

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)

Editorial members
Archives of Aesthetic Plastic Surgery Editorial Office
101-2003, Lotte Castle President, 109 Mapodaero, Mapo-gu, Seoul 04146, Korea

TEL : +82-2-3472-4243
FAX : +82-2-3472-4254
E-mail: ksaps@ksaps.or.kr
Website: <http://submit.e-aaps.org/>

101-2003, Lotte Castle President, 109 Mapodaero, Mapo-gu, Seoul 04146, Korea

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5 injection of polydeoxyribonucleotide (PDRN) and platelet-rich-plasma (PRP) for scar regeneration and rapid
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21 **Keywords:** Ectropion, Lower blepharoplasty, Polydeoxyribonucleotide (PDRN), Platelet-rich-plasma (PRP)

22

23 **Introduction**

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

37

38 **Patients and Methods**

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

47 *Injection and Follow-Up*

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

52 14.5ml for anemic patients. After centrifugation for four minutes, the buffy coat in the center of the kit was
53 extracted using an adjustable lever. Then, 1.5-2.0cc of PRP was collected using a long needle. The prepared PRP
54 and PDRN (PLACENTEX ®; PharmaResearch) were evenly injected intradermally into the lower eyelid using a
55 30-gauge needle. After injection, outpatient follow-up was conducted at one- or two-week intervals to monitor the
56 patient's condition. If symptoms persisted or improvement was slow, additional PDRN with PRP therapy was
57 administered using the same method previously described. Outpatient observation continued until the ectropion
58 was completely corrected. Long-term follow-up was conducted at 12 and 24 weeks to monitor the patient's
59 condition, and patient satisfaction was assessed using a 5-point scale at 24 weeks (1-very dissatisfied, 2-dissatisfied,
60 3-neither satisfied nor dissatisfied, 4-satisfied, 5-very satisfied).

61

62 **Results**

63 The study included 12 female patients and 9 male patients. The average age was 62 years old (range: 48-80), and
64 the patients had accompanying conditions such as diabetes, hypertension, and hyperlipidemia. 15 patients
65 underwent primary lower blepharoplasty, 5 patients underwent secondary lower blepharoplasty, and 1 patient
66 underwent their third lower blepharoplasty. There were 5 patients who smoked, and the occurrence of ectropion
67 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
68 injection was administered within 2-6 weeks of ectropion onset (average 3.8 weeks). 10 patients received a single
69 injection, all patients developed symptoms after primary blepharoplasty. And 11 patients received two or more
70 injections of PDRN with PRP. Among them, 5 patients developed ectropion after primary lower blepharoplasty, 5
71 after secondary blepharoplasty, and 1 after their third surgery. The average time for complete ectropion
72 improvement after injection was 9.3 weeks (range: 6-14 weeks). Patient satisfaction survey results showed an
73 average of 4.3 (range: 3-5). Average follow-up duration was 34.9 weeks (range: 24 -52 weeks). Table 2 was shown
74 detailed results.

75 *Case 1*

76 A 63-year-old male patient, who had undergone two previous lower blepharoplasty surgeries but was still
77 experiencing eyelid bags and was dissatisfied with the results, planned to undergo a third surgery with
78 transcutaneous lower blepharoplasty. The patient had diabetes and was taking medication for high blood pressure,
79 but his condition was relatively well controlled. During an outpatient visit 4 weeks after surgery, ectropion
80 symptoms were observed on the right side, and the patient complained of discomfort. Therefore, PDRN one-ample

81 and PRP were injected intradermally into the right lower eyelid, and even after 8 weeks of outpatient follow-up,
82 the symptoms were significantly improved, but the lid position itself was still not normal, so additional PDRN +
83 PRP injections were performed. During the follow-up period, an additional injection was performed at 12 weeks
84 after surgery, and the patient's symptoms improved, and the ectropion was corrected by 14 weeks after surgery. At
85 20 weeks after surgery, the fat bulging under the eyes was improved with symmetry on both sides, resulting in a
86 satisfactory outcome as scale 4 (Fig. 1).

