taping, steroid injection, or massage, have demonstrated limited efficacy.

In this report, we attempted to use PDRN with PRP therapy for the treatment of ectropion, which was previously treated with conservative methods, in order to improve patients' symptoms more rapidly than existing methods. PDRN and PRP are increasingly used in cosmetic surgery to improve wrinkles, skin elasticity, and quick recovery after surgery for aesthetic purposes. PDRN and PRP have shown potential in various applications and effects, including both clinical and molecular levels [14-23]. However, clinical data regarding their efficacy in improving outcomes after cosmetic surgery, particularly for temporary ectropion following lower blepharoplasty, are limited.

As an adenosine A2A receptor (A2AR) agonist, PDRN exerts angiogenic effects via vascular endothelial growth factor (VEGF) augmentation [17,18] and tissue-repair effects via fibroblast stimulation [14,19,20]. Additionally, the activation of A2AR has an anti-inflammatory effect due to the inhibition of several pro-inflammatory mediators [14-16]. To put it simply, several research studies have shown that the following three roles have had the most positive effects [14]. (1) Increased collagen production: PDRN injections can stimulate the synthesis of collagen deposit, which is a protein that gives skin its strength and elasticity. (2) Reduced inflammation: PDRN injections have been shown to have anti-inflammatory effects, which can help to reduce redness, swelling, and pain etc. (3) Accelerated wound healing: PDRN injections can promote angiogenesis of wound, which can help to promote the healing of wounds.

And at the molecular level, PRP injections have been shown to release various growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF). These growth factors are involved in various cellular processes, including cell proliferation, differentiation, migration, and angiogenesis [21-23]. PDGF is a potent mitogen (a substance that stimulates cell division) for mesenchymal cells, which are involved in tissue repair and regeneration.

TGF-β is involved in the regulation of the immune response and has been shown to promote the formation of extracellular matrix, which is important for tissue repair. VEGF promotes angiogenesis, which is essential for tissue regeneration, and IGF stimulates cell proliferation and differentiation [21-23].

We attempted a preliminary trial in 21 cases and obtained relatively satisfactory results. Patients' satisfaction was relatively high (average 4.3), and the resolution time of ectropion was found to be somewhat faster (average 9.3 weeks) than the usual 3-6 months based on past experience [13], presumably due to the collagen synthesis increase and anti-inflammatory effect of PDRN, as well as the tissue repair and angiogenesis effects that are further enhanced by the use of PRP. After the PDRN and PRP injection, the outpatient follow-up was conducted at intervals of 2-4 weeks, and the point at which the patient's symptoms or lid position had completely improved was recorded, so there may be a difference of 1-2 weeks from the expected timing of improvement of ectropion. Therefore, it is thought that the actual improved period was much faster than the average. In addition, since the time when the lid returned to completely normal was measured, the improvement in symptoms perceived by the patient improved significantly after a single injection at the time it was actually discovered.

15 primary cases were performed, of which 10 showed relatively good effects even with only one injection. On the other hand, 6 patients who had undergone surgery two or more times were included, and all of them received two or more injections. In the case of secondary surgery, contraction and scarring are naturally more severe than in primary surgery, so additional injections were needed. As a result, the time for ectropion to disappear was slightly delayed compared to primary patients. Despite the numerous positive effects, there are still factors that may cause inconvenience or resistance for patients, such as the need for blood withdrawal and centrifugation for PRP injection, additional costs associated with PDRN injection, and the need for frequent outpatient follow-up after injection. This study was retrospective and had a small sample size, which may have resulted in selection bias. Additionally, the lack of comparison with a group of patients who did not receive any injection therapy makes it difficult to make an accurate numerical comparison of the improvement in ectropion. It is also difficult to confirm whether the effects observed were due to PDRN or PRP alone. Nevertheless, this study is the first to use a combination of PDRN and PRP for the improvement of temporary ectropion after lower blepharoplasty, and it is a part of the effort to shorten the uncomfortable period experienced by patients after surgery. We will continue to make efforts to improve patients' complications through further comparative studies and studies on the effects of PDRN or PRP alone.

CONFLICT OF INTEREST

All authors have no conflicts of interest to declare.

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This report has received no external funding. There is no more author who does not meet all four ICMJE criteria for authorship.

ETHICAL APPROVAL

The study was performed in accordance with the principles of the Declaration of Helsinki. The study was approved for exemption by the Institutional Review Board (IRB exemption No. 2022-12-045).

