Original Article

Analgesic Effect of Topical Sodium Diclofenac before Retinal Photocoagulation for Diabetic Retinopathy: A Randomized Double-masked Placebo-controlled Intraindividual Crossover Clinical Trial

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Purpose: To evaluate the analgesic effect of topical sodium diclofenac 0.1% before retinal laser photocoagulation for diabetic retinopathy.

Methods: Diabetic patients who were candidates for peripheral laser photocoagulation were included in a randomized, placebo-controlled, intraindividual, two-period, and crossover clinical trial. At the first session and based on randomization, one eye received topical sodium diclofenac 0.1% and the other eye received an artificial tear drop (as placebo) three times before laser treatment. At the second session, eyes were given the alternate drug. Patients scored their pain using visual analogue scale (max, 10 cm) at both sessions. Patients and the surgeon were blinded to the drops given. Difference of pain level was the main outcome measure.

Results: A total of 200 eyes of 100 patients were enrolled. Both treatments were matched regarding the applied laser. Pain sensation based on visual analogue scale was 5.6 ± 3.0 in the treated group and 5.5 ± 3.0 in the control group. The calculated treatment effect was 0.15 (95% confidence interval, –0.27 to 0.58; \(p = 0.486\)). The estimated period effect was 0.24 (\(p = 0.530\)) and the carryover effect was not significant (\(p = 0.283\)).

Conclusions: Pretreatment with topical sodium diclofenac 0.1% does not have any analgesic effect during peripheral retinal laser photocoagulation in diabetic patients.

Key Words: Analgesic effect, Diabetic retinopathy, Laser photocoagulation, Topical sodium diclofenac

The annual incidence of new cases of proliferative diabetic retinopathy (PDR) is 2.7% to 4% for patients with type 1 diabetes and 0.6% to 3.2% for patients with type 2 diabetes [1]. Untreated high risk characteristic PDR results in a 33% risk of severe vision loss at 3 years [2]. This risk, however, is reduced by 50% by adequate panretinal laser photocoagulation (PRP) [2]. The procedure can be painful, leading to undertreatment in a large number of pain intolerant patients [3].

Non-steroidal anti-inflammatory drugs (NSAIDs) are a
group of compounds used systemically or locally as analgesic, antipyretic, and anti-inflammatory agents. They have been used after cataract [4,5] and photorefractive surgery [6-8] as well as in patients with corneal abrasions [9]. Topical NSAID diclofenac was found to have greater analgesic action than topical betamethasone 0.1% in patients undergoing scleral buckling and vitrectomy [10]. Therefore, it might be preferred to use topical NSAIDs before performing PRP in order to diminish pain sensation during the procedure. This hypothesis has been investigated in a number of PRP or macular grid laser therapy cases and seems to be effective [11].

In this trial, we evaluated the analgesic effect of topical diclofenac sodium as a pretreatment drug for diabetic patients undergoing PRP. Pain sensation, the main outcome measure of this study, is susceptible to subjectivity bias, and we therefore designed this placebo-controlled trial as an intraindividual, two-period, and crossover study.

Materials and Methods

This study was performed as a randomized, double-blinded, placebo-controlled, intraindividual, two-period, and crossover clinical trial. After fully explaining the study protocol and its probable safety and efficacy, written informed consent was obtained from all patients. This clinical trial was approved by the review board/ethics committee of the Ophthalmic Research Center of Shahid Beheshti University of Medical Sciences.

All patients with severe non-PDR and early or high-risk characteristic PDR who were considered as candidates for bilateral PRP by a retina specialist were included in this trial. Patients with a history of intraocular surgery, peripheral retinal laser therapy, or any eye disease that may interfere with the study protocol in either eye were excluded. Vitreous hemorrhage or other media opacity precluding proper laser therapy in either eye was also used as exclusion criteria. A data sheet was completed for all included patients.