87 *Case 2*

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

97

98 **Discussion**

99 The desire to appear younger and more attractive is universal among individuals of all ages and ethnicities. As
100 people age, gravitational effects may cause fat bulging and decreased elasticity around the eyelids, resulting in an
101 older appearance [1-3]. Various surgical methods have been proposed to improve this, including the relatively
102 simple and attractive blepharoplasty technique, particularly lower blepharoplasty, which can remove fat bulging
103 and sagging skin to create a younger and more attractive eye appearance [3-8]. However, there are potential
104 complications, such as ectropion, especially in cases of severe lid laxity due to denervation of the orbicularis oculi
105 muscle or excessive skin resection. Ectropion may also occur due to hematoma or inflammation after surgery [6-
106 8]. The frequent occurrence of ectropion after facial bone fracture surgery, even without excessive skin excision,
107 demonstrates that hematoma and traumatic traction can cause ectropion [9,10]. Additionally, heavy smokers may
108 experience blood vessel constriction, leading to a significant increase in wrinkles due to an increased inflammatory
109 response. While numerous reports have discussed the relationship between smoking and increased wrinkles, no

110 specific research has examined the correlation between smoking and ectropion [11,12]. Various surgical techniques,
111 such as lateral canthopexy, canthoplasty, sling operation or other procedure including transconjunctival approach,
112 have been widely reported and modified to prevent ectropion in patients who are expected to develop it after
113 surgery [4-7,12]. However, many cases occur where standard lower blepharoplasty and fat repositioning are
114 performed without predicting ectropion, resulting in temporary ectropion. Although most cases improve over time,
115 this process can take several months [13], causing significant discomfort for patients. Preventing these
116 complications is important, but if they occur, it is essential to quickly restore lid position to reduce patient
117 discomfort and increase satisfaction. Previous methods, such as taping, steroid injection, or massage, have
118 demonstrated limited efficacy.

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

125 As an adenosine A_{2A} receptor (A_{2A}R) agonist, PDRN exerts angiogenic effects via vascular endothelial growth
126 factor (VEGF) augmentation [17,18] and tissue-repair effects via fibroblast stimulation [14,19,20]. Additionally,
127 the activation of A_{2A}R has an anti-inflammatory effect due to the inhibition of several pro-inflammatory mediators
128 [14-16]. To put it simply, several research studies have shown that the following three roles have had the most
129 positive effects [14]. (1) Increased collagen production: PDRN injections can stimulate the synthesis of collagen
130 deposit, which is a protein that gives skin its strength and elasticity. (2) Reduced inflammation: PDRN injections
131 have been shown to have anti-inflammatory effects, which can help to reduce redness, swelling, and pain etc. (3)
132 Accelerated wound healing: PDRN injections can promote angiogenesis of wound, which can help to promote the
133 healing of wounds.

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

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

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

152 15 primary cases were performed, of which 10 showed relatively good effects even with only one injection. On
153 the other hand, 6 patients who had undergone surgery two or more times were included, and all of them received
154 two or more injections. In the case of secondary surgery, contraction and scarring are naturally more severe than
155 in primary surgery, so additional injections were needed. As a result, the time for ectropion to disappear was
156 slightly delayed compared to primary patients. Despite the numerous positive effects, there are still factors that
157 may cause inconvenience or resistance for patients, such as the need for blood withdrawal and centrifugation for
158 PRP injection, additional costs associated with PDRN injection, and the need for frequent outpatient follow-up
159 after injection. This study was retrospective and had a small sample size, which may have resulted in selection
160 bias. Additionally, the lack of comparison with a group of patients who did not receive any injection therapy makes
161 it difficult to make an accurate numerical comparison of the improvement in ectropion. It is also difficult to confirm
162 whether the effects observed were due to PDRN or PRP alone. Nevertheless, this study is the first to use a
163 combination of PDRN and PRP for the improvement of temporary ectropion after lower blepharoplasty, and it is
164 a part of the effort to shorten the uncomfortable period experienced by patients after surgery. We will continue to
165 make efforts to improve patients' complications through further comparative studies and studies on the effects of
166 PDRN or PRP alone.