PATIENT CONSENT STATEMENT

Informed consent for publication of the study was obtained from the patient.

Reference

1. Tanenbaum M. Aesthetic oculoplastic surgery. Curr Opin Ophthalmol. 1998;9:54-61.

2. Knoll BI, Attkiss KJ, Persing JA. The influence of forehead, brow, and periorbital aesthetics on perceived expression in the youthful face. Plast Reconstr Surg. 2008;121:1793-802.

3. Murri M, Hamill EB, Hauck MJ, et al. An Update on Lower Lid Blepharoplasty. Semin Plast Surg. 2017;31:46-50.

4. Sobti M, Joshi N. Lower Eyelid Blepharoplasty: Minimizing Complications and Correction of Lower Eyelid Malposition. Facial Plast Surg. 2023;39:28-46

5. Yu Q, Sheng L, Li Q, et al. Post-Blepharoplasty Hematoma Caused Lower-Lid Ectropion and Early Correction. J Craniofac Surg. 2015;26:2232-3.

6. Carraway JH, Mellow CG. The prevention and treatment of lower lid ectropion following blepharoplasty. Plast Reconstr Surg. 1990;85:971-81.

7. Hsieh MW, Lai YW, Wang YC, et al. Lateral Tarsoplasty for Managing Ectropion and Laxity of the Lower Eyelid. Ann Plast Surg. 2022;88:S62-7.

8. Rohrich RJ, Mohan R. Preventing Lateral Canthal Malposition in Modern Blepharoplasty. Plast Reconstr Surg. 2020;145:324e-8e.

9. North VS, Reshef ER, Lee NG, et al. Lower eyelid malposition following repair of complex orbitofacial trauma. Orbit. 2022;41:193-8.

10. Oh SJ, Kim KS, Choi JH, et al. Scar formation after lower eyelid incision for reconstruction of the inferior orbital wall related to the lower eyelid crease or ridge in Asians. Arch Craniofac Surg. 2021;22:310-8.

11. Aksam E, Uyar I, Turan O. Evaluation of the Effect of Subciliary Approaches on Lower Eyelid Position in Infraorbital Rim Fractures. Facial Plast Surg. 2022 Dec 23 [Epub]. https://doi.org/10.1055/s-0042-1759757

12. Hjelm N, Sanan A, Krein H, et al. Safety of Concurrent Endoscopic Browlift and Blepharoplasty. Facial Plast Surg. 2019;35:546-8.

13. Damasceno RW, Osaki MH, Dantas PE, et al. Involutional entropion and ectropion of the lower eyelid: prevalence and associated risk factors in the elderly population. Ophthalmic Plast Reconstr Surg. 2011;27:317-20.

14. Jeong W, Yang CE, Roh TS, et al. Scar Prevention and Enhanced Wound Healing Induced by Polydeoxyribonucleotide in a Rat Incisional Wound-Healing Model. Int J Mol Sci. 2017;18:1698.

15. Bitto A, Polito F, Irrera N, et al. Polydeoxyribonucleotide reduces cytokine production and the severity of collagen-induced arthritis by stimulation of adenosine A(□A) receptor. Arthritis Rheum. 2011;63:3364-71.

16. Bitto A, Oteri G, Pisano M, et al. Adenosine receptor stimulation by polynucleotides (PDRN) reduces inflammation in experimental periodontitis. J Clin Periodontol. 2013;40:26-32.

17. Bitto A, Polito F, Altavilla D, et al. Polydeoxyribonucleotide (PDRN) restores blood flow in an experimental model of peripheral artery occlusive disease. J Vasc Surg. 2008;48:1292-300.

18. Bitto A, Galeano M, Squadrito F, et al. Polydeoxyribonucleotide improves angiogenesis and wound healing in experimental thermal injury. Crit Care Med. 2008;36:1594-602.

19. Sini P, Denti A, Cattarini G, et al. Effect of polydeoxyribonucleotides on human fibroblasts in primary culture. Cell Biochem Funct. 1999;17:107-14.

20. Galeano M, Bitto A, Altavilla D, et al. Polydeoxyribonucleotide stimulates angiogenesis and wound healing in the genetically diabetic mouse. Wound Repair Regen. 2008;16:208-17.

21. Peng GL. Platelet-Rich Plasma for Skin Rejuvenation: Facts, Fiction, and Pearls for Practice. Facial Plast Surg Clin North Am. 2019;27:405-11.