Enrolled patients were scheduled to receive three or four sessions of PRP. However, the study protocol was performed only for the first two sessions of treatment. For each person, randomization was performed before the first session. The right eye of each person was randomly assigned to one group based on a randomized permuted block with randomly selected block lengths of 4 and 6. The left eye was assigned to the other group. At the first session and based on randomization, one eye received topical sodium diclofenac ophthalmic solution 0.1% and the other eye topical artificial tear drop (as placebo) three times, 5 minutes apart, at least 20 minutes before laser treatment. At the second session, the eyes were given the alternate drug with the same schedule. An argon laser was used with a wavelength of 532 nm, spot size of 200 μm, exposure time of 0.2 ms, and energy level of 100 to 500 mW.

In this study, pain level was scored using a visual analogue scale (VAS). It consisted of a 10 cm scale arranged from no pain to the worst pain imaginable. Markings of the subjects on the scale are translated to a number from 0 to 10. Before applying the laser, patients were instructed on how VAS works. Patients unable to cooperate with the VAS test were excluded.

Laser therapy was performed based on the Early Treatment Diabetic Retinopathy Study protocol, and started with the right eyes. Surgeons were encouraged to use nearly the same power and amount of laser for both eyes at each stage and to apply the laser on the same quadrants of both eyes, avoiding the area of long ciliary nerves. At the end of laser treatment in each session, patients scored the pain in each eye.

Patients, the nurse who instilled the drops, and the surgeons who performed the laser operation and asked about the pain were all blinded to the drops given. The difference of pain level was compared between the two drugs as the main outcome measure.

Statistical analysis

To describe data, we used the mean ± standard deviation, median (range), and frequency (%). To evaluate differences between the groups in each session, we used McNemar and Wilcoxon signed-rank tests. We evaluated the carryover, period (session), and treatment effect by means of a generalized linear mixed model. All statistical analyses were performed using SAS ver. 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 200 eyes of 100 diabetic patients enrolled in
and completed the study. The mean age was 54 ± 10 years (range, 26 to 75) and 63% were female. The laser procedure data for each group are presented in Table 1. Groups were comparable regarding the mean number of laser applications, mean energy level of laser, and frequency of the treated quadrants. The mean time interval between instillation of drops and laser procedure was 119 ± 55 minutes, with 114 ± 55 minutes for the first session and 124 ± 55 minutes for the second session.

Pain sensation according to VAS at the first session was 5.9 ± 3.1 in the diclofenac group and 5.5 ± 3.0 in the placebo group (Table 1). The corresponding values for the second session were 5.4 ± 2.8 and 5.5 ± 2.9. Fig. 1 demonstrates change in pain scores in each subject in every session. Collecting both sessions together, pain sensation was 5.6 ± 3.0 and 5.5 ± 3.0 based on VAS in the treated and control groups, respectively. In total, the calculated treatment effect was 0.15 (95% confidence interval [CI], 0.08 to 0.27) and there was no statistically significant difference between the treatments (95% CI, 0.08 to 0.27; $p = 0.486$). Carryover effect was statistically insignificant ($p = 0.283$) and the estimated period effect was 0.24 (95% CI, 0.10 to 0.38; $p = 0.30$).

**Discussion**

This trial demonstrated that pretreatment with topical sodium diclofenac ophthalmic solution 0.1% did not diminish pain during PRP in diabetic patients. Pain experienced during PRP is very variable but appears to be more common with retreatment and with treatment applied anterior to the equator, especially in the 3, 6, 9, and 12 o'clock positions (corresponding to the location of the long ciliary nerves) [3]. As suggested by various authors, there are several ways of mitigating this pain. Some patients respond to pretreatment oral analgesia. Others may even require local anesthetic blockade or general anesthesia in order to tolerate treatment. However, these interventions carry the risk of side effects and require additional monitoring of the patient. Pain sensation according to VAS at the first session was 5.9 ± 3.1 in the diclofenac group and 5.5 ± 3.0 in the placebo group (Table 1). The corresponding values for the second session were 5.4 ± 2.8 and 5.5 ± 2.9. Fig. 1 demonstrates change in pain scores in each subject in every session. Collecting both sessions together, pain sensation was 5.6 ± 3.0 and 5.5 ± 3.0 based on VAS in the treated and control groups, respectively. In total, the calculated treatment effect was 0.15 (95% confidence interval [CI], 0.08 to 0.27) and there was no statistically significant difference between the treatments (95% CI, 0.08 to 0.27; $p = 0.486$). Carryover effect was statistically insignificant ($p = 0.283$) and the estimated period effect was 0.24 (95% CI, 0.10 to 0.38; $p = 0.30$).