167

168 CONFLICT OF INTEREST

169 All authors have no conflicts of interest to declare.

170

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

174

175 ETHICAL APPROVAL

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

178

179 PATIENT CONSENT STATEMENT

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

181

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228

229 **Table 1. Patient demographics**

| Characteristic | Value | |
|--|--------------|-----|
| | | 230 |
| Sex | | |
| Male | 9 (42.9) | 231 |
| Female | 12 (57.1) | 232 |
| Total | 21 | 233 |
| Age (year) | | |
| Male | 62.9 (51-75) | 234 |
| Female | 61.3 (48-80) | 235 |
| Total | 62.0 | 236 |
| History of lower blepharoplasty | | 237 |
| Primary | 15 (71.4) | 238 |
| Secondary | 5 (23.8) | 239 |
| Tertiary | 1 (4.8) | 240 |
| Accompanying diseases | | |
| DM | 6 | 241 |
| HTN | 8 | 242 |
| Hyperlipidemia | 4 | 243 |
| Smoking history (Pack-year) | | |
| 10~20 | 2 | 244 |
| 21~30 | 3 | 245 |
| Location of Ectropion (Right, Left, Both) | | 246 |
| Right | 10 (47.6) | 247 |
| Left | 11 (52.4) | 248 |
| Both | 0 | |

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

250

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251 **Table 2. Detailed results related to injection**

| Variable | Value | 252 |
|---|-------------------|-----|
| Timing of injection for ectropion (weeks) | Mean: 3.8 | |
| 2 | 1 | 253 |
| 3 | 6 | 254 |
| 4 | 12 | |
| 5 | 0 | 255 |
| 6 | 2 | 256 |
| Total injection count | Mean: 1.76 | |
| 1 | 10 (47.6) | 257 |
| 2 | 7 (33.3) | 258 |
| 3 | 3 (14.3) | |
| 4 | 1 (4.8) | 259 |
| Additional injection timeline | | 260 |
| total 2 inj. | | |
| 3 rd – 6 th | 1 | 261 |
| 3 rd – 8 th | 1 | 262 |
| 4 th – 8 th | 2 | |
| 4 th – 10 th | 2 | 263 |
| 6 th – 10 th | 1 | 264 |
| total 3 inj. | | |
| 2 nd – 6 th – 8 th | 1 | 265 |
| 4 th – 8 th – 10 th | 1 | 266 |
| 4 th – 8 th – 12 th | 1 | |
| total 4 inj. | | 267 |
| 3 rd – 5 th – 6 th – 8 th | 1 | 268 |
| Resolution time after surgery (weeks) | Mean: 9.3 | |
| 6 | 5 (23.8) | 269 |
| 8 | 6 (28.6) | |
| 10 | 3 (14.3) | 270 |
| 12 | 6 (28.6) | 271 |
| 14 | 1 (4.8) | |
| Patient satisfaction scale (1-5) | Mean: 4.3 | 272 |
| 1 (very dissatisfied) | 0 | 273 |
| 2 (dissatisfied) | 0 | |
| 3 (neither satisfied nor dissatisfied) | 2 (9.5) | 274 |
| 4 (satisfied) | 10 (47.6) | 275 |
| 5 (very satisfied) | 9 (42.9) | |
| Follow-up period (weeks) | Mean: 34.9 | 276 |
| 24 | 8 | 277 |
| 26 | 1 | |
| 30 | 1 | 278 |
| 32 | 1 | 279 |
| 36 | 2 | |
| 40 | 3 | 280 |
| 52 | 5 | 281 |

282 Values are presented as number (%).

283

284 **Figure legends**

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

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

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

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

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

292 Fig. 1F. Preoperative oblique view.

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

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

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

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

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

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

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

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

304 Fig. 2E. Preoperative oblique view.

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

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

307 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. 11



Fig. 1J



Fig. 2A



Fig. 2B



Fig. 2C



Fig. 2D



Fig. 2E



Fig. 2F



Fig. 2G



Fig. 2H

