Oral gabapentin for photorefractive keratectomy pain

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PURPOSE: To compare the efficacy of oral gabapentin versus placebo for the control of severe pain after photorefractive keratectomy (PRK).

SETTING: Center for Refractive Surgery, Walter Reed Army Medical Center, Washington, DC, USA.

DESIGN: Randomized masked clinical trial.

METHODS: This single-center clinical trial comprised active-duty United States Army soldiers aged 21 years or older having bilateral PRK for myopia with or without astigmatism. Patients received gabapentin 300 mg or placebo 3 times daily for 7 days beginning 2 days before and continuing for 4 days after surgery. Current and maximum pain levels were assessed using the Visual Analog Pain scale 2 hours after surgery and then daily on days 1 through 4. Repeated-measures analysis of variance (ANOVA) was used to compare the current and maximum pain scores over time between the gabapentin group and the placebo group. The Fisher exact test was used to determine whether there was a difference in severe pain (>7/10) between the 2 groups.

RESULTS: Forty-two patients received gabapentin and 41 patients, placebo. The repeated-measures ANOVA showed no significant difference between the 2 groups in current pain ($P=.84$) or in maximum pain over time ($P=.35$). Oxycodone–acetaminophen use in the gabapentin group was significantly higher than in the placebo group 1 day postoperatively ($P=.034$).

CONCLUSION: When added to a standardized postoperative pain regimen, gabapentin use led to no additional improvement in PRK pain control compared with a placebo at the dose and the time intervals tested.

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Since approval by the U.S. Food and Drug Administration (FDA) in 1995, laser vision correction with the excimer laser has increased in frequency and popularity in the United States. An estimated 1.1 million procedures were performed in the U.S. in 2003.[1] Although laser in situ keratomileusis (LASIK) is the predominant procedure of choice for most patients and surgeons, photorefractive keratectomy (PRK) remains a viable alternative for the correction of low to moderate myopia or hyperopia. This is especially true for eyes that have reduced central corneal thickness or anterior-basement-membrane dystrophy, for moderately dry eyes, and for patients who are occupationally or recreationally susceptible to trauma and thus have an increased risk for LASIK flap dislocation.[2,3]

Although slower visual recovery, prolonged use of topical steroidal agents, and postoperative corneal haze are considered drawbacks to PRK compared with LASIK,[4,5] the primary disadvantage of PRK is postoperative pain. Topical and oral nonsteroidal anti-inflammatory drugs (NSAIDs) and other oral analgesic agents, usually acetaminophen with various opioid derivatives, are the mainstays of postoperative pain control. Studies[4,6] show that topical NSAIDs effectively control PRK pain without decreasing the rate of corneal reepithelialization.

Despite lack of data from clinical trials, many refractive surgeons have adopted the off-label use of medications as an adjunct treatment for the management of PRK pain based largely on anecdotal evidence of efficacy. One of these medications is gabapentin (Neurontin), an alkylated analogue of the neurotransmitter gamma-aminobutyric acid. Gabapentin is not currently FDA approved for use to decrease pain after

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14. ABSTRACT

PURPOSE: To compare the efficacy of oral gabapentin versus placebo for the control of severe pain after photorefractive keratectomy (PRK). SETTING: Center for Refractive Surgery, Walter Reed Army Medical Center, Washington, DC, USA. DESIGN: Randomized masked clinical trial. METHODS: This single-center clinical trial comprised active-duty United States Army soldiers aged 21 years or older having bilateral PRK for myopia with or without astigmatism. Patients received gabapentin 300 mg or placebo 3 times daily for 7 days beginning 2 days before and continuing for 4 days after surgery. Current and maximum pain levels were assessed using the Visual Analog Pain scale 2 hours after surgery and then daily on days 1 through 4. Repeated-measures analysis of variance (ANOVA) was used to compare the current and maximum pain scores over time between the gabapentin group and the placebo group. The Fisher exact test was used to determine whether there was a difference in severe pain (>7/10) between the 2 groups. RESULTS: Forty-two patients received gabapentin and 41 patients, placebo. The repeated-measures ANOVA showed no significant difference between the 2 groups in current pain (PZ.84) or in maximum pain over time (PZ.35). Oxycodone?acetaminophen use in the gabapentin group was significantly higher than in the placebo group 1 day postoperatively (PZ.034). CONCLUSION: When added to a standardized postoperative pain regimen, gabapentin use led to no additional improvement in PRK pain control compared with a placebo at the dose and the time intervals tested.