**Table 1. Laser characteristics and pain level of the two groups in each session separately and in both sessions together**

|                      | First session |                      | Second session |                      | Both sessions |                      |
|----------------------|--------------|----------------------|----------------|----------------------|--------------|----------------------|
|                      | Diclofenac (n = 100) | Placebo (n = 100) | $p$-value* | Diclofenac (n = 100) | Placebo (n = 100) | $p$-value† | Diclofenac (n = 200) | Placebo (n = 200) | $p$-value‡ |
| No. of applications  | 361 ± 66 (200–510) | 372 ± 58 (204–218) | 0.098 | 377 ± 89 (200–720) | 374 ± 80 (200–600) | 0.792 | 368 ± 77 (3–720) | 373 ± 68 (200–600) | 0.331 |
| Energy level (mW)    | 372 ± 164 (100–900) | 372 ± 153 (100–900) | 0.673 | 376 ± 168 (140–900) | 364 ± 162 (102–800) | 0.648 | 374 ± 165 (140–900) | 368 ± 157 (100–900) | 0.485 |
| Time interval (min)‡ | 115 ± 56 (20–310) | 113 ± 54 (15–240) | 0.571 | 124 ± 55 (40–270) | 123 ± 56 (40–260) | 0.842 | 120 ± 56 (20–310) | 118 ± 55 (15–260) | 0.241 |
| Treated quadrants (%)| ST 16 (0.3–11.5) | 18 (0.3–11.5) | 0.649 | ST 13 (0.3–11.5) | 14 (0.3–11.5) | 0.306 | ST 15 (0.3–11.5) | 16 (0.3–11.5) | 0.428 |
|                      | SN 25 (0.3–11.5) | 24 (0.3–11.5) | 0.918 | SN 26 (0.3–11.5) | 30 (0.3–11.5) | 0.918 | SN 25 (0.3–11.5) | 27 (0.3–11.5) | 0.918 |
|                      | IT 6 (0.3–11.5) | 7 (0.3–11.5) | 0.918 | IT 51 (0.3–11.5) | 47 (0.3–11.5) | 0.918 | IT 26 (0.3–11.5) | 25 (0.3–11.5) | 0.918 |
|                      | IN 53 (0.3–11.5) | 50 (0.3–11.5) | 0.918 | IN 51 (0.3–11.5) | 47 (0.3–11.5) | 0.918 | IN 34 (0.3–11.5) | 32 (0.3–11.5) | 0.918 |
| Pain score           | 5.9 ± 3.1 (0.3–11.5) | 5.5 ± 3.0 (0.3–11.5) | 0.215 | 5.4 ± 2.8 (0.5–11.8) | 5.5 ± 2.9 (0.3–11.6) | 0.918 | 5.6 ± 3.0 (0.3–11.8) | 5.5 ± 3.0 (0.3–11.6) | 0.486 |

Values are presented as mean ± standard deviation (range). ST = supratemporal; SN = supranasal; IT = infratemporal; IN = inferonasal. Based on McNemar and Wilcoxon signed-rank test; †Based on generalized linear mixed model; ‡Times between drop administration and laser applications.
The feasibility of manual acupuncture for reducing pain during PRP treatment was also investigated in a prospective, comparative nonrandomized study and was found to be helpful [12]. In a recent published randomized controlled trial, single spot short duration time (20 ms) was compared with conventional laser therapy as another option for diabetic retinopathy treatment. The investigators found that short pulse laser was significantly less painful but just as effective as conventional laser during 6 months of follow-up [13].

The analgesic effect of NSAIDs is believed to apply through inhibition of the arachidonic acid cascade. This cascade divides into the cyclo-oxygenase and the lipo-oxygenase pathways. The main products of the cyclo-oxygenase pathway are prostaglandins that take part in maintaining and amplifying the cellular and humoral phases of the inflammatory response. During an inflammatory response, several mediators are released that stimulate pain producing nerve fibers [11].