22. Atiyeh B, Oneisi A, Ghieh F. Platelet-Rich Plasma Facial Rejuvenation: Myth or Reality? Aesthetic Plast Surg. 2021;45:2928-38.

23. Evans AG, Ivanic MG, Botros MA, et al. Rejuvenating the periorbital area using platelet-rich plasma: a systematic review and meta-analysis. Arch Dermatol Res. 2021;313:711-27.

Table 1. Patient demographics

Characteristic	Value
Sex	
Male	9 (42.9)
Female	12 (57.1)
Total	21
Age (year)	
Male	62.9 (51-75)
Female	61.3 (48-80)
Total	62.0
History of lower blepharoplasty	
Primary	15 (71.4)
Secondary	5 (23.8)
Tertiary	1 (4.8)
Accompanying diseases	
DM	6
HTN	8
Hyperlipidemia	4
Smoking history (Pack-year)	
10~20	2
21~30	3
Location of Ectropion (Right, Left, Both)	
Right	10 (47.6)
Left	11 (52.4)
Both	0

Values are presented as number (%), mean (range).

Table 2. Detailed results related to injection

Variable	Value
Timing of injection for ectropion (weeks)	**Mean: 3.8**
2	1
3	6
4	12
5	0
6	2
Total injection count	**Mean: 1.76**
1	10 (47.6)
2	7 (33.3)
3	3 (14.3)
4	1 (4.8)
Additional injection timeline	
total 2 inj.	
3rd – 6th	1
3rd – 8th	1
4th – 8th	2
4th – 10th	2
6th – 10th	1
total 3 inj.	
2nd – 6th – 8th	1
4th – 8th – 10th	1
4th – 8th – 12th	1
total 4 inj.	
3rd – 5th – 6th – 8th	1
Resolution time after surgery (weeks)	**Mean: 9.3**
6	5 (23.8)
8	6 (28.6)
10	3 (14.3)
12	6 (28.6)
14	1 (4.8)
Patient satisfaction scale (1-5)	**Mean: 4.3**
1 (very dissatisfied)	0
2 (dissatisfied)	0
3 (neither satisfied nor dissatisfied)	2 (9.5)
4 (satisfied)	10 (47.6)
5 (very satisfied)	9 (42.9)
Follow-up period (weeks)	**Mean: 34.9**
24	8
26	1
30	1
32	1
36	2
40	3
52	5

Values are presented as number (%).

Figure legends

Fig. 1A. The preoperative frontal view showed no fat bulging due to past surgery, but wrinkles and tear through deformity were observed in the lower parts of both eyes.

Fig. 1B. Ectropion was observed on the right side in the frontal view taken 4 weeks after surgery.

Fig. 1C. The symptoms improved in the frontal view taken 8 weeks after surgery, but ectropion remained.

Fig. 1D. Ectropion completely improved after a total of 3 injections in the frontal view taken 14 weeks after surgery.

Fig. 1E. In the frontal view taken 20 weeks after surgery, wrinkles improved compared to pre-operation, and tear through deformity also improved.

Fig. 1F. Preoperative oblique view.

Fig. 1G. Postoperative 4-week oblique view.

Fig. 1H. Postoperative 8-week oblique view.

Fig. 1I Postoperative 14-week oblique view (complete resolution of ectropion).

Fig. 1J. Postoperative 20-week oblique view.

Fig. 2A. The preoperative frontal view shows symptoms of fat bulging and tear through deformity.

Fig. 2B. The postoperative 3-week frontal view shows ectropion symptoms on the left eye. PRP + PDRN injection was performed.

Fig. 2C. The postoperative 8-week frontal view shows that symptoms improved after one injection, but ectropion remains, so additional injection was performed.

Fig. 2D. The postoperative 12-week frontal view shows that the ectropion symptom has completely improved and the fat bulging and tear through deformity have also improved.

Fig. 2E. Preoperative oblique view.

Fig. 2F. Postoperative 3-week oblique view.

Fig. 2G. Postoperative 8-week oblique view.

Fig. 2H. Postoperative 12-week oblique view. (complete resolution of ectropion).

Fig. 1A

Fig. 1B

Fig. 1C

Fig. 1D

Fig. 1E

Fig. 1F

Fig. 1G

Fig. 1H

Fig. 1I

Fig. 1J

Fig. 2A

Fig. 2B

Fig. 2C

Fig. 2D

Fig. 2E

Fig. 2F

Fig. 2G

Fig. 2H