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PRK. To date, there has been only 1 prospective cohort study comparing gabapentin with oxycodone–acetaminophen for the treatment of PRK pain.[7] To our knowledge, there has been no prospective randomized controlled clinical trial comparing gabapentin and a placebo in combination with commonly used topical and oral medications after PRK.

PATIENTS AND METHODS

In this single-center double-masked randomized placebo-controlled clinical trial, active-duty U.S. Army soldiers aged 21 years or older having bilateral PRK for myopia, with or without astigmatism, were voluntarily enrolled. Before the study, institutional review board approval was obtained from the Walter Reed Army Medical Center Department of Clinical Investigation. All patients provided informed consent, and the study was in accordance with the principles of the Declaration of Helsinki. This trial was registered in the National Institutes of Health Clinical Trials.[A]

The study consisted of 4 in-office study visits as follows: an enrollment examination with instruction for pain level assessment, a visit on the day of surgery, and visits 1 day and 4 days postoperatively. In addition, 2 postoperative telephone interviews were conducted at 2 days and 3 days to assess pain scores. All visits beyond 4 days were regularly scheduled standard-of-care postoperative visits at 1, 3, 6, and 12 months; no study data were collected during these visits. At enrollment, a detailed review of medical and ophthalmic histories and current medications was recorded and an examination performed. The examination included pupil size, anterior segment biomicroscopy, corneal clarity, manifest

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refraction, uncorrected and corrected distance visual acuity, corneal topography, intraocular pressure, corneal thickness, cycloplegic refraction, and posterior segment ocular evaluation. At their enrollment visit, after giving voluntarily consent, patients were randomized to receive gabapentin or a placebo; randomization was performed using a software program based on random number generation.

All patients were prescribed oral ascorbic acid 1 g daily for 3 months postoperatively. Patients were also prescribed topical agents to include moxifloxacin 0.5% ophthalmic solution (Vigamox) 1 drop 4 times a day until corneal reepithelialization; fluorometholone (0.1%) 1 drop 4 times a day for 4 weeks, followed by a 6-week taper (decrease 1 drop every 2 weeks); carboxymethylcellulose 0.5% (Refresh Plus) 1 drop 4 times a day for 2 weeks and then as needed; topical ketorolac tromethamine 0.4% (Acular LS) up to 4 times daily for the first 48 hours after surgery as needed; and oxycodone–acetaminophen (Percocet), 5 mg/325 mg 1 to 2 tablets every 4 to 6 hours as needed for postoperative pain. Patients were allowed to use an oral NSAID, such as ibuprofen. Use of oral nonsteroidal or other oral analgesic medicines was not recorded.

Patients were instructed on the use and documentation of the Visual Analog Scale (VAS)[8–10] during their enrollment examination and on the day of surgery. Clinician examiners and patients were masked to selection of the study medication. Patients assigned to the gabapentin group received a loading dose of gabapentin, 300 mg, 3 times a day for 2 days before surgery, 3 times daily on the day of surgery, and days 1 through 4 postoperatively. Patients assigned to the placebo group were treated with the same dosing schedule.