Sodium diclofenac 0.1% belongs to the phenylacetic acid chemical class and appears to have a dual effect on both cyclo-oxygenase and lipo-oxygenase pathways [14]. It is believed that it acts on the posterior segment of the eye either by diffusion into the vitreous from the aqueous or by “desensitization” of the entire distribution of the trigeminal nerve fibers around the globe [11].

The analgesic effect of topical sodium diclofenac 0.1% during PRP and macular laser photocoagulation was evaluated in a prospective, double-blinded, crossover, randomized, and clinical study [11]. In this report, the study population included 87 patients, 45 with PDR treated with PRP (group A) and 42 with non-PDR and clinically significant macular edema (group B) who received grid treatment of the posterior pole. Treatment of the posterior pole was associated with no, mild, or negligible pain and this was attributed to the lower power levels used for grid photocoag-

![Fig. 1. Drop lines showing the changes in pain scores in each subject for the two treatment groups in every session, separately.](image-url)
ulation. However, they found a statistically significant effect \((p = 0.01)\) by paired \(t\)-test) in group A by using topical diclofenac. It should be noted that even in this group, nine patients out of 45 had more pain when using diclofenac than using sodium chloride and seven patients had similar levels of pain using both treatments. Nevertheless, the mean reported level of pain was 44.2% when sodium diclofenac 0.1% drops were used and 53.1% when sodium chloride 0.9% drops were used. Although the difference between the groups was statistically significant, the reported level of pain sensation did not differ significantly from the clinical point of view. The mean pain score in our study was similar to the sodium chloride group of this study. It was 5.4 in the treated group and 5.3 in the control group, and we found no significant difference between the groups. The difference between two studies might be due to the different times of drop installations before PRP and the various characteristics of laser application.

In another randomized, double-masked, and placebo-controlled clinical trial, the authors compared oral diclofenac, topical diclofenac, and placebo in pain reduction during PRP and concluded that a single dose of oral diclofenac was an effective pretreatment analgesic agent for reducing pain experienced during PRP for PDR. They found a significantly lower pain level in patients receiving pretreatment of oral diclofenac compared to the controls. However, the difference between topical diclofenac and placebo was not significant in univariate analysis \([15]\). Although this latter result was comparable to our result, multivariate regression analysis for age, gender, and total laser energy in their study demonstrated a significantly lower pain level for topical diclofenac versus placebo \([15]\).

Despite the above reported beneficial effect of the topical sodium diclofenac 0.1% during PRP, there is another study with a conclusion similar to our results. In this trial, the investigators evaluated the effect of topical ketorolac 0.5%, another topical NASAID, for ocular pain relief during PRP \([16]\). It was a prospective, randomized, double-blinded, and controlled study with 60 eyes of 30 consecutive PDR patients. One hour before laser treatment, ketorolac tromethamine 0.5% was instilled to one eye and artificial tear drop to the fellow eye. Directly after treatment, patients were asked for the severity of pain in both eyes using VAS. Mean pain level for placebo-instilled eyes was 4.8 and 4.4 for ketorolac-instilled eyes. There was no significant difference for pain levels between the groups \((p = 0.29)\). The conclusion of this study was parallel to ours, but instead using a different type of topical NSAID.

In the present trial, the mean time interval between instillation of the drops and laser treatment was about 115 minutes. Although this waiting time would not be convenient for daily practice, it was an appropriate interval in order to achieve near maximum analgesic effect of topical sodium diclofenac 0.1%. The highest average concentration of this drug to be found in the aqueous humor was 82 ng/mL at 2.4 hours after instillation \([17]\). This time interval was 68.3 minutes in the study using diclofenac \([11]\) and 1 hour in the trial using ketorolac 0.5% \([16]\).

Our study was sufficiently powered with 100 cases, 200 eyes, and 400 interventions. Performing a randomized double-masked placebo-controlled intrindividual crossover clinical trial enabled us to overcome many biases and limitations as the subjective-dependent main outcome of this study, which was pain sensation. Nonetheless, we used the VAS test, which has been found to be correlative and reproducible \([18]\). It is an acceptable and widely used method for measuring pain sensation. Additionally, surgeons were encouraged to try to apply the laser on the same quadrants of both eyes in each session since the level of pain sensation may vary based on different quadrants receiving the laser.