All procedures were performed at the Center for Refractive Surgery, Walter Reed Army Medical Center, Washington, DC. Corneal epithelial removal was performed with an Amoils epithelial scrubber (Innovative Excimer Solutions, Inc.). The ablation was performed using the Allegretto Wave Eye-Q 400 MHz laser platform (WaveLight AG). Immediately after, the ablated stromal bed was irrigated with a chilled balanced salt solution. Topical mitomycin-C (MMC) 0.02% was applied to the stromal bed for 20 seconds with a methylcellulose-soaked sponge in all eyes in which the ablation depth exceeded 70 μm. The MMC was then rinsed from the ocular surface by copious irrigation with balanced salt solution. Postoperatively, all patients were treated with a high-oxygen-transmissible therapeutic soft contact lens (Focus Night & Day, Ciba Vision) that remained in place until complete corneal reepithelialization.

The primary outcome measure was the level of postoperative pain, which was assessed using the VAS. Pain was assessed 2 hours after surgery (in person or via telephone interview) and once daily on days 1 through 4 postoperatively. The 1-day and 4-day pain assessment was in person during the normally scheduled postoperative examinations. The 2-day and 3-day assessments were by telephone interview. Pain scores were assessed on the VAS for current (at the time of questioning) pain, average pain over the preceding 24 hours, and maximum pain over the preceding 24 hours. The time of day the patients were questioned was not standardized.

An estimation of the sample size needed to determine efficacy/pain reduction was based on previous results from the Center for Refractive Surgery, in which 70% of patients having PRK reported pain on the first postoperative day. It was assumed that 1 day postoperatively, 70% of patients in the placebo group would have pain (>0 on the pain scale)

compared with 40% of the patients in the gabapentin group. Controlling the probability of a Type I error at $\alpha = 0.05$, a sample of 48 patients per group was projected to have 80% power to detect a difference of 30% in the incidence of pain (ie, 40% versus 70%). Because pain was measured on a scale from 0 to 10 rather than as a nominal yes/no variable, the study may have had a greater power to find a difference between treatment groups with fewer patients.

Pain score results in the gabapentin group and the placebo group were compared. All data were analyzed using SPSS software (version 15.0, SPSS, Inc.). Repeated-measures analysis of variance (ANOVA) was used to compare the 2 groups over time for current, average, and maximum pain scores. For data that did not meet sphericity assumptions, the Greenhouse-Geisser corrected P values are presented. Post hoc testing of group differences was examined using the 2-sample t test. A Mann-Whitney test was used to compare age, manifest spherical equivalent (SE), ablation depth, and total oral oxycodone–acetaminophen used in the gabapentin group and the placebo group with a significance of $\alpha = 0.05$. The Fisher exact test was used to determine whether there was a difference in severe pain, defined as more than 7 out of 10, between the gabapentin group and the placebo group. A stepwise regression analysis was used to determine whether age, sex, ablation depth, treatment (gabapentin or placebo), use of MMC, or mean manifest SE were potential predictors of maximum pain 1 day postoperatively. The Fisher exact test was used to further examine the independent variables affecting postoperative maximum pain at 1 day. Data are presented as the mean ± standard deviation (SD) unless otherwise indicated.

RESULTS

Of the 83 patients enrolled in the study, 42 were randomized to receive gabapentin and 41 to receive placebo. No patient withdrew consent for participation in the study. One patient in the gabapentin group withdrew from the study due to excessive nausea 1 day postoperatively. Although it was believed that the nausea was secondary to oxycodone–acetaminophen use, the study pill (gabapentin) was stopped. This patient's data were not used in the statistical analysis, leaving 41 patients in the gabapentin data analysis group. No other patient was lost to follow-up or discontinued the intervention.

Table 1 shows the preoperative patient characteristics. Patients were predominately male in both treatment groups. There was no difference between the gabapentin group and the placebo group preoperatively in sex distribution, age, manifest SE, or ablation depth. There were slightly lower levels of refractive errors and ablation depths in the gabapentin-treated group than in the placebo group, although the difference was not statistically significant. Six patients in the gabapentin group and 7 patients in the placebo group received topical MMC treatment.

Pain score reporting was 95% at the 2-hour interview and 100% and 98% at the in-person office visits (1 day and 4 days, respectively). However, the pain

Table 1. Preoperative demographic data.

Characteristic	Gabapentin Group	Placebo Group	P Value
Females/males (n)	2/39	7/34	.16
Age (y)			.059
Mean ± SD	30.4 ± 8.0	33.2 ± 7.8	
Range	21 to 48	21 to 46	
Manifest SE (D)			.59
Mean ± SD	−2.89 ± 1.37	−3.22 ± 1.72	
Range	−0.82 to −7.51	−0.88 to −7.88	
Ablation depth (μm)			.43
Mean ± SD	48.15 ± 18.44	53.25 ± 23.31	
Range	19.33 to 102.75	19.32 to 117.37	

SE = spherical equivalent, mean of both eyes

reporting decreased to 89% for both telephone interviews (2 days and 3 days) in the gabapentin group and the placebo group. Patients were not always accessible for the telephone interview, thereby lowering the response rate. Table 2 shows the current, average, and maximum pain scores at time of questioning on each postoperative day. In both groups, the maximum pain scores (over the preceding 24 hours) were highest 1 day postoperatively and gradually diminished each day thereafter (Figure 1). Repeated-measures ANOVA showed no significant difference in current, average, or maximum pain between the gabapentin group and the placebo group over time ($P=.84$, $P=.56$, and $P=.35$ for the interaction of time and group) (Table 2). Very severe pain (maximum pain scores $\geq 7/10$) compared with none to moderate pain (scores <7), when examined daily, was not significantly different between gabapentin group and the placebo group 1 through 3 days postoperatively (Figure 2). At 4 days, however, 4 patients in the placebo group reported severe pain versus no patient in the gabapentin group ($P=.055$). The mean maximum pain level 1 day postoperatively was 0.68 higher in the gabapentin group than in the placebo group. The difference in pain scores has a 95% confidence interval (CI) of −0.48 to 1.84, which T indicates that the best-case scenario for pain relief for gabapentin, taking into account sample size, would be an improvement in maximum pain of 0.48 on a 10-point scale.

The stepwise linear regression analysis of the dependent variable of maximum pain on postoperative day 1 showed that the independent variables of age and use of MMC were significant, accounting for 16.8% of the variability in maximum pain 1 day postoperatively ($r^2 = 0.17$, $P=.001$). To further examine age, patients were divided into the following 2 age categories using the median age in the cohort: 30 years or younger and 31 years or older. Younger patients

Table 2. Pain scores reported using the VAS (0 to 10).

| Characteristic | Mean Score ± SD (Range) | | P Value* |
	Gabapentin Group	Placebo Group	
Total oxycodone–acetaminophen used	7.54 ± 3.45 (0.0–16.0)	7.15 ± 3.90 (0.0–15.0)	.76
Current pain			.84
2 Hours	2.22 ± 2.10 (0.0–7.5)	2.71 ± 1.84 (0.0–7.5)	.28
Day 1	2.54 ± 2.29 (0.0–7.0)	2.90 ± 2.58 (0.0–8.5)	.52
Day 2	1.99 ± 1.86 (0.0–8.0)	2.71 ± 2.22 (0.0–8.0)	.14
Day 3	1.00 ± 1.15 (0.0–5.0)	1.56 ± 2.00 (0.0–8.0)	.16
Day 4	0.44 ± 0.67 (0.0–2.0)	0.64 ± 1.20 (0.0–5.0)	.36
Average pain			.56
Day 1	3.85 ± 2.05 (0.0–8.0)	4.09 ± 2.38 (1.0–10)	.64
Day 2	3.00 ± 2.01 (0.0–9.0)	4.00 ± 1.97 (0.0–8.0)	.035
Day 3	2.09 ± 1.57 (0.0–5.5)	2.58 ± 2.08 (0.0–8.0)	.28
Day 4	1.30 ± 1.16 (0.0–4.0)	1.86 ± 1.96 (0.0–7.0)	.12
Maximum pain			.35
Day 1	5.85 ± 2.67 (2.0–10)	5.17 ± 2.58 (1.0–10)	.25
Day 2	5.01 ± 2.27 (1.0–10)	5.13 ± 2.09 (1.0–9.0)	.82
Day 3	3.60 ± 2.39 (0.0–9.0)	4.14 ± 2.69 (1.0–10)	.39
Day 4	2.04 ± 1.78 (0.0–6.0)	2.74 ± 2.52 (0.0–9.0)	.15

*Comparison of the 2 groups

(71%) reported severe pain (maximum pain score at 1 day ≥7) significantly more often than patients older than 30 years (29%) (P = .023). To further examine the use of MMC, the incidence of severe pain, as described above, in patients who received topical MMC and in those who did not was compared. No patient treated with MMC and 45.6% of patients who did not receive MMC reported severe pain (P = .001).

DISCUSSION

In humans, gabapentin has FDA approval for the management of post-herpetic neuralgia in adults and as adjunctive therapy in the treatment of partial seizures in patients with epilepsy.[B] Gabapentin has been used in many off-label situations[11] as well as in many surgical settings to mitigate perioperative and postoperative pain.[12,13] A metaanalysis of 12 studies of postoperative pain scores in patients treated perioperatively with gabapentin (including 4 randomized controlled trials using the VAS) showed a decrease in overall opioid use by patients who received gabapentin. Results of this metaanalysis suggest that pain reduction was most pronounced from 20 to 24 hours postoperatively and as such, it was reasoned that gabapentin may have a true preventive effect on postoperative neuropathic pain in the trials analyzed.[14]

Case reports describe the successful use of gabapentin for pain reduction in a blind, painful eye secondary to glaucoma[15] and in a patient with neuropathic orbital pain.[16] Only 1 previous trial evaluated the role of gabapentin for pain after PRK. Nissman et al.[7]
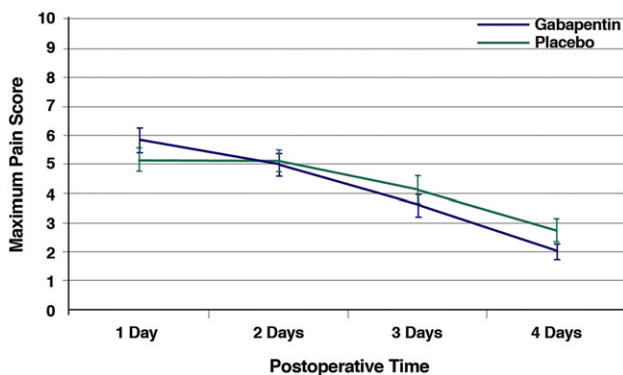

Figure 1. Maximum pain at daily intervals. Error bars represent the standard error of the mean.
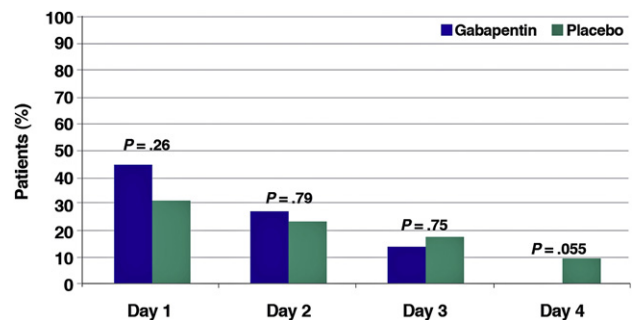

Figure 2. Percentage of patients reporting severe pain in each treatment group.

showed that subjective PRK pain levels in patients who received gabapentin alone were comparable to those in patients who received oral oxycodone–acetaminophen. Based on these results, we performed a randomized prospective placebo-controlled study examining PRK pain at commonly used follow-up intervals. All patients had bilateral PRK with epithelial removal via a rotary epithelial scrubber, and similar numbers of patients in each treatment group received topical MMC application after epithelial removal. Last, we used a pain scale that has been validated in previous trials of gabapentin for treatment of postoperative pain.[14]

Despite an adequate study design, we realize that our study had limitations. Our patients were predominately young and male, not surprising in an active-duty military setting. Therefore, the results cannot necessarily be extrapolated to a broader age range or to female PRK patients. Several variables remained uncontrolled despite our efforts, which included the use of rescue medications including a topical NSAID and an oral narcotic analgesic agent. Patients were authorized to use oral narcotics on an as-needed basis, which is customary in our institution. Whether any diminution of gabapentin's neuropathic pain modification occurs when combined with an oral opioid is unknown, although this has been suggested in trials of gabapentin for treatment of post-herpetic neuralgia.[11,17] The effect of MMC use on postoperative pain is unknown; however, our small cohort of patients who received MMC application reported significantly less severe pain than those who did not. We have no explanation for this finding.

Pain-level intervals that coincided with intervals commonly used to follow patients after PRK were chosen, and maximum pain levels were included to record peaks of daily pain. Complete standardization of pain-level collection (direct face-to-face questioning versus telephone questioning) was not possible for logistical reasons.

Gabapentin is a drug that can be titrated to perceived clinical benefit, and gabapentin oral dosing varies widely for various conditions. We acknowledge that the proper milligram dosing of gabapentin for treatment of pain after PRK is not known. Bioavailability of gabapentin has been shown to be highest (approximately 60%) at 300 mg per oral dose[12,B]; therefore, patients in the gabapentin group received 300 mg 3 times daily beginning 2 days before surgery; they continued this dosage on the day of surgery and from 1 day through 4 days postoperatively. A previous dose-response study of the treatment of post-herpetic neuralgia[18–20] showed that oral gabapentin 900 mg daily achieved the best results in overall pain relief, that gabapentin doses ranging from 200 to
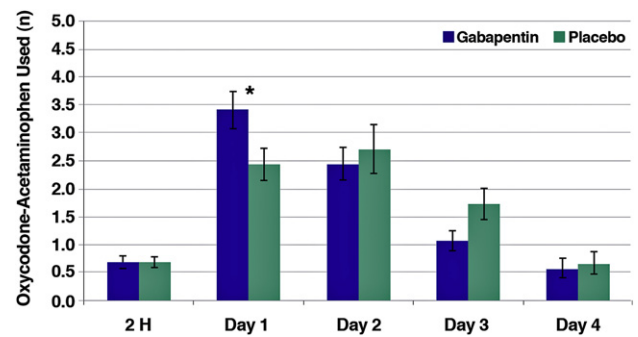

Figure 3. Daily oxycodone–acetaminophen use. Error bars represent the standard error of the mean.

600 mg were similar in side-effect profiles, and that gabapentin was well-tolerated in doses up to 3600 mg per day. A review of 5 other randomized placebo-controlled trials that used gabapentin for neuropathic pain[21] suggests that gabapentin therapy should be initiated at 900 mg per day. Cumulatively, these results suggest that reduction in pain after PRK could occur at higher doses of gabapentin than those we studied.

In our study, Mann-Whitney tests showed a strong trend for daily oral oxycodone–acetaminophen use to be higher in the gabapentin group than in the placebo group 1 day postoperatively. Tracking the number of pills by performing in-person counts of the number of remaining oxycodone–acetaminophen tablets prescribed was difficult because a small number of patients had their initial prescription of oxycodone–acetaminophen tablets refilled. We regret that these results cannot be included in our data set; however, the daily reported oxycodone–acetaminophen is shown in graph form in Figure 3. This lack of a secondary outcome measure of decreased opioid consumption, which has been studied in many trials using gabapentin for neuropathic and postoperative pain, may decrease the potential power of our study to determine this clinically useful parameter.

In this study, gabapentin offered no benefit over a placebo in controlling PRK pain when added to a standard postoperative regimen consisting of topical agents and an oral narcotic. Further study is required to evaluate the possible role of gabapentin as a replacement for oral narcotic agents in postoperative pain management. Continued study of developing treatments to diminish or eliminate pain after PRK may increase acceptance of surface ablation procedures by both surgeons and patients.

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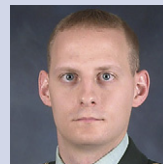
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