In summary, we report that using topical diclofenac sodium as an analgesic before PRP in patients with diabetic retinopathy was not helpful in pain reduction during the procedure. As previously reported, the drug is supposed to act on the posterior segment of the eye either by diffusion into the vitreous from the aqueous or by “desensitization” of the entire trigeminal nerve fibers around the globe \([11]\). However, we did not observe any effect using this type of intervention in our study. We believe that the concentration of the drug around the corresponding nerves with the aforementioned method of administration would not be enough to diminish pain level during a relatively painful procedure like PRP. Further studies evaluating other modalities and routes of administration are warranted.

**Conflict of Interest**

No potential conflict of interest relevant to this article was reported.
References

1. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of diabetic retinopathy. XIV: ten-year incidence and progression of diabetic retinopathy. *Arch Ophthalmol* 1994;112:1217-28.

2. Photocoagulation treatment of proliferative diabetic retinopathy: clinical application of Diabetic Retinopathy Study (DRS) findings, DRS report number 8. The Diabetic Retinopathy Study Research Group. *Ophthalmology* 1981;88:583-600.

3. Cook HL, Newsom RS, Mensah E, et al. Entonox as an analgesic agent during panretinal photocoagulation. *Br J Ophthalmol* 2002;86:1107-8.

4. Fry LL. Efficacy of diclofenac sodium solution in reducing discomfort after cataract surgery. *J Cataract Refract Surg* 1995;21:187-90.

5. Herbert CP, Jauch A, Othenin-Girard P, et al. Diclofenac drops to treat inflammation after cataract surgery. *Acta Ophthalmol Scand* 2000;78:421-4.

6. Epstein RL, Laurence EP. Effect of topical diclofenac solution on discomfort after radial keratotomy. *J Cataract Refract Surg* 1994;20:378-80.

7. Sher NA, Golben MR, Bond W, et al. Topical bromfenac 0.09% vs. ketorolac 0.4% for the control of pain, photophobia, and discomfort following PRK. *J Refract Surg* 2009;25:214-20.

8. Durrie DS, Kennard MG, Boghossian AJ. Effects of non-steroidal ophthalmic drops on epithelial healing and pain in patients undergoing bilateral photorefractive keratectomy (PRK). *Adv Ther* 2007;24:1278-85.

9. Salz JJ, Reader AL 3rd, Schwartz LJ, Van Le K. Treatment of corneal abrasions with soft contact lenses and topical diclofenac. *J Refract Corneal Surg* 1994;10:640-6.

10. Lesnonsi G, Coppe AM, Manni G, et al. Analgesic effect of topical diclofenac versus betamethasone after posterior segment surgery. *Retina* 1995;15:34-6.

11. Weinberger D, Ron Y, Lichter H, et al. Analgesic effect of topical sodium diclofenac 0.1% drops during retinal laser photocoagulation. *Br J Ophthalmol* 2000;84:135-7.

12. Chiu HH, Wu PC. Manual acupuncture for relieving pain associated with panretinal photocoagulation. *J Altern Complement Med* 2011;17:915-21.

13. Mirshahi A, Lashay A, Roozbahani M, et al. Pain score of patients undergoing single spot, short pulse laser versus conventional laser for diabetic retinopathy. *Graefes Arch Clin Exp Ophthalmol* 2013;251:1103-7.

14. Ku EC, Lee W, Kothari HV, Scholer DW. Effect of diclofenac sodium on the arachidonic acid cascade. *Am J Med* 1986;80:18-23.

15. Zakrzewski PA, O’Donnell HL, Lam WC. Oral versus topical diclofenac for pain prevention during panretinal photocoagulation. *Ophthalmology* 2009;116:1168-74.

16. Esgin H, Samut HS. Topical ketorolac 0.5% for ocular pain relief during scatter laser photocoagulation with 532 nm green laser. *J Ocul Pharmacol Ther* 2006;22:460-4.

17. Ellis PP, Ploff DS, Bloedow DC, Riegel M. Intraocular diclofenac and flurbiprofen concentrations in human aqueous humor following topical application. *J Ocul Pharmacol Ther* 1994;10:677-82.

18. Scott J, Huskisson EC. Graphic representation of pain. *Pain* 1976;2:175-